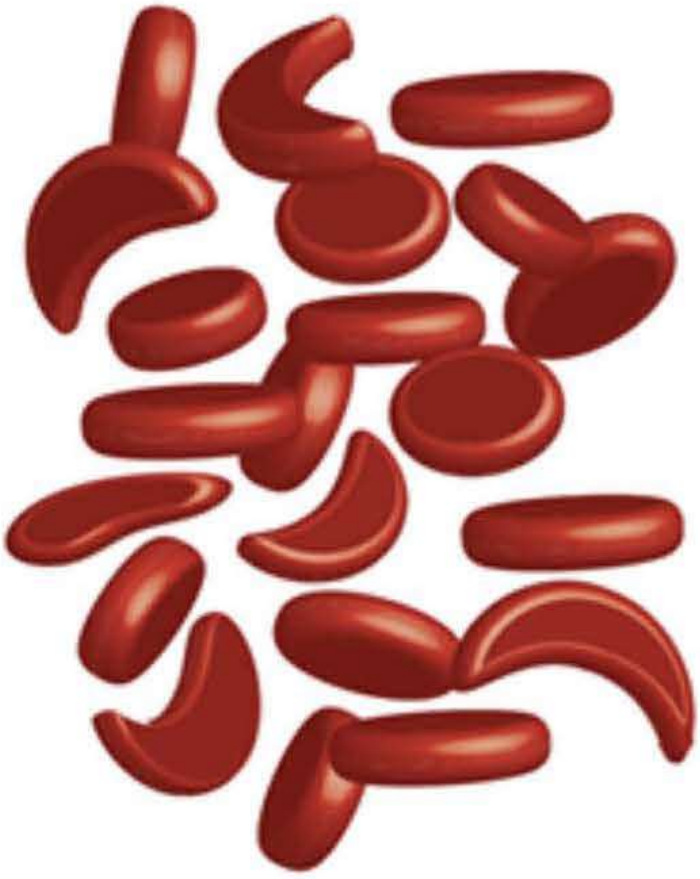
HEMOGLOBIN SWITCHING MEETING

PROGRAMS

1ST – 21ST CONFERENCES

(1978 – 2018)



George Stamatoyannopoulos
1934-2018

FIRST CONFERENCE ON HEMOGLOBIN SWITCHING

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The1st Hemoglobin Switching Meeting
Battelle Institute Seattle: 1978

This conference was a small gathering (75 participants) of physicians, cell biologists, and molecular biologists . The program covered the whole field of hemoglobin switching as of 1978..

Erythropoiesis
Structure of Globin Genes (mainly Southern Blotting)
Chromatin Structure
Hb Switching

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Hemoglobin Switching

Meeting Review

Arthur W. Nienhuis
Clinical Hematology Branch
National Heart, Lung and Blood Institute
Bethesda, Maryland 20014
George Stamatoyannopoulos
Medical Genetics
University of Washington
Seattle, Washington 98195

Introduction

On June 19-21, 1978, a conference was held to review the current state of knowledge on the mechanism of regulation of hemoglobin switching. The transitions from embryonic to fetal (or adult) hemoglobin synthesis occurring early in embryogenesis and the transition from fetal to adult production at about the time of birth in several species were discussed. These switches represent models in which one can examine the regulation of individual globin genes both at the molecular level and during the various stages of cellular differentiation that lead to production of red blood cells containing particular hemoglobins. The ability to stimulate fetal hemoglobin (Hb F) production in adults might be of therapeutic benefit in patients with sickle cell anemia or severe variants of homozygous β thalassemia. In addition, certain mutations in humans are characterized by enhanced production of Hb F. Thus at this conference an effort was made to examine the known clinical, genetic and experimental observations directly pertinent to various developmental or physiological switches in hemoglobin phenotype, and to relate these data to recent developments in cellular and molecular biology, in an effort to develop a framework for the progressive understanding of the control of individual globin genes.

Hb F Production beyond the Neonatal Period

Weatherall (Oxford) reviewed the various human genetic conditions in which there is substantial synthesis of Hb F beyond the neonatal period. In two, pan-cellular hereditary persistance of fetal hemoglobin (HPFH) and homozygous $\delta\beta$ thalassemia, Hb F is found in all red cells; these conditions reflect deletion of all or a part of the δ- and β-globin genes. Mapping of the globin gene region by restriction endonuclease analysis using the "blotting" technique yielded the information that more DNA sequences are missing in certain patients with HPFH than in those with $\delta\beta$ thalassemia (Bank; Columbia), perhaps accounting for the generally more adequate synthesis of Hb F in HPFH.

All other conditions characterized by increased Hb F production appear to reflect an increase in the proportion of "F cells." F cells contain 5-8 pg of Hb F (14-28% of total) and 24-27 pg of Hb A (Boyer; Johns Hopkins); 0.2-7% of the red cells in normal humans are F cells. In various heterocellular HPFH syndromes (genetic states characterized by increased Hb F production in the absence of other changes in the red cell) the number of F cells is increased. Linkage analysis (Weatherall; Oxford) appears to suggest that the gene for heterocellular HPFH is linked to the human γ-δ-β gene complex known to be on chromosone 11 (Deisseroth; NIH). In the Saudi Arabian population of patients with sickle cell anemia, clinical manifestations are very mild and Hb F comprises 20-40% of the total hemoglobin. Heterozygotes for the β^S gene in this population have little increase in Hb F, excluding heterocellular HPFH as the basis for increased Hb F production in the SS individuals. The anemic stress due to sickle cell anemia brings out a propensity for Hb F production in this genetic isolate, in contrast to the much smaller amounts of Hb F seen in most black patients with SS disease. In patients with homozygous β thalassemia, red cell production may be increased more than 25 fold. The increase in Hb F may be accounted for by simple amplification of the F cell population, since those cells containing Hb F have a selective advantage both during erythropoiesis in the bone marrow and circulation of red cells in the blood stream.

Thus a consideration of the various genetic conditions which lead to increased Hb F production in adults identifies several potential mechanisms: gene deletion, mutations in a regulatory locus linked to the γ-δ-β globin gene complex, activation of a latent potential for Hb F production by anemia, or amplification of the normal F cell population by severe erythropoietic stress. A further complexity was revealed by the sensitive immunodiffusion assay utilized by Boyer (Johns Hopkins) to quantitate the amount of Hb F in each F cell. Considerable variation was found, and some evidence is available which indicates that the quantity of Hb F per F cell may be under genetic influences separate from those which affect F cell production.

Stress Erythropoiesis and Hemoglobin Switching

Further insight into potential mechanisms of regulation of hemoglobin switching might be gained from consideration of the changes in hemoglobin phenotype which occur as a result of bone marrow stress. These can be separated into two types. The first is erythropoietic stress due to anemia or hypoxia, which reliably results in a switch to synthesis of a new hemoglobin, and the second is a severe disturbance in erythroid cell differentiation, which in man is variably associated with an acquired increase in Hb F production. Among the physiological switches, the transition to Hb C ($\alpha_2\beta_2^C$) synthe-

sis in certain anemic sheep has been extensively studied. Under certain circumstances, stem cells committed to generate erythroblasts that make Hb C can be found by culturing marrow from animals which have been injected with erythropoietin, although Hb C synthesis does not occur in vivo (Barker; NIH). Thus induction of Hb C synthesis was separated into two steps: the commitment of erythroid stem cells and the maturation of these committed cells to form erythroblasts that make Hb C. Sheep also possess a γ gene which is expressed during fetal life but, as in humans, activation of this gene does not regularly occur in anemic animals.

In contrast, DeSimmone (Chicago) reported that anemia or hypoxia in the baboon, Papio cynocephelus, leads to a reversion from Hb A ($\alpha_2\beta_2$) to Hb F ($\alpha_2\gamma_2$) synthesis. The γ-globin produced during erythropoietic stress appears to be identical to the γ-globin produced during gestation in this species. The human analogy to this switch is the Saudi Arabian population with sickle cell anemia, in which enhanced Hb F production appears to occur as a result of erythropoietic stress. A further example of a switch in globin gene expression due to anemia was uncovered rather unexpectedly. Among various recombinant plasmids into which had been inserted globin gene sequences synthesized using mRNA from the reticulocytes of anemic chicks, Salser (UCLA) identified sequences for α-like globins that were identical to neither the normal adult nor the embryonic α-globins of this species. Presumably anemia had led to expression of new α-globin gene.

Thus in sheep, baboon and chick, anemia leads to a switch in globin gene expression. In the sheep, a unique β-globin is produced; in the baboon, the fetal γ-globin gene is reactivated; and in the chick, a new α-globin is possibly produced. The common feature which leads to expression of these genes during erythroid stress is presumably unrelated to the encoded globin; perhaps similarities will be found in the flanking or intervening DNA sequences of these genes that might provide insight into their common pattern of expression during erythroid stress.

In humans, enhanced synthesis of Hb F is not a regular consequence of severe acute or chronic anemia. Increased numbers of F cells are produced by women in the early stages of pregnancy. Enhanced production of F cells may also be seen in certain pathological states characterized by bone marrow hypoplasia and/or bone marrow repopulation. Boyer (Johns Hopkins) studied several patients with acquired hypoplasia. Using an antibody specific for Hb F in a single cell immunodiffusion assay, he was able to follow the production of F reticulocytes. The general observation was that F reticulocytes were the first to disappear during acquired hypoplasia and the first to reappear as the bone marrow began to function. Both in patients with congenital hypoplastic anemia and during repopulation of the bone marrow following bone marrow transplantation, Hb F production is frequently elevated (Alter; Boston). The pattern of Hb F distribution is nonuniform or heterocellular. Thus severe disturbances in erythroid stem cell differentiation may tip the balance toward production of F cells.

Hemoglobin Switching and Erythroid Stem Cell Differentiation

There is now evidence that once cells leave the compartment of pluripotent hematopoietic cells, they undergo an amplification and differentiation process within the committed erythroid stem cell compartment of erythropoiesis. Connie Eaves (British Columbia) described her studies which have led to the concept that there is a continuum of erythroid stem cells. The earliest of these committed erythroid progenitors, the primitive BFU-E, is perhaps one or two cell divisions away from the pluripotent stem cell, whereas the most mature of the erythroid stem cell population (CFU-E) are the precursors to the morphologically defined proerythroblasts. The early progenitors are recognized in vitro by their high proliferative potential; the colonies are large (even macroscopic) and usually composed of multiple subcolonies. These early stem cells or BFU-E have high erythropoietin requirements for growth, while the later erythroid progenitors (CFU-E) give rise to single and rather small colonies that require less erythropoietin for growth. The BFU-E appear to divide several times in culture; the daughter cells may migrate for short distances in semi-solid medium before they enter the terminal phases of erythroid maturation. Eaves has also defined two populations of BFU-E, primitive (BFU-Ep) and mature (BFU-Em); BFU-Em have a lower erythropoietin requirement, greater fractional kill by ^{3}H-thymidine, fewer subcolonies, and require a shorter time to form mature colonies in vitro than do BFU-Ep.

The phrase "hemoglobin switching" really applies only to the gradual replacement, in the blood stream, of red cells containing predominantly one hemoglobin with red cells which contain predominantly another. Such switches in hemoglobin phenotype do not reflect an intracellular switch within individual erythroblasts from production of one globin mRNA to the production of another. Rather, switches occur as a population of erythroblasts making the new globin mRNA appear in the bone marrow. This has been most clearly demonstrated for the Hb A ($\alpha_2\beta_2^A$) to Hb C ($\alpha_2\beta_2^C$) switch in sheep. Injection of a young animal with a large dose of erythropoietin is marked within 12 hr by the ap-

pearance in the bone marrow of stem cells committed to form erythroblasts which make Hb C (Benz; NIH). These committed stem cells are demonstrated by an in vitro assay for colony-forming cells. Accumulation of the β^C-globin mRNA in the bone marrow did not occur until 24–36 hr after the committed stem cells were first demonstrable. Thus the primary regulatory events leading to expression of the β^C globin gene appear to occur in erythroid stem cells which are a few divisions away from the erythroblasts that accumulate globin mRNA.

Both Hb F and Hb A are found in individual red cells in man and other species, eliminating the simple possibility that Hb F and Hb A are the products of totally separate cell lines. Adult red cells are of two distinct types, however: F cells which contain variable amounts of Hb F, and A cells which appear to contain only Hb A. What is the evidence that F cells and A cells are derived from a common erythroid stem cell population? Two lines of evidence are available (Papayannopoulou; Seattle). First, certain hematological disorders in man occur by virtue of somatic cell mutations that affect a single pluripotent stem cell. The progeny of this abnormal stem cell partially or completely replace the normal hematopoietic cells in the bone marrow and peripheral blood. If F cells were derived from a pluripotent stem cell separate from that which gave rise to A cells, patients with these clonal disorders should either have only F cells or no F cells at all. The F cell frequency in these clonal disorders, however, is similar to the distribution found in normal humans (Papayannopoulou; Seattle). Second, when individual burst colonies derived from single human bone marrow or peripheral blood BFU-E are examined with antibodies specific for adult hemoglobin or Hb F, individual subcolonies within a single burst may be found which contain Hb F *and* adult hemoglobin or *only* adult hemoglobin. These data favor the notion that at least primitive BFU-E are bipotent with respect to their ability to generate F cells or A cells.

It has also become clear that the old idea that yolk sac-derived red cells make only embryonic hemoglobins is incorrect. Chui (Hamilton, Ontario) reported that the primitive embryonic red cells of yolk sac origin in the mouse began to synthesize adult mouse hemoglobins at 13–14 days of gestation; earlier in gestation these cells contain only embryonic hemoglobins. The onset of adult globin synthesis in the yolk sac-derived red cells coincided with the initiation of erythropoiesis in the fetal liver. Either the embryonic cells were preprogrammed to begin making adult globins at that time, or they responded to some humoral substance in the circulation which also activated the hepatic stage of erythropoiesis. Tobin (UCLA) used fluorescent antibodies specific for the embryonic Hb P of the chick to show that early erythroblasts of the definitive red cell line contained embryonic hemoglobins. These were no longer detectable in the mature erythrocytes. Transient expression of the embryonic globin genes thus appeared to occur during the early cell divisions of definitive red cell formation. On the basis of Chui and Tobin's results, the notion that yolk sac-derived red cells make only embryonic hemoglobins while definitive erythroblasts fail to make embryonic hemoglobin must be discarded.

Hemoglobin Switching in Culture

In vitro studies of human erythroid colony formation make it seem probable that the cell in which the individual globin genes are regulated is an early erythroid stem cell. Stamatoyannopoulos and co-workers (Seattle) have found stimulation of Hb F production in clonal cultures of erythroid progenitors from adults without increased Hb F synthesis in vivo. The use of fluorescent antibody probes for identification of specific hemoglobins in individual colonies has shown that those clones with Hb F synthesis come from cells with growth characteristics of BFU-Es. BFU-Es but not CFU-Es are found in the peripheral blood; cultures of these circulating erythroid stem cells yield colonies that make Hb F. Stamatoyannopoulos (Seattle) also found heterogeneity among BFU-Es in their ability to initiate Hb F synthesis in erythroid clones; this ability was characteristic of BFU-Es which, by their proliferative potential, could be placed at the earliest differentiation stage (BFU-Ep).

The possibility that more primitive progenitors in adult hematopoietic tissue retain the ability to express Hb F was tested by two other approaches. Ogawa (South Carolina) measured Hb F biosynthetically in adult erythroid colonies coming from either highly differentiated CFU-E or primitive BFU-E; there was no Hb F production in CFU-E-derived colonies, while approximately 20% of the hemoglobin produced in BFU-Ep colonies was fetal hemoglobin. Messner (Toronto) obtained mixed colonies of granulocytic and erythroid precursors by adding to his cultures a conditioned medium obtained by stimulating spleen cells with phytohemaglutinin (PHA). These mixed colonies were presumably derived from a very early, at least bipotent (erythroid and granulocyte) stem cell. Messner demonstrated that PHA-leukocyte-conditioned medium promoted the formation of burst colonies containing Hb F.

Housman (MIT) found that colonies derived from BFU-E in human peripheral blood made Hb F, but failed to find evidence for Hb F synthesis in burst colonies derived from bone marrow stem cells of hematologically normal adults. On the basis of these data, he proposed that the peripheral blood

BFU-E represented a distinct population of stem cells unique by virtue of their ability to give rise to colonies that synthesize fetal hemoglobin. Ogawa (South Carolina), Stamatoyannopoulos (Seattle) and Messner (Toronto) all found Hb F synthesis in bursts derived from human bone marrow. Variation in culture conditions, the use of relatively impure erythropoietin and the probable presence of differing amounts of other factors necessary for burst colony formation could all contribute to the variability in the yield of colonies making Hb F and account for the somewhat different results obtained in the various laboratories.

Current evidence would indicate that the mechanisms leading to enhanced Hb F production in vitro are operative at the stage of differentiation characteristic of primitive BFU-E. The analysis of Hb F synthesis in cultures of human bone marrow and peripheral blood may be most applicable to the phenomenon of F cell formation. In normal adults synthesizing mostly Hb A, a small number of cells containing Hb F do appear in the circulation; culture conditions devised in vitro to favor differentiation of early erythroid stem cells may unwittingly foster the formation of F cells and therefore lead to enhanced Hb F production.

Certain properties of the erythroid stem cell, which responds to a high concentration of erythropoietin by producing erythroid colonies making Hb C in the sheep, were deduced by analysis of the size of colonies and therefore by the number of cell divisions that had occurred during their formation in vitro. The "switching stem cell" appears to divide seven or more times, giving rise to large colonies; it is in cell-cycle as revealed by sensitivity to ^{3}H-thymidine, and is concentrated among the physically smaller stem cell population which sediments slowly at unit gravity (Nienhuis; NIH). BFU-E found in sheep fetal liver exhibited these properties and also gave rise to burst colonies which made large amounts of Hb C at high erythropoietin concentrations. The results were most consistent with regulation of the individual globin genes occurring in a stem cell at the transition from BFU-E to CFU-E.

In Vitro Analysis of the Hb F to Hb A Switch

Additional evidence supporting the notion that regulation occurs at the level of the primitive erythroid stem cell came from in vitro analysis of progenitors from earlier developmental stages. Erythroid stem cells from the human fetus produce BFU-Ep-derived colonies that synthesize predominantly Hb F in a pattern characteristic of the fetal developmental stage. The normal transition from Hb F to Hb A synthesis in humans begins shortly before birth and is nearly complete a few weeks after; thus the switch-over period is focused at 40 weeks of gestational age. In cultures of cord blood containing BFU-E-derived colonies, Hb A in amounts similar to those synthesized in the newborn was detected biosynthetically and, in addition, BFU-Ep gave rise to colonies containing Hb F and adult hemoglobin or only adult hemoglobin (Stamatoyannopoulos; Seattle). Ogawa (South Carolina) also studied Hb F synthesis by burst colonies derived from cord blood stem cells. The fraction of Hb A synthesis in these burst colonies was greater than the fraction of Hb A in cord blood red cells. The 14 day interval required for development of the burst colonies, however, may have accounted for this discrepancy.

How do these in vitro data relate to the switching mechanisms operative in vivo? Stamatoyannopoulos (Seattle) proposed the hypothesis that hemoglobin switching is related to the phenomenon of erythroid stem cell differentiation per se. Erythroid precursors derived from maturation of the earliest stem cells (BFU-Ep) may have a chromatin structure that favors γ gene transcription, while erythroblasts derived from more mature stem cells (BFU-Em) may have a chromatin structure that permits β gene transcription; hemoglobin ontogeny was attributed to progression of the differentiation process of erythroid stem cells. The phenomenon of Hb F synthesis in cultures of adult marrow or blood may be due to recruitment of earlier stem cells in vitro. In patients with severe disturbances of erythroid stem cell differentiation, primitive BFU-Ep may rapidly mature, leading to increased F cell formation.

Regulation of Erythroid Stem Cell Differentiation

If primitive BFU-E are bipotent with respect to their ability to generate F cells and A cells, then it should be possible to identify those cellular interactions or humoral substances that might influence the propensity toward F cell formation. Several examples of the importance of cell-cell interaction in hemopoietic cell differentiation were reviewed by Cline (UCLA). The production of burst-promoting or enhancing activity (BEA) by phytohemaglutinin-stimulated spleen cells (Messner; Toronto) or adherent bone marrow (Eaves; British Columbia) seem to be among the most important; BEA promotes the division of BFU-E during the earliest steps of erythroid stem cell differentiation and reduces the amount of erythropoietin required for burst formation. Nathan (Boston) has demonstrated that T lymphocyte-conditioned medium enhances burst colony formation by BFU-E found in human peripheral blood. The various burst-enhancing activities demonstrated by these investigators may involve identical molecules or different substances. Of greater interest is whether a specific BEA might enhance Hb F synthesis by fostering the propensity

of BFU-E to generate F cells. Preliminary data were presented by Messner (Toronto). Addition of PHA-stimulated leukocyte-conditioned medium to bone marrow cultures increased the number of Hb F-containing bursts, while the number of Hb F negative bursts remained unchanged.

Messner's results raise a point which is absolutely critical to the interpretation of all attempts to define factors that might enhance Hb F synthesis. Did some factor in the leukocyte-conditioned medium actually interact with individual BFU-Es and directly influence their propensity to generate erythroblasts making Hb F or, as Messner believes, did the conditioned medium foster the development in culture of the most primitive BFU-E which then displayed in inherent tendency towards formation of cells containing Hb F? This question is impossible to resolve at the moment, but must be considered in interpreting all results obtained in the analysis of Hb F synthesis in vitro. Ogawa (South Carolina) reported that relatively high concentrations of erythropoietin favored Hb F synthesis in burst colonies derived from normal individuals, but that the concentration of erythropoietin used had little effect on the amount of Hb F produced by burst colonies derived from peripheral blood BFU-E of patients with sickle cell anemia. No direct role for erythropoietin in regulating Hb F synthesis can be inferred from these experiments, however, for under some circumstances erythropoietin could merely influence the colony-forming efficiency of stem cells with an inherent propensity towards F cell formation.

Hormonal Effects on Hemoglobin Switching

Erythroid stem cells are exposed to many hormones that might conceivably influence their tendency towards differentiation into erythroblasts synthesizing Hb F; certainly there are drastic changes in the concentration of various hormones which coincide with the transition from fetal to adult hemoglobin synthesis at the time of birth. The identification of potentially important influences of hormones on erythroid stem cells has been attempted in vitro. Golde (UCLA) reported that dexamethasone, a prototype glucocortiosteroid, potentiates erythroid colony formation in vitro, and postulated that steroids may modulate erythropoietin sensitivity. Growth hormone stimulates colony formation in a species-specific manner. Thyroid hormone, β-adenergic agonists and prostaglandins of the E series all potentiate erythroid colony formation, particularly at suboptimal concentrations of erythropoietin, but none of these replace the requirement for erythropoietin to support erythroid colony formation. The accumulated data indicate that many endocrine hormones affect the growth and differentiation of erythroid stem cells.

A few results pertinent to the effect of various hormones on hemoglobin switching are available. Hoffman (Yale) reported that human chorionic gonadotropin and human growth hormone enhanced the proportion of β- (Hb A) compared to γ-globin (Hb F) synthesis in burst colonies derived from BFU-E present in human umbilical cord blood. Wood (Oxford) reported that removal of the thyroid, kidney, adrenal or pituitary gland from fetal sheep did not prevent the onset of the switch from fetal to adult hemoglobin synthesis. The switch was somewhat delayed in a hypophysectomized fetus, although this animal exhibited general developmental retardation. Zanjani (Minnesota) reported that chronic administration of thyroxine resulted in an accelerated rate of adult hemoglobin synthesis in a fetal sheep. Thyroidectomy had no effect in his experiments, either. Extensions of these preliminary observations and further analysis of the effects of hormones at physiological concentrations in vitro will be required to determine whether hormonal modulation of the potential for Hb F synthesis is significant.

Commitment and Erythroid Cell Differentiation

For the purpose of studying stem cell differentiation, it would be highly desirable to have a continuously replicating population of early progenitors such as primitive BFU-E, which could be induced to differentiate in response to specific stimuli, perhaps erythropoietin, and form erythroid colonies with high efficiency. Cell lines with these properties would undoubtedly assist greatly in deducing the mechanisms of regulation of the individual globin genes. Ingram (MIT) reported on his initial attempts to obtain continuously replicating cultures of hemopoietic stem cells by viral transformation of mesenchymal cells from very early chick embryos. A few promising results have been obtained.

Mouse erythroleukemia (MEL) cells are currently available. These erythroid cells, infected with Friend virus complex, are able to proliferate continuously in suspension culture, but MEL cells appear to have progressed well beyond the stage of the erythroid stem cell. Their biochemical and morphological properties put them at the proerythroblast stage of erythroid maturation and thus MEL cells cannot be used to examine the early steps in stem cell differentiation. Nonetheless, MEL cells provide a unique opportunity to define the sequence of biochemical events which occurs during maturation of erythroblasts, and also to examine the process of commitment at the cellular and molecular levels.

When Me_2SO, hexamethylene bisacetamide (HMBA) or one of many other inducers is added to cultures of MEL cells, the cells accumulate globin mRNA and hemoglobin and cease to divide over a period of 3–4 days. To define commitment of these cells, a two step assay has been used; inducer is added to MEL cells in suspension, and after variable periods of time, aliquots are transfered to methylcellulose cultures that do not contain inducer. Commitment to complete the pattern of erythroid maturation appears to begin within 12 or 13 hr after the addition of an inducer to continuously replicating cells; more than 95% of the cells are committed to form colonies composed of benzidine-positive cells by 44 hr (Rifkind; Columbia). During the interval between 12 and 44 hr, benzidine-positive colonies, sectored colonies containing both benzidine-positive and -negative cells and benzidine-negative colonies containing uninduced cells are formed in the semi-solid medium. These studies appear to define a discrete point at which MEL cells become committed to complete the later stages of erythroid maturation.

The membrane protein spectrin appears to behave differently during induction of MEL cell differentiation. This marker of the erythroid cell is found in low concentrations in uninduced cells, but its concentration increased 10–20 fold during terminal maturation. Rifkind (Columbia) described an assay in which the amount of fluorescent tagged anti-spectrin bound to individual MEL cells in suspension was quantitated by flow microfluorometry. Within a few hours after addition of the inducer to cultures of MEL cells, an increase in spectrin concentration was found in all cells. Removal of the inducer was followed by a gradual reduction in the membrane spectrin content. Thus this marker of erythroid maturation appeared to vary continuously during the induction process, in contrast to the discrete threshold for commitment defined for the later stages of erythroid maturation.

Other efforts to dissect the commitment process were detailed by Marks (Columbia). MEL cells were synchronized at the G1-S boundary. Upon addition of Me_2SO, HMBA or butyric acid, these cells progressed synchronously through S, G2 and M; the subsequent G1 phase was prolonged compared to that of control cells synchronized but incubated without inducers. The initial acceleration of transcription of the globin genes was detected during this prolonged G1 phase. The time required for appearance of the first committed MEL cells in unsynchronized cultures (Rifkind) coincided with the time at which acceleration of globin mRNA synthesis was observed in Marks's studies. Thus commitment observed in the cellular assay might reflect accelerated transcription of the globin genes. Hemin may induce MEL cells by different mechanisms, since no prolongation of G1 was observed with this agent and the initial increase in globin mRNA synthesis occurred within 3–6 hr.

Ingram (MIT) provided a provocative model that attempted to relate the possible effect of various inducers on metabolic events which could alter the proliferative potential of MEL cells and lead to highly selective accumulation of particular mRNA species. By acting on the cell or mitochondrial membranes, inducers might cause an increase in the amount of oxidized niacin-adenine-dinucleotide (NAD^+). NAD^+ is thought to stimulate ADP-ribosylation of various proteins including a particular DNAase. Inactivation of this endonuclease by the ribosylation reaction might be related to the ultimate decline in DNA synthesis and cessation of cell division which occurs during MEL cell maturation. Furthermore, an increase in NAD^+ concentration is thought to enhance heme synthesis. An increase in intracellular heme might lead to inhibition of several nuclear phosphokinases which act on nonhistone chromosomal proteins. Restriction of transcriptional activity to a subset of genes involved in erythroid maturation might be the result. It is noteworthy that the hemin-induced differentiation of MEL cells results in prompt acceleration of transcription of the globin genes (Marks; Columbia), while the inhibitory effects on DNA cell synthesis and the commitment to undergo maturation are delayed. One interesting feature of Ingram's model is that it attempts to relate the concentration of defined metabolic co-factors to known enzymatic processes in accounting for erythroid maturation of MEL cells without invoking undefined regulatory substances.

Anderson (NIH) has embarked upon a major effort to find such putative regulatory factors. Using uninduced MEL cells or HeLa cells as a cellular assay, he plans to inject, into either the nucleus or cytoplasm, extracts from MEL cells that have been induced. The cell assay may work, since he reported that injection of a recombinant plasmid containing the rabbit β-globin gene ($p\beta G1$) into HeLa cells leads to production of immunologically detectable rabbit β-globin.

Molecular Basis for Regulation of Hemoglobin Switching

Synthesis and accumulation of various globin mRNAs during erythroid maturation is reflected by the synthesis of specific hemoglobins. Globin mRNA synthesis appears to begin in earnest at the proerythroblast stage of maturation, although the important regulatory events which determine whether a particular gene is expressed may, as noted above, occur much earlier in erythroid stem cell differentiation. What can be learned by analysis of globin gene expression in erythroblasts are the

molecular details which result in preferential accumulation of particular globin mRNAs; the relationship between these molecular events and stem cell differentiation remains to be defined. Many details regarding the arrangement of globin gene sequences in cellular DNA are now available. The primary transcript products of the mouse globin genes and the steps by which these are processed into mature globin mRNA have been elucidated. Finally, analysis of chromatin structure has provided certain insights into globin gene regulation.

Gene Structure

Several investigators reported on their efforts to map the human globin genes using various restriction endonucleases to digest genomic DNA; DNA fragments containing globin gene sequences were demonstrated by various modifications of the "blotting" technique. Most of the available information concerns the δ- and β-globin genes. Taking advantage of the relative simplicity of the Lepore gene, a crossover gene containing the N terminal coding region for δ-globin and the C terminal coding region for β-globin, Bank and coworkers (Columbia) have compared the DNA fragments containing β-globin sequences in this DNA to those found normally. Their results indicate that the δ and β genes are separated by at least 7 kb of DNA. Each gene contains an intragenic insert of approximately 700 bases present between the Bam H1 site, corresponding to amino acid 100 in the globin chain, and the Eco RI site, corresponding to position 121-122 of the globin. A second smaller intervening sequence may be present in the δ gene near the N terminal region. Williamson (London) reported that all of the δ and β gene sequences are included in a single 12.3 kb Xba I fragment, verifying the intergenic distance of 7 kb. With regard to the α-globin genes, Orkin (Boston) reported that all α gene sequences are found in a single 22 kb Eco RI fragment. Two α-globin structural genes are found in this fragment. Their centers, defined by a Hind III site corresponding to position 90-91 of α-globin, are approximately 3.7 kb apart.

Williamson (London) reported informally that a large fragment generated by digestion of genomic DNA with Bgl I contains all of the γ-globin gene sequences. At least two γ-globin genes are present in the human genome. The existence of the γ-β fusion gene represented in Hb Kenya indicates that at least one of these is to the left of the δ and β genes; the new data provided by restriction endonuclease analysis suggest that both genes are in this position. Forget (Yale) reported that γ gene-specific and β gene-specific probes anneal to 4.5 kb Eco RI fragments. In light of Williamson's results, it seems improbable that both γ and β sequences are found in a single fragment. Rather, Eco RI must give fragments of similar size containing either β or γ sequences.

The existence of two γ loci in humans is established by the presence of globins with either glycine or alanine at position 136 in all individuals (Schroeder; Cal Tech). γ-globin with threonine rather than isoleucine at position 75 has been found with a frequency of 10-30%, although the exact frequency may vary in different ethnic groups, geographical localities or hematological conditions. Evidence was presented (Schroeder; Cal Tech) indicating that the threonine replacement probably occurs in globins having alanine at position 136. Thus the globin containing threonine is apparently not due to the existence of a third γ locus in the genome, but rather to a polymorphism at the $^{A}\gamma$ locus.

The entire sequence of the human α- and β-globin mRNA and large portions of the γ-globin mRNA have been determined (Forget; Yale and Kan; San Francisco). Comparison of the sequences of the human β- and γ-globin mRNA indicate that significant evolutionary drift has occurred. A silent substitution rate of approximately 38% is thought to be very close to neutral evolution, and stands out in contrast to the 20% rate observed between rabbit and human β-globin mRNA. A common hexanucleotide sequence, CUUCUG, is found near the 5′ end of α, β and γ mRNA (Kan; San Francisco), and may be complementary to a sequence near the 3′ terminus of eucaryotic 18S ribosomal mRNA. Features common to the 3′ untranslated region include a hexanucleotide sequence (AAUAAA) and palindromic sequences of variable lengths. Capping of mouse and human globin mRNA appears to occur by mechanisms common to other eucaryotic mRNAs (Kazazian; Johns Hopkins).

An important development which will undoubtedly lead to the definition of the fine structure of the human γ-, δ-, and β-globin genes and their surrounding regions was reported by Tom Maniatis and his co-workers (Cal Tech); they have cloned fragments containing each of these genes into bacteriophage lambda. Randomly sheared 20 kb fragments of genomic DNA were produced by partial digestion with Hae III and Alu I (Lacy; Cal Tech). Protection of Eco RI sites by methylation and linkage of synthetic Eco RI sites to these fragments allowed their insertion into the phage Charon 4A. Using the "packaging" technique which provides highly efficient infection of the appropriate host, the entire human globin genome was cloned. Several plaques containing the human δ and β sequences were identified. Preliminary restriction endonuclease mapping of the fragments containing δ and β sequences (Lawn; Cal Tech) agreed with the more detailed studies reported by

others using uncloned genomic DNA. The enormous advantage provided by these recombinants in analysis of the regions surrounding the human globin genes and in identifying potentially important regulatory sequences will undoubtedly be realized in the near future.

The most detailed knowledge regarding particular globin genes is the information provided by the elegant data of Leder and his co-workers (NIH), obtained by separately cloning DNA fragments containing the β^{maj} and β^{min} genes of mice. The globins encoded by these genes differ in only six amino acid positions. Electron microscopic examination of the duplexes formed between recombinants containing either the β^{maj} or β^{min} genes permitted definition of the regions of homology in the flanking and intervening sequences. The intervening sequences in these two genes have diverged considerably. Only small portions of the intervening sequences adjacent to the coding portions of the gene have been conserved. Small segments of the regions immediately flanking the coding portions of the genes are also homologous. It can be speculated that the lack of homology in the flanking and intervening sequences protects these genes from recombinational events that might lead to gene amplification or deletion. The important regulatory signals in DNA sequence which result in coordinated expression of these genes most probably exist in the small regions of homology defined by these studies.

RNA Metabolism

Detailed knowledge of the sequence of the globin genes and their arrangement in genomic DNA has not yet led to predictions on the mechanism of regulation of these genes at the molecular level. Analysis of RNA metabolism may provide some clues. The mouse α- and β-globin genes are transcribed into precursor molecules containing 870 and 1860 nucleotides, respectively, both of which are considerably larger than cytoplasmic globin mRNAs, which contain 700–750 nucleotides (Ross; Wisconsin). Two intervening sequences are present within the coding portion of the mouse β-globin genes (Leder; NIH). Processing of the β-globin mRNA precursor apparently occurs first by excision of the nucleotides corresponding to the larger intervening sequence, yielding an intermediate from which the nucleotides corresponding to the smaller intervening sequence are excised (Ross; Wisconsin and Lingrel; Cincinnati). The half-life of the larger β precursor is only 1.5–2 min, while the half-life of the smaller precursor is approximately 17 min. It appears that the α-globin precursor RNA is cleaved post-transcriptionally in a single step to generate α-globin mRNA (Ross). The 27S RNA molecule rendered radioactive during a short pulse of MEL cells with ^{3}H-uridine apparently does not contain globin mRNA sequences. Hence it might be a precursor or mRNA for a protein synthesized in reticulocytes (Lingrel; Cincinnati). The 1860 nucleotide β-globin mRNA precursor is thought to represent the primary product of transcription of the β-globin genes.

The several metabolic events necessary to progress from β-globin mRNA precursor to mature β-globin mRNA might potentially serve as a focus for regulation. Lingrel and co-workers (Cincinnati) determined whether a change in processing efficiency occurs during erythroid cell maturation. MEL cells at various stages in the induction process were incubated in ^{3}H-uridine for 10 min, and the ratio of radioactivity in the precursor to that found in globin mRNA was compared. The ratio remained constant, indicating that there was no change in the rate of processing of the large precursor to mature β-globin mRNA during induction. A potentially important difference in mRNA stability in uninduced and induced cells was found, however. The half-life of globin mRNA in uninduced MEL cells and during the early phases of induction was 50 hr, while the half-life of globin mRNA in fully induced cells agreed with the previous estimate of 17 hr. Other mRNA species did not exhibit a change in stability, and thus a unique characteristic of globin mRNA or of a factor which binds to it must underlie this remarkable change in stability. Stabilization of globin mRNA during early stages of maturation might account for the large and rapid accumulation of globin mRNA in erythroid cells.

The mechanism for differential accumulation of γ- rather than β-globin mRNA was studied in sheep fetal erythroid cells (Benz; NIH). Incubation of sheep fetal liver cells in ^{3}H-uridine for 8 min resulted in selective incorporation of isotope into γ-globin mRNA sequences as opposed to those for the adult β-globin genes. Selective accumulation of γ mRNA in these cells would thus appear to be mediated at a transcriptional level.

Chromatin Structure

Nuclear DNA is very generally divided into two fractions of chromatin: euchromatin, which is actively transcribed, and condensed heterochromatin, which is inactive in supporting transcription. Actively transcribed DNA sequences in differentiated cells are found in a conformation in chromatin which renders them sensitive to pancreatic DNAase I (Weintraub; Princeton). Specifically, the chick globin genes in nuclei from chick erythrocytes are DNAase I-sensitive, while these genes are not sensitive in fibroblasts or brain nuclei. Weintraub reported that a particular fraction of nonhistone proteins eluted from chromatin by 0.35 M

NaCl was required for this DNAase I sensitivity. This 0.35 M salt wash contained the high mobility group (HMG) of nonhistone proteins. Addition of these proteins from chick brain chromatin to erythrocyte chromatin that had been exposed to 0.35 M NaCl restored the DNAase I sensitivity of the globin genes. These studies appear to identify proteins which, while necessary to maintain the active or DNAase I-sensitive conformation of genes in chromatin, are not specific for particular genes. Presumably there are other proteins which are gene-specific.

Young (NIH) has examined the DNAase I sensitivity of the individual γ and β genes in sheep erythroid cells. In nuclei from fetal liver, the γ genes but not the β genes are DNAase I-sensitive, a fact consistent with active transcription of the γ genes only. In adult bone marrow nuclei, however, the γ and β genes are DNAase I-sensitive despite the absence of γ mRNA sequences in these cells. These results seem to imply that once the γ gene is included among the active fraction of chromatin during erythropoiesis in the fetus, it remains in that active fraction in adult erythroid cells. Furthermore, selective accumulation of the β rather than γ mRNA sequences in adult red cells must be due to regulation at the transcriptional or a post-transcriptional stage of mRNA metabolism.

Both Deisseroth (NIH) and Anderson (NIH) reported results that may be pertinent with regard to factors that influence the structure of globin genes in chromatin. Expression of the human globin genes in somatic cell hybrids formed between MEL cells and various cell lines was described. Deisseroth reviewed his studies, which utilized somatic cell hybrids to obtain the chromosomal assignment of the human globin genes; the α genes are on chromosome 16 and the γ-δ-β complex is on chromosome 11. He has developed a MEL cell line deficient in adenosyl ribosyl phosphotransferase. A medium which requires that cells have this enzyme to survive can be used to select for those hybrid cells, formed between human bone marrow and this deficient MEL cell line, which retain human chromosome 16. The human APRT locus is on this chromosome. A MEL cell x human bone marrow cell hybrid produced in this fashion was shown to accumulate α-globin mRNA upon induction in Me_2SO. Anderson's studies utilized selection of a different sort; isolates obtained by fusing human fibroblasts with 2S MEL cells were examined for their content of LDH-A, an enzyme known to be encoded by a gene on chromosome 11. Six isolates were identiifed in which the human enzyme was present in relatively high concentrations. Each of these, when grown in inducer, was found to contain human β-globin mRNA sequences along with mouse globin mRNA; the relative amounts of human mRNA correlated very well with the activity of the LDH-A human isozyme in these cell lines.

The somatic cell hybrid experiments are most consistent with the existence of regulatory factors that interact with human globin genes in the hybrid cell. If such putative regulatory factors are indeed DNA sequence-specific, it is interesting to note that mouse factors can activate human globin genes. These results would predict that regions of homology must exist in the flanking or intervening sequences of the human and mouse globin genes.

SECOND CONFERENCE ON HEMOGLOBIN SWITCHING
AIRLIE HOUSE, AIRLIE, VIRGINIA
PROGRAM

PART I. ONTOGENY

Sunday, June 22nd, 1980

4.00-6.30 pm	Poster Session A. HEMOGLOBINS IN EARLY DEVELOPMENT
	Poster Session B. FETAL HEMOGLOBINS
	Poster Session C. SWITCHING OF OTHER RED CELL CHARACTERS
6.30 pm	Dinner
7.30-10.30	HEMOGLOBIN ONTOGENY Session Chairman: G. Stamatoyannopoulos
7.30-8.30	V. Ingram (Cambridge, MA) Introductory Lecture: Hemoglobin switching
8.30-9.00	S.H. Boyer (Baltimore, MD) In vivo hemoglobin switching in man and primates: Major observations and interpretations
9.00-9.30	Discussants: W. Wood (Oxford, England) Hemoglobin: Switching in vivo
	E. Zanjani (Minneapolis, MN) Hemoglobin switching in sheep
9.30-10.30	Poster and general discussion Discussion Leader: V. Ingram

PART II. GLOBIN GENE ORGANIZATION AND EXPRESSION

Monday, June 23rd, 1980

8.30-11.30 am	A. ORGANIZATION AND STRUCTURE OF THE GLOBIN GENES Session Chairman: Oliver Smithies
8.30-9.30	T. Maniatis (Pasadena, CA) The human globin genes
9.30-9.50	M.H. Edgell (Chapel Hill, NC) General organization of the mouse non-α globin genes and a description of the β-like "WAW-A" gene
9.50-10.10	Y. Nishioka (Bethesda, MD) Mouse α globin genes: Their structure and evolution
10.10-10.30	Coffee break

10.30-10.50 J. Lingrel (Cincinnati, OH)
Hemoglobin switching in goats: Structural organization of the globin genes, pseudogenes, and clues concerning regulatory mechanisms

10.50-11.10 P. Kretschmer (Bethesda, MD)
Comparison of the structure of the sheep γ and β^A globin genes

11.10-11.30 R. Hardison (University Park, PA)
Structure and linkage arrangement of the rabbit embryonic and adult β-like globin genes

12.00 LUNCH

1.00-3.30 Poster Session D. GENE STRUCTURE

Poster Session E. mRNA METABOLISM – PROTEIN SYNTHESIS

Poster Session F. THALASSEMIA

3.30-5.30 B. PANEL DISCUSSION: STRUCTURE AND FUNCTION OF THE GLOBIN GENOMIC REGIONS
Discussant Leader: T. Maniatis

Participants:
B. Forget
R. Flavell
C. Hutchison
J. Lingrel
O. Smithies

Gene Structure – Recombinational Events
(Introduced by O. Smithies)

Nature and Role of Repetitive DNA Sequences
(Introduced by B. Forget)

Pseudogenes
(Introduced by C. Hutchison and O. Smithies)

Regulatory Sequences
(Introduced by J. Lingrel)

6.00 DINNER

7.30-10.30 C. RNA METABOLISM
Session Chairman: R. Williamson

7.30-8.30 J. Ross (Madison, WI)
RNA Processing: General mechanisms and regulation

8.30-8.45 J. Kantor (Bethesda, MD)
Globin mRNA precursor and mature mRNA during haemoglobin switching

8.45-9.00	P. Curtis (Philadelphia, PA) Transcription of the β^{maj} and β^{min} genes in mouse erythroleukemia cells
9.00-9.15	A. Tobin (Los Angeles, CA) Analysis of the transcriptional and post transcriptional contributions to differential globin gene expression during chicken development
9.15-10.30	Poster and General Discussion Discussion Leader: R. Williamson

Tuesday, June 24th, 1980

8.30-10.00 am	D. IN VITRO TRANSCRIPTION Session Chairman: B. Forget
8.30-9.10	D. Luse (St. Louis, MO) Polymerase II dependent gene transcription: Role of transcriptional factors
9.10-9.30	C.A. Talkington (Bethesda, MD) Selective transcription of mouse globin genes in vitro: Characterization of the region recognized by RNA polymerase II
9.30-9.50	R. Flavell (London, England) Expression of globin genes in vitro
9.50-10.15	N. Proudfoot (Pasadena, CA) In vitro transcription of human globin genes
10.15-10.30	General Discussion
10.30-10.45	Coffee Break
10.45-12.00	E. CHROMATIN ORGANIZATION Session Chairman: R. Flavell
10.45-11.45	H. Weintraub (Seattle, WA) Hemoglobin switching and globin chromatin structure
11.45-12.00	General Discussion
12.00	LUNCH
1.00-3.30	Poster Session G. HEMOPOIETIC CELLS
	Poster Session H. REGULATORS AND THEIR ACTIONS
	Poster Session I. INTERACTIONS
6.00	DINNER
7.30-9.15	F. PANEL: GLOBIN GENE PATHOLOGY Discussion Leader: A. Bank

7.30-8.15 Deletion mutations and HbF production
(Introduced by A. Bank)

Discussants: R. Flavell
S. Ottolenghi

R. Mulivor
NIGMS human genetic mutant cell repository

8.15-8.45 Evidence that β^+ thalassemia is an RNA processing disease
(Introduced by J. Ross)

Discussants: E. Benz
J. Kantor

8.45-9.00 Structure – function analysis of a cloned α-thalassemia gene
(Introduced by S. Orkin)

9.00 Coffee break

9.15-10.30 pm G. GENE TRANSFER AND IN VIVO EXPRESSION
Session Chairman: W.F. Anderson

9.15-10.00 W.F. Anderson (Bethesda, MD)
Gene transfer and in vivo expression

Discussants: P. Henthorn
T. Maniatis

10.00-10.30 W. Salser (Los Angeles, CA)
Gene transfer into hematopoietic stem cells in vivo

PART III. REGULATION OF HEMOPOIETIC CELLS

Wednesday, June 25th, 1980

8.30-11.45 am A. PROLIFERATION AND EARLY COMMITMENT EVENTS
Session Chairman: P. Marks

8.30-9.15 J.M. Dexter (Manchester, England)
Differentiating cell lines and factors controlling proliferation

9.15-10.00 C. Eaves (Vancouver, Canada)
Self renewal of hemopoietic stem cells: Evidence for stochastic regulatory processes

10.00-10.15 Coffee break

10.15-11.00 G.R. Johnson (Melbourne, Australia)
Mixed colony progenitors and the factors controlling them

11.00-11.45 A. Axelrad (Toronto, Canada)
Gene control of progenitor cell proliferation during erythropoietic differentiation

12.00 LUNCH

1.00-3.00 B. PANEL: REGULATORS AND THEIR ACTIONS

Participants: J. Adamson
A. Axelrad
C. Eaves
D. Golde
E. Goldwasser
G. Johnson
R. Rifkind
G. Wagemaker
E. Zanjani

Discussion Leader: P. Marks

1. Erythropoietin
   (Introduced by C. Eaves)

2. Burst promoting activity
   (Introduced by G. Wagemaker)

3. Hormones and erythropoiesis
   (Introduced by J. Adamson)

4. Regulators and ontogeny
   (Introduced by A. Axelrad)

3.00-3.15 pm Coffee break

3.15-6.30 C. T-CELLS AND CELL INTERACTIONS
Session Chairman: A. Axelrad

3.15-3.20 A. Axelrad – Introduction

3.20-4.20 S. Schlossman (Boston, MA
The human T-cell circuit: Biological and clinical implications

4.20-5.00 E.W. Felfand (Toronto, Canada)
A genetic approach to the analysis of early events in T-cell differentiation

5.00-5.40 D. Nathan (Boston, MA)
T-cells in erythropoiesis

5.40-6.30 Poster and General Discussion

6.30 DINNER

7.30-10.30 Poster Session J. HEMOGLOBIN SWITCHING IN CULTURE

Poster Session K. EXPRESSIONS OF OTHER RED CELL CHARACTERS IN CULTURE

Poster Session L. STUDIES OF K562 CELLS

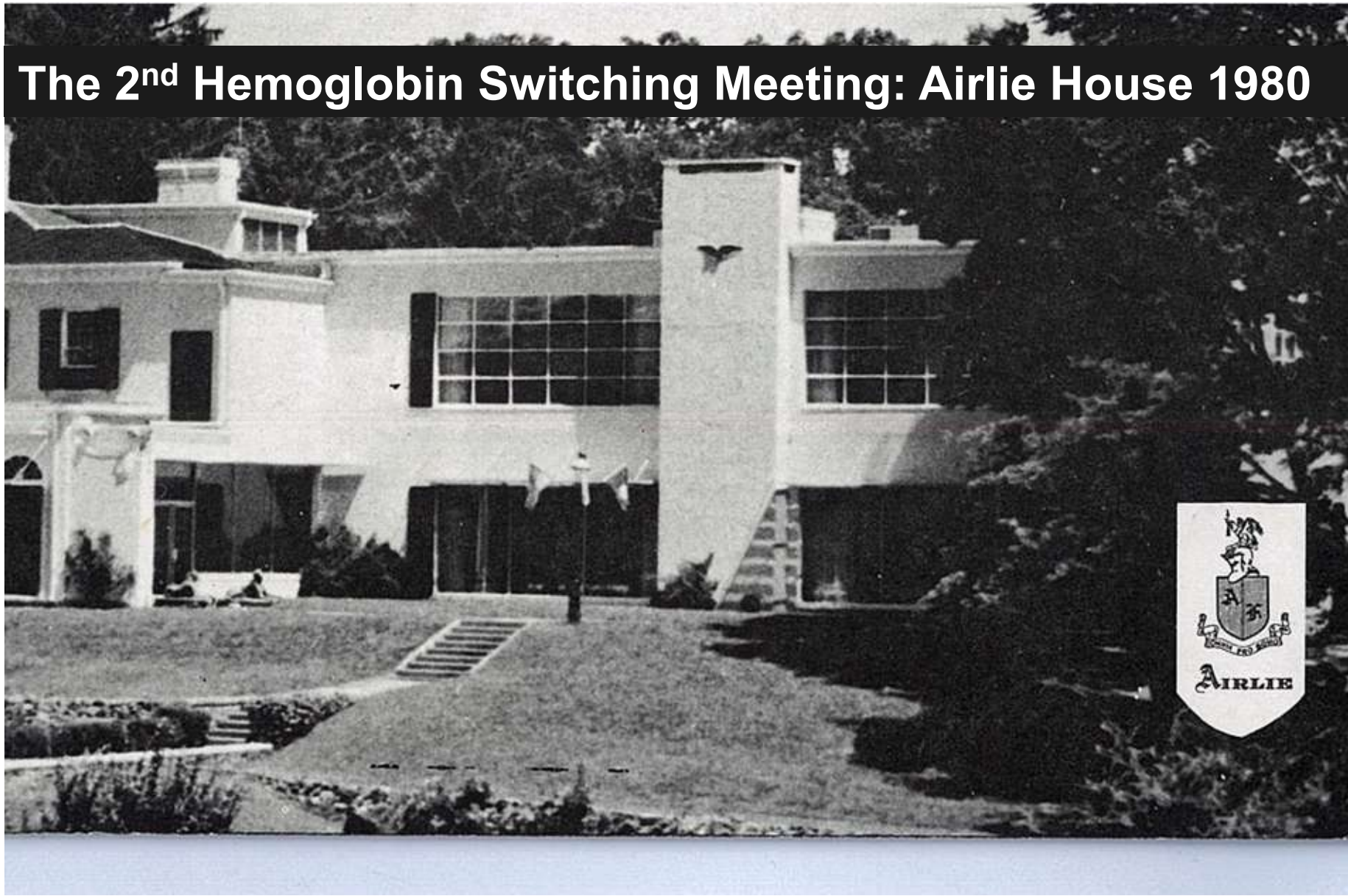
Poster Session M. COMMITMENT AND MEL CELLS

PART IV. CELLULAR REGULATION OF Hb SWITCHING

Thursday, June 26th, 1980

8.30-11.45 am	A. HEMOGLOBIN SWITCHING IN VITRO Session Chairman: W. Wood
8.30-9.30	G. Stamatoyannopoulos (Seattle, WA) Hemoglobin switching in human erythroid cell cultures
9.30-9.45	D. Chui (Hamilton, Ontario, Canada) Adult haemoglobin is synthesized in BFU-E derived erythroid colonies during early fetal mouse development
9.45-10.00	B. Alter (New York, NY) Three classes of erythroid progenitors that regulate haemoglobin synthesis during ontogeny in the primate
10.00-10.15	Coffee break
10.15-11.45	Poster and general discussion Discussion leader: G. Stamatoyannopoulos
12.00	LUNCH
1.00-3.00	B. COMMITMENT Session Chairman: A.W. Nienhuis
1.00-2.00	D. Housman (Cambridge, MA) How do the cells decide to express their programs?
2.00-2.45	R. Rifkind (New York, NY) Commitment and cell cycle events
3.00	END OF THE PROGRAM

The 2nd Hemoglobin Switching Meeting: Airlie House 1980



PROGRAM FOR

THIRD CONFERENCE ON HEMOGLOBIN SWITCHING

September 12-15, 1982

ROSARIO, ORCAS ISLAND, WASHINGTON

Sunday, September 12

5.00 pm RECEPTION AND REGISTRATION – DISCOVERY HOUSE

6.30 pm DINNER – DISCOVERY HOUSE

Monday, September 13

7.15 – 8.15 am BREAKFAST – DISCOVERY HOUSE

PERSPECTIVE ON GENE REGULATION
Chairman: Vernon Ingram

8.30 am Philip Leder – "Globin and Immunoglobulin Genes: The Odd Couple"

SESSION 1: CHROMATIN STRUCTURE AND GENE EXPRESSION
Chairmen: Vernon Ingram and Richard Flavell

9.30 am Harold Weintraub – "Features of Chromatin which Facilitate Gene Expression"

10.15 am COFFEE BREAK

10.30 am James McGhee – "Higher Order Chromatin Structure of Chicken Globin Genes"

11.15 am Richard Rifkind – "Relationship of Chromatin Structure and Transcriptional Activation in MEL Cells"

11.45 am Mark Groudine – "Structural Features of Chromatin in Various Developmental Stages"

12.15 pm General Discussion

12.30 pm LUNCH – ORCAS ROOM – MANSION

SESSION II: ERYTHROPOIESIS AND SWITCHING: DESCRIPTIVE APPROACHES

Chairmen: Paul Marks and David Golde

3.00 pm Gregory Johnson – "Progenitors, Factors and Switching"

3.30 pm Discussion

3.40 pm Connie Eaves – "Long-term Cultures"

4.10 pm Discussion

4.20 pm Beverly Storb – "Interactions: The Ia System"

4.35 pm Discussion

4.45 pm George Stamatoyannopoulos – "Hb Switching in Culture"

5.15 pm Discussants: David Nathan
Cesare Peschle
Yoji Ikawa
Blanche Alter

6.30 – 7.30 pm DINNER – ORCAS ROOM – MANSION

7.30 – 10.00 pm POSTER SESSION 1 – DISCOVERY HOUSE

POSTER PAPERS

1. B.P. Alter, R.S. Weinberg, J.D. Goldberg, D.G. Nathan and J.M. Lipton
2. N. Anagnou, A. Deisseroth and A.W. Nienhuis
3. E.C. McFarland and J.E. Barker
4. E.H. Birkenmeier, P.C. Hoppe and J.E. Barker
5. E. Benz
6. T. Boussios and J.F. Bertles
7. M. Brice, Th. Papayannopoulou and G. Stamatoyannopoulos
8. A.R. Dorn and R.H. Broyles
9. D.J. Smith, P.B. Maples, A.R. Dorn, W.J. Saucier and R.H. Broyles
10. W.G. Wood and C. Bunch
11. J. Burch, C. Kane, P.F. Cheng and H. Weintraub
12. J. Burch and H. Weintraub
13. A. Cao, R. Galanello, M.A. Melis, S. Ottolenghi and L.F. Bernini
14. C. Casimir, M. Groudine and H. Weintraub
15. S.W. Chung and D.H.K. Chui
16. M. Cohen-Solal and B. Forget

17. A. Dean and A. Schechter
18. M. Farace and M.H. Edgell
19. G. Ginder
20. R. Hardison
21. D.R. Higgs, P. Winichagoon, S.E.Y Goodbourn, J.B. Clegg and D.J. Weatherall
22. M.A. Horton, S.J. Cedar, D. Maryanka and C. Turberville
23. Y. Ikawa, G. Soma, T. Matsugi and N. Imai
24. R. Kaufman
25. K. Kidoguchi
26. G. Krystal
27. Th. Papayannopoulou, S. Kurachi, B. Nakamoto, E. Zanjani and G. Stamatoyannopoulos
28. C. Lau and Y.W. Kan

Tuesday, September 14

7.15 – 8.15 am BREAKFAST – DISCOVERY HOUSE

SESSION III: STRUCTURE – FUNCTION CORRELATES AND EXPRESSION SYSTEMS
Chairmen: Y.W. Kan and Samuel Boyer

8.30 am Thomas Maniatis – "Expression of Globin Genes in Cells in Culture"

9.15 am Richard Flavell – "Expression of Human Globin Genes in Transformed MEL Cells and Fibroblasts"

10.15 am COFFEE BREAK

10.30 am Elizabeth Lacy – "Expression of Globin Genes in Transgenic Mice"

10.50 am Richard Palmiter – "Function of Metallothionein Promoter in Transgenic Mice"

11.10 am General Discussion

Discussants : R. Keith Humphries
J.G. Williams

11.45 am French Anderson – "Human Globin Gene Expression in MEL/Human Hybrids"

12.15 pm Discussion

Discussants : Arthur Skoultchi
Albert Deisseroth

12.30 pm LUNCH – ORCAS ROOM – MANSION

SESSION IV: GLOBIN GENE ORGANIZATION AND EXPRESSION

Chairmen: Arthur Bank and Thomas Maniatis

3.00 pm Jerry Lingrel – "Globin Gene Organization and Switching in Goats"

3.30 pm Discussion

3.40 pm Bernard Forget – "Mutants that Increase HbF Production: Molecular Studies"

4.10 pm Discussion

4.20 pm Paula Henthorn – "Insights from Sequencing of HPFH and δβ Thalassemia Mutants"

4.40 pm Discussion

4.50 pm P. Dierks – "DNA Sequences Important for Globin Gene Function"

5.20 pm General Discussion – "Structure-Expression Relationships in Thalassemia Mutants"

Discussants: Stuart Orkin
Haig Kazazian

6.30 – 7.30 pm DINNER – ORCAS ROOM – MANSION

7.30 – 10.00 pm POSTER SESSION II – DISCOVERY HOUSE

POSTER PAPERS

1. P. Charnay and T. Maniatis
2. P. Henthorn, E.F. Vanin, F. Grosveld and O. Smithes
3. J. Lipton and D. Nathan
4. P. Mellon, M. Chao, P. Charnay, R. Axel and T. Maniatis
5. B. Miller and D. Nathan
6. J. Murray, R. Gelinas, M. Farquhar and M. Yagi
7. C. Peschle
8. M. Pirastu and Y.W. Kan
9. J. Powell and J. Adamson
10. P.A. Powers and O. Smithies
11. P.A. Powers and E. Vanin
12. R.P. Revoltella

13. G.B. Rossi, L. Cioe, E. Affabris, G. Romeo, C. Jemma and P. Meo
14. P.T. Rowley, B.M. Ohisson-Wilhelm, L. Wisniewski, C.B. Lozzio and B.B. Lozzio
15. J. Rosa, W. Vainchecker and U. Testa
16. J. Rosa, Ph. Fessas and D. Loukopoulos
17. G. Saglio, C. Camaschella, M. Aglietta, W. Piacibello, R. Cambrin and A. Capadli
18. M. Poncz, S. Surray and E. Schwartz
19. J. Hess, M. Fox, C. Schmid and C-K.J. Shen
20. F. Sieber
21. R.A. Spritz and K.M. Lang
22. A.J. Sytkowski, S.P. Perrine, K.A. Bicknell and C.J. Kessler
23. A. Torrealba de Ron and Th. Papayannopoulou
24. T. Townes and J. Lingrel
25. J.G. Williams, R.K. Patient, M. Bendig and D. Baniville
26. M. Yagi and R. Gelinas

Wednesday, September 15

7.15 – 8.15 am BREAKFAST – DISCOVERY HOUSE

PERSPECTIVES ON GENE REGULATION
Chairman: Philip Leder

8.30 am Howard Holtzer – "DNA Synthesis, Cell Replication and the Generation of Cell Diversity"

SESSION V: NEW APPROACHES IN THE ANALYSIS OF HEMATOPOIESIS
Chairmen: Philip Leder and E.A. McCulloch

9.15 am E.A. McCulloch – "Markers of Hematopoietic Differentiation"

10.00 am Discussion

10.15 am COFFEE BREAK

10.30 am David Hankins – "Analysis of Fetal and Adult Erythropoiesis Using RNA Tumor Viruses"

11.15 am Hartmut Beug – "Use of Temperature-Sensitive Viral Mutants to Study Hematopoiesis"

12.00 noon General Discussion

12.30 pm LUNCH – ORCASE ROOM – MANSION

SESSION VI: ERYTHROLEUKEMIA LINES
Chairman: Arthur Nienhuis

3.00 pm General Discussion: Lines; Characteristics; Studies of Commitment

Discussants: Thalia Papayanopoulou
Neal Young
Michael Horton

SESSION VII: MANIPULATION OF Hb SWITCHING *IN VIVO*
Chairman: David Nathan

4.00 pm William Wood – "Hemoglobin Switching in Fetal Cells Transplanted in Adult Sheep"

4.15 pm General Discussion

Discussants: George Dover
Joseph DeSimone

6.30 pm DINNER – SALMON BARBECUE – MANSION LAWN
(or Discovery House in case of rain)

Thursday. September 16

6.45 – 8.30 am BREAKFAST – MORAN ROOM – MANSION


3rd Conference
Took Place on
Orcas Island

FOURTH CONFERENCE ON HEMOGLOBIN SWITCHING

Co-Chairmen: G. Stamatoyannopoulos and A. Nienhuis

Dates: September 30 – October 3, 1984

Location: Airlie House, Airlie, Virginia

Sunday, September 30

6.00 pm Reception – No Host Cocktails
7.00 pm Outdoor Barbecue

Monday, October 1

8.30 am SESSION I: Molecular Analysis of Hematopoietic Factors
Chairman: Arthur Axelrad, University of Toronto

Speakers: Donald Metcalf, Walter and Eliza Hall Institute, Australia: "Cellular and Molecular Analysis of Hematopoietic Factors"

Richard Stanley, Albert Einstein College of Medicine, New York: "Hemopoietins I and II and CSF-I: Nature and Mechanism of Action"

G. Wong, Genetics Institute, Boston: "Molecular Cloning of a Human GM-CSF cDNA"

Judith Gasson, University of California, Los Angeles: "Biochemistry and Molecular Cloning of Burst Promoting Activity"

10.45 am Coffee Break

11.00 am SESSION II: Biochemistry and Molecular Biology of Erythropoietin
Chairman: Eugene Goldwasser, University of Chicago

Speakers: Sylvia Lee-Huang, New York University: "Biochemical and Molecular Characterization of Erythropoietin"

Ryuzo Sasaki, Kyoto University: "Erythropoietin: Isolation with Monoclonal Antibody and Characterization"

Fukuen Lin and Joan Egrie, Amgen Corporation, Thousand Oaks, California: "Cloning and Expression of Human and Monkey Erythropoietin"

1.00 pm Lunch

3.00 – 6.00 pm Poster Session I

6.00 pm Dinner

7.30 pm Overview: David J. Weatherall, University of Oxford: "The Developmental Genetics of Human Hemoglobin"

8.15 pm SESSION III: Chromatin Structure and Transcriptional Regulatory Factors
Chairman: French Anderson, National Institutes of Health, Bethesda

Speakers: Gary Felsenfeld, National Institutes of Health, Bethesda "Molecular Analysis of Globin Chromatin"

Harold Weintraub, Fred Hutchinson Cancer Research Center, Seattle: "Anti-sense RNA: A potential Tool for Genetics"

Paul Marks, Memorial Sloan-Kettering Cancer Center, New York: "Modulation of Gene Expression During Terminal Cell Differentiation"

Tuesday, October 2

8.30 am SESSION IV: Molecular Analysis of Gene Expression
Chairman: Jeff Ross, University of Wisconsin, Madison

Speakers: George Khoury, National Institutes of Health, Bethesda: "Enhancer Sequences"

Tom Maniatis, Harvard University: "Expression of Human Alpha and Beta Globin Genes in Mouse Erythroleukemia Cells"

10.30 am Coffee Break

10.45 am Frank Grosveld, MillHill Medical Research Institute, London: "Sequences that Control Induction of Globin Genes in Mouse Erythroleukemia Cells"

John Paul, Beatson Institute, Glasgow: "DNA Sequences that Modulate Globin Gene Promoter Function"

Arthur Bank, Columbia University, New York: "Expression of Epsilon and Beta Globin Genes in K562 Cells"

Discussant: Alan Schechter, National Institutes of Health, Bethesda

Nicholas Proudfoot, University of Oxford: "Termination of Polyadenylation of Globin Genes"

1.00 pm Lunch

3.00 – 6.00 pm Poster Session II

6.00 pm Dinner

7.30 pm SESSION V: Gene Transfer and Integration
Chairman: Tom Maniatis, Harvard University

Speakers: Oliver Smithies, University of Wisconsin, Madison: "Site Directed Gene Insertion"

Thalia Papayannopoulou, University of Washington, Seattle: "Analysis of Globin Expressing Heterospecific Somatic Cell Hybrids"

Jerry Lingrel, University of Cincinnati:
"Globin Gene Expression in Transgenic Mice"

K. Chada, Columbia University:
"Developmental Regulation of Human Globin Genes in Transgenic Mice:

Stuart Orkin, Harvard Medical School:
"Gene Transfer"

Discussant: Albert Deisseroth, University of California, San Francisco

Wednesday, October 3

8.30 am SESSION VI: Molecular Analysis of Mutants
Chairman: Oliver Smithies, University of Wisconsin, Madison

Speakers: Bernard Forget, Yale University:
"Characterization of Mutants that Increase HbF Production"

Richard Gelinas, Fred Hutchinson Cancer Research Center, Seattle: "Sequencing of the $^{A}\gamma$ HPFH Gene"

Sergio Ottolenghi, University of Milan:
"Analysis of HPFH and Delta-Beta Thalassemia Mutations"

Discussants: Dixie Mager, University of Wisconsin

Nick Anagnou, National Institutes of Health

Ronald Nagel, Albert Einstein College of Medicine

John Gilman, Medical College of Georgia

10.45 am Coffee Break

11.00 am — SESSION VII: Experimental Manipulation of Fetal Hemoglobin Synthesis

Chairman: George Stamatoyannopoulos, University of Washington, Seattle

Speakers:

David Nathan, Harvard Medical School:
"Influence of Inhibitors of Mitosis on Hemoglobin F Production"

George Dover, Johns Hopkins University, Baltimore: "In Vivo and In Vitro Responses to 5'Azacytidine and Hydroxyurea: Clues to Mechanisms"

Joseph DeSimone, University of Illinois, Chicago:
"Experimental Studies in Baboons"

William Wood, University of Oxford:
"The Sheep Transplantation Model, an Update"

Discussants:

Blanche Alter, Mt. Sinai Medical School, New York

Cesare Peschle, Instituto Superiore de Sanita, Rome, Italy

1.00 pm — Lunch

2.30 pm — Departures of Buses for National and Dulles Airports

FIFTH CONFERENCE ON HEMOGLOBIN SWITCHING

Co-Chairmen: G. Stamatoyannopoulos & A.W. Nienhuis
Dates: September 28 – October 1, 1986
Location: Airlie House, Airlie, Virginia

Sunday, September 28

2.00 – 8.00 pm Registration
6.00 pm Reception – No Host Cocktails
7.00 pm Outdoor Barbecue

Monday, September 29

7.00 – 8.15 am Breakfast

8.30 am Session I: Cell Biology of Hematopoiesis
Chairman: David Nathan, Harvard Medical School, Boston

Speakers: Steve Clark, Genetics Institute, Cambridge, Mass.
"Molecular cloning of human IL-3"

Peter Wong, National Institutes of Health, Bethesda
"Infection of hemopoietic cells with vectors producing IL-3"

John Adamson, University of Washington, Seattle
"The biology of human GM-CSF"

Colin Sieff, Harvard Medical School, Boston
"Role of monocytes in hematopoiesis"

Robert Donahue, Genetics Institute, Cambridge, Mass.
"*In vivo* effects of GM-CSF"

10.30 am Coffee Break

10.45 am Eugene Goldwasser, University of Chicago
"Studies of the regulation of erythropoietin gene expression"

Samuel Boyer, Johns Hopkins University, Baltimore
"Biology of purified murine CFUe"

11.30 am Session II: Somatic Gene Therapy
Chairman: Jeff Ross, University of Wisconsin, Madison

Speaker: Dusty Miller, Fred Hutchinson Cancer Research Center, Seattle
"Gene transfer using retroviruses"

Discussant: Philip Kantoff, National Institutes of Health, Bethesda

Speakers: Stuart Orkin, Harvard Medical School, Boston
"Gene transfer and expression in hemopoietic cells"

Stefan Karlsson, National Institutes of Health, Bethesda
"Retroviral mediated transfer of human globin genes"

Discussant: Elaine Dzierzak, Massachusetts Institute of Technology, Cambridge, Mass.

1.15 pm Lunch

3.00 – 6.00 pm Poster Session I

6.00 pm Dinner

7.30 pm Session III: Molecular Analysis of Globin Gene Expression
Chairman: Tom Maniatis, Harvard University, Cambridge, Mass

Speakers: Gary Felsenfeld, National Institutes of Health, Bethesda
"Chromatin structure of the chicken globin genes during development"

Roger Patient, King's College, London, England
"Cis and trans effects of β globin gene expression and chromatin structure"

James Douglas Engel, Northwestern University, Evanston
"Tissue- and developmental-stage specific regulation of the chicken β type globin genes"

Timothy Ley, Washington University, St. Louis
"Structure-function relationships of the γ globin promoter"

Jerry Lingrel, University of Cincinnati
"Globin gene binding proteins"

Tuesday, September 30

7.00 – 8.15 am Breakfast

8.30 am Session IV: Molecular Analysis of Globin Gene Expression
Chairman: W. French Anderson, National Institutes of Health, Bethesda

Speakers: Frank Grosveld, Mill Hill Medical Research Institute, London, England
"Globin gene regulatory sequences"

Frank Costantini, Columbia University, New York
"Expression of human globin genes in transgenic mice"

Discussant: Timothy Townes, University of Alabama, Birmingham

Speakers: Marshall Edgell, University of North Carolina, Chapel Hill
"Impacts of L1 elements on the β globin locus"

Paul Marks, Sloan-Kettering Cancer Center, New York
"Inducer mediate changes in gene expression during erythroleukaemia differentiation"

10.30 am Coffee Break

10.45 am — Session V: Molecular Analysis of Globin Gene Expression
Chairman: A.W. Nienhuis, National Institutes of Health, Bethesda

Speakers: Arthur Bank, Columbia University, New York
"Nucleotide sequences affecting human globin gene expression"

Alan Schechter, National Institutes of Health, Bethesda
"Elements controlling human β globin expression"

Nick Proudfoot, University of Oxford, Oxford, England
"Control of ζ globin expression"

12.30 pm — Session VI: HbF and β Locus Haplotypes
Chairman: Bernard Forget, Yale University, New Haven

Speakers: Ronald Nagel, Albert Einstein College of Medicine, Bronx, New York
"Hemoglobin F expression and sickle cell anemia"

Barbara Miller, Harvard Medical School, Boston
"Studies of high haemoglobin F production in Saudis"

Andreas Kulozik, University of Oxford, Oxford, England
"Haplotypes, HbF and hemoglobinopathies"

1.15 pm — Lunch

3.00 – 6.00 pm — Poster Session II

6.00 pm — Dinner

7.30 pm — Session VII: Molecular Analysis of Globin Gene Expression
Chairman: Mark Groudine, Fred Hutchinson Cancer Research Center, Seattle

Speakers: Arthur Skoultchi, Albert Einstein College of Medicine, New York:
"Globin gene expression after homologous or non-homologous recombination"

Thalia Papannopoulou, University of Washington, Seattle
"Analysis of γ to β switch using somatic cell hybrids"

Discussant: Albert Deisseroth, University of California, San Francisco
"Studies of ζ gene expression in hybrids"

Speakers: Margaret Baron, Harvard University, Cambridge, Mass.
"Rapid reprogramming of globin gene expression"

Mark Groudine, Fred Hutchinson Cancer Research Center, Seattle
"Developmental aspects of globin chromatin"

Discussant: Dorothy Tuan, Mass. Institute of Technology, Cambridge, Massachusetts
"Studies of an ε gene enhancer"

Wednesday, October 1

7.00 – 8.15 am Breakfast

8.30 am Session VIII: Modulation of HbF Production
Chairman: G. Stamatoyannopoulos, University of Washington, Seattle

Speakers: George Dover, Johns Hopkins University, Baltimore
"Pharmacologic agents which alter HbF production in sickle cell disease: lessons regarding mechanisms"

Marelyn Wintour, Walter & Eliza Hall Institute, Melbourne, Australia
"Effects of fetal adrenal hormones and prematurity on hemoglobin switching in sheep"

William Wood, Oxford University, Oxford, England
"Altered hemopoietic cell kinetics and hemoglobin switching"

Esmail Zanjani, University of Minnesota, Minneapolis
"An *in vivo* study of the humoral control of switching"

Titus Huisan, Medical College of Georgia, Augusta
"The AγM chain, a novel γ chain associated with increased $^{A}\gamma$ production"

Discussants: Susan Perrine, University of California, San Francisco
Donald Rucknagel, University of Michigan, Ann Arbor
Constance Noguchi, National Institutes of Health, Bethesda

10.30 am Coffee Break

10.45 am Session IX: Molecular Analysis of Mutants
Chairman: Haig Kazazian, Johns Hopkins University, Baltimore

Speakers: Bernard Forget, Yale University, New Haven
"Cis-active sequences responsible for the HPFH phenotype"

Francis Collins, University of Michigan, Ann Arbor
"Studies of deletion and non-deletion HPFH's"

David Bodine, National Institutes of Health, Bethesda
"Analysis of γ gene promoter function in HPFH mutants"

Richard Gelinas, Fred Hutchinson Cancer Research Center, Seattle
"Analysis of non-deletion HPFH mutants"

Discussants: Sergio Ottolenghi, University of Milan, Milan, Italy
John Gilman, University of Georgia, Augusta

1.00 pm Lunch

2.00 & 2.30 pm Departure of buses for National and Dulles Airports

PROGRAM
SIXTH CONFERENCE ON HEMOGLOBIN SWITCHING

Saturday, September 24

2.00 – 8.00 pm Registration
5.00 pm Reception – No Host Cocktails
7.00 pm Outdoor Barbecue

Sunday, September 25

7.00 – 8.15 am Breakfast

8.30 am Session I: In Vivo Manipulation of HbF Synthesis
Chairman: G. Stamatoyannopoulos, University of Seattle, WA

Speakers: G. Stamatoyannopoulos, University of Seattle, WA
"Manipulation of HbF synthesis by growth factors and drugs"

Kevin McDonagh, National Institutes of Health, Bethesda, MD
"Pharmacologic manipulation of HbF production by growth factors and hydroxyurea"

George Dover, Johns Hopkins Medical School, Baltimore, MD
"Stimulation of feta hemoglobin production by hydroxurea"

Griffin Rodgers, National Institutes of Health, Bethesda, MD
"Induction of HbF by hydroxurea: The NIH Experience"

Gordon Ginder, University of Iowa Medical School, Iowa City
"Induction of embryonic globin by butyrate and 5-azacytidine"

Susan Perrine, Children's Hospital, Oakland, CA
"Modulation of fetal to adult globin switching by butyrate"

10.30 am Coffee Break

10.45 am Session II: Molecular and Cell Biology of Hematopoiesis and Cell Commitment
Chairman: Paul Marks, Memorial Sloan-Kettering Cancer Center, New York, NY

Speakers: Paul Marks, Memorial Sloan-Kettering Cancer Center, New York, NY
"Introductory Remarks"

Makio Ogawa, University of South Carolina, Charleston, SC
"Growth factor regulation of hematopoietic stem cells"

Alan Bernstein, University of Toronto, Toronto, Ontario
"Analysis of hematopoietic stem function using transgenic and mutant mice"

Hal Weintraub, Fred Hutchinson Cancer Research Center. Seattle, WA
"Molecular biology of commitment"

1.00 pm Lunch

2.00 – 6.00 pm Poster Session I

6.00 pm Dinner

7.30 pm Session III: Molecular Control of Switching: Insights from Studies in Chicken and Frogs
Chairman: Gary Felsenfeld, National Institutes of Health, Bethesda, MD

Speakers: Gary Felsenfeld, National Institutes of Health, Bethesda, MD
"Regulatory protein action and chromatin structure in the neighbourhood of chicken globin genes during development"

Beverly Emerson, The Salk Institute, San Diego, CA
"In vitro transcription of chicken β-globin genes"

Douglas Engel, Northwestern University, Evanston, IL
"Elements that control globin gene switching in chickens"

Roger Patient, King's College, London, England
"Activation mechanisms of the Xenopus β-globin gene"

Monday, September 26

7.00 – 8.15 am Breakfast

8.30 am Session IV: Transcriptional factors participating in mammalian globin gene expression
Chairman: Tom Maniatis, Harvard University, Cambridge, MA

Speakers: Frank Grosveld, National Institute for Medical Research, London, England
"Transcriptional factors of the β locus"

Sergio Ottolenghi, University of Milano, Milano, Italy
"DNA binding nuclear proteins and the regulation of γ and β-globin gene expression"

Kevin McDonagh, National Institutes of Health, Bethesda, MD
"DNA binding proteins that interact with the γ-globin gene promoter"

Stuart Orkin, Harvard Medical School, Boston
"Cell specific γ promoter DNA binding factors: characterization and function"

10.30 am Coffee Break

10.45 am Session IV: Transcriptional factors, continues:
Chairman: Tom Maniatis, Harvard University, Cambridge, MA

Francis Collins, University of Michigan, Ann Arbor, MI
"Cis and transacting elements regulating fetal globin expression"

Richard Myers, University of California, San Francisco, CA
"Factors involved in regulation of β-globin gene expression in murine erythroleukaemia cells"

Maryann Donovan-Feluso, Columbia University, New York
"Factors in K562 cells that interact with sequences 5' and 3' to the γ and β-globin genes"

S.X. Cao, National Institutes of Health, Bethesda, MD
"A transcriptional silencer 5' to the human ε-globin gene which interacts with three cellular factors"

Michael Sheffery, Sloan-Kettering Cancer Center, New York
"Erythroid cell proteins that interact with the promoter of the murine α-globin gene"

James Shen, University of California, Davis, CA
"The human α2- α1-θ1 locus"

1.15 pm Lunch

2.30 – 6.00 pm Poster Session II

6.00 pm Dinner

7.30 pm Session IV: Transcriptional Factors, continues
Chairman: Tom Maniatis, Harvard University, Cambridge, MA

Speakers: Tom Maniatis, Harvard University, Cambridge, MA
"Factors interacting with mammalian α and β-globin gene clusters: summary and synthesis of the work presented in Session IV"

Session V: Biology of Gene Expression: No Footprints Allowed
Chairman: Y.W. Kan, University of California, San Francisco, CA

Speakers: Nick Proudfoot, University of Oxford, Oxford, England
"Negative regulation of the human embryonic globin genes ζ and ε"

Tariq Enver, University of Washington, Seattle, WA
"Globin gene switching in somatic cell hybrids"

Andy Jarman, University of Oxford, Oxford, England
"α and β locus attachments sites on nuclear matrix"

Paul-Henri Romeo, University of Paris, Creteil, France
"Regulation of human PBG-D during erythroid differentiation"

Tuesday, September 27

7.00 – 8.15 am Breakfast

8.30 am Session VI: Molecular Analysis of the Locus Activating Regions
Chairman: A.W. Nienhuis, National Institutes of Health, Bethesda, MD

Speakers: Mark Groudine, Fred Hutchinson Cancer Research Center, Seattle, WA
"Structure and replication of the human β-globin domain"

David Greaves, Medical Research Council, London, England
"β-globin domain control region"

Tim Townes, University of Alabama, Birmingham, AL
"High level erythroid specific expression of human globin genes in transgenic mice"

Dorothy Tuan, Massachusetts Institute of Technology, Cambridge, MA
"Characterization of the enhancer sequence upstream of the human β-like globin genes"

10.20 am Coffee Break

10.30 am Session VII: Insights from Studies of Mutants and Polymorphisms
Chairman: William Wood, Oxford University, Oxford, England

Speakers: Bernard Forget, Yale University, New Haven, CT
"Molecular analysis of mutants"

Joe DeSimone, University of Illinois, Chicago, IL
"Promoter structure of baboons displaying high or low HbF production in response to acute erythropoietic stress"

Discussion: β Locus Polymorphisms and HbF Expression

11.30 am Session VIII: Globin Gene Transfer in Hemopoietic Cells
Chairman: Vernon Ingram, Massachusetts Institute of Technology, Cambridge, MA

Speakers: David Bodine, National Institutes of Health, Bethesda, MD
"Retroviral transfer of human β-globin genes into primitive murine hemopoietic cells"

Elaine Dzierzak, Whitehead Institute, Cambridge, MA
"Human β-globin gene transfer and expression in murine bone marrow recipients"

Richard Gelinas, Fred Hutchinson Cancer Research Center, Seattle, WA
"Expression of β-globin genes after retroviral transfer to BFUe and murine bone marrow cells"

12.45 pm Session IX: Epilogue

Speaker: David Nathan, Harvard Medical School, Cambridge, MA
"Hemoglobin Switching – Ten Years of Progress"

1.05 pm Lunch

2.00 pm Departure of buses for National and Dulles Airports

PROGRAM
SEVENTH CONFERENCE ON HEMOGLOBIN SWITCHING
AIRLIE HOUSE, AIRLIE, VIRGINIA

Saturday, September 8, 1990

2.00 – 8.00 pm	Registration
5.00 – 7.30 pm	No Host Cocktails
7.30 pm	Dinner

Sunday, September 9, 1990

7.00 – 8.30 am	Breakfast
8.30 – 10.30	SESSION I: ANALYSIS OF HEMOGLOBIN SWITCHING IN TRANSGENIC MICE Chairman: Y.W. Kan, UCSF, San Francisco, CA
8.30	T. Enver, University of Washington, Seattle, WA "Autonomous and competitive control of globin gene switching in man"
9.00	P. Fraser, MRC Mill Hill, London "Developmental regulation of the β-like globin genes"
9.30	T. Townes, University of Alabama, Birmingham, AL "Molecular analysis of Hb Switching"
10.00	Steve Shapiro, University of Maryland, College Park, MD "Regulation of human ε-globin gene in transgenic mice"
10.10	M. Albitar, S. Liebhaber, University of Pennsylvania, Philadelphia, PA "Regulation of the human embryonic and ζ adult α-globin in transgenic mice"
10.20	E. Rubin, University of California, Berkeley, CA "Control of human ζ -globin gene in transgenic mice"
10.30 – 11.00	COFFEE BREAK
11.00 – 1.00	SESSION II: TRANSCRIPTIONAL FACTORS Chairman: A.W. Nienhuis, Bethesda, MD
11.00	G. Felsenfeld, NIH, Bethesda, MD "Regulatory protein action and chromatin structure in the neighborhood of chicken globin genes during development"
11.30	D. Engel, Northwestern University, Evanston, IL "β-globin gene switching in chickens"

12.00	S. Orkin, Harvard Medical School, Boston, MA "Molecular genetics and function of the erythroid transcription factor (GF-1/NFE-1/Eryf1)
12.30	F. Costantini, Columbia University, New York, NY "Homologous recombination at the NFE-1 locus"
12.45	S. Ottolenghi, University of Milan, Milan, Italy "Studies of erythroid nuclear factors"
1.00 – 2.30	LUNCH
2.30 – 6.00	POSTER SESSION I
6.00 – 7.30	DINNER
7.30 – 10.00	SESSION III: CELLULAR AND MOLECULAR ANALYSES OF SWITCHING Chairman: F. Grosveld, MRC Mill Hill, London, England
7.30	M. Groudine, Fred Hutchinson Cancer Research Center, Seattle, WA "Chromatin structure and replication of the β-globin domain"
8.00	B. Emerson, Salk Institute, San Diego, CA "Promoter-enhancer communications in the chicken system"
8.25	D. Tuan, MIT, Cambridge, MA "Mechanism of function of the far upstream HSII globin enhancer: looping or tracking?"
8.45 – 9.00	COFFEE BREAK
9.00	R. Patient, Kings College, London, England "Regulation of Xenopus globin gene expression"
9.25	David Bodine, National Institutes of Health, Bethesda, MD "Globin gene transfer into murine and primate hematopoietic stem cells"

Monday, September 10, 1990

7.00 – 8.30	BREAKFAST
8.30 – 10.15	SESSION IV: LOCUS ACTIVATION REGION/DOMINANT CONTROL REGION Chairman: M. Groudine, Fred Hutchinson CRC, Seattle, WA
8.30	F. Grosveld, MRC Mill Hill, London, England "Factors and regulatory regions of the β-globin locus"
9.00	P. Ney, NIH, Bethesda, MD "Characterization of the HS-II enhancer"

9.30	D. Higgs, University of Oxford, Oxford, England "Organization, structure and function of cis-active elements around the human α globin cluster"
10.00	Q. Li, Shanghai Institute of Biochemistry, Shanghai, China and University of Washington, Seattle, WA "β-globin locus activation regions: conservation of the organization, structure and function"
10.20	T. Ley, Washington University, St. Louis, MO "Cloning and functional analysis of the mouse HS II"
10.40 – 11.15	COFFEE BREAK AND CONFERENCE PHOTOGRAPH
11.15 – 1.00	SESSION V: TRANSCRIPTIONAL FACTORS Chairman: G. Felsenfeld, NIH, Bethesda, MD
11.15	P-H. Romeo, INSERM, Paris, France "Hematopoietic activity of the human NF-E1 gene family"
11.40	J. Shen, University of California, Davis, CA "Nuclear factor-DNA interactions and promoter functioning of human embryonic globin genes"
12.00	J. DeSimone, University of Illinois, Chicago, IL "A fetal-specific nuclear protein bings to the Aγ protein enhancer and promoter"
12.15	D. Gumucio, University of Michigan, Ann Arbor, MI "γ globin gene regulation: an evolutionary approach"
12.30	P. Curtis, University of Pennsylvania, Philadelphia, PA "A stage specific DNA binding factor in mouse erythroleukaemia cells"
12.45	N. Proudfoot, University of Oxford, Oxford, England.
1.00 – 2.30	LUNCH
2.30 – 6.00	POSTER SESSION II
6.00 – 7.30	DINNER
7.30 – 10.00	SESSION VI: PAPERS SELECTED FROM POSTERS Chairman: Arthur Bank, Columbia University, New York, NY

Tuesday, September 11, 1990

7.00 – 8.30	BREAKFAST
8.30 – 10.30	SESSION VII: MANIPULATION OF Hb SWITCHING IN VIVO Chairman: G. Stamatoyannopoulos, Univ of Washington, Seattle, WA

8.30	G. Stamatoyannopoulos, Univ of Washington, Seattle, WA "Overview: Induction of HbF in the Adult"
8.45	George Dover, Johns Hopkins University, Baltimore, MD "Pharmacologic manipulation of fetal haemoglobin in sickle cell patients"
9.00	K. McDonagh, NIH, Bethesda, MD "Interaction of hydroxyurea with erythropoietin, hematopoietic growth factors or sodium butyrate in stimulating F-reticulocyte production in non-human primates"
9.15	G. Rodgers, NIH, Bethesda, MD "Interaction of hydroxyurea and Epo in treatment of sickle cell disease"
9.30	Ron Nagel, Albert Einstein College of Medicine, Bronx, NY "Erythropoietin treatment of patients with sickle cell disease"
9.45	M. Wintour, University of Melbourne, Parkville, Australia "Hemoglobin Switching and erythropoietin in fetal and neonatal sheep"
10.00	S. Perrine, Children's Hospital, Oakland, CA "Modulating globin gene switching in the perinatal period"
10.15	G. Ginder, University of Minnesota, Minneapolis, MN "Reversed switching induced by butyrate compounds"
10.30 – 11.00	COFFEE BREAK
11.00 – 1.15	SESSION VIII: UPDATE OF HEMATOPOIESIS Chairman: D. Nathan, Harvard Medical School, Boston, MA
11.00	D. Nathan, Harvard Medical School, Boston, MA "Overview of hematopoiesis and growth factors"
11.15	B. Forget, Yale Medical School, New Haven, CT "Erythropoietin and other growth factor receptors"
11.30	C. Eaves, Terry Fox Laboratory, Vancouver, BC "Stem cell biology and microenvironmental interactions"
12.00	C. Peschle, Institute Superiore Di Sanita, Rome, Italy "Purification of erythroid progenitors from adult and cord blood"
12.15	Douglas Williams, Immunex Corp., Seattle, WA "Identification of a ligand for the c-kit proto-oncogene"
12.45	END OF CONFERENCE
1.00 – 2.30	LUNCH
2.30	DEPATURE OF BUSES

ATTENTION SPEAKERS: ALLOCATED TIMES INCLUDE FIVE MINUTES DISCUSSION

PLENARY SESSIONS: SATELLITE HALL
POSTER SESSIONS: DISCOVERY HOUSE

PROGRAM
EIGHTH CONFERENCE ON HEMOGLOBIN SWITCHING
ROSARIO RESORT, ORCAS ISLAND, WASHINGTON
May 29 – June 2, 1992

FRIDAY, MAY 29, 1992

1.00 – 8.00 pm REGISTRATION – DISCOVERY HOUSE

5.00 – 7.30 pm NO HOST COCKTAILS – DOLPHIN HOUSE – DISCOVERY HOUSE

7.30 pm DINNER – DISCOVERY HOUSE

SATURDAY, MAY 30, 1992

7.30 – 8.15 BREAKFAST – DISCOVERY HOUSE

SESSION I: HEMOGLOBIN SWITCHING IN TRANSGENIC MICE
Chairman: Bernie Forget

8.30 Frank Grosveld, MRC Mill Hill, London, England
"Regulation of the human β globin domain"

9.05 Quliang Li and George Stamatoyannopoulos, University of Washington, Seattle, WA
"Regulation of globin gene switching"

9.35 Tom Ryan, University of Alabama, Birmingham, AL
"Human γ- to β-globin gene switching in transgenic mice"

9.55 Discussants:
Kathy Anderson, University of Cincinnati, Cincinnati, Ohio
"Developmental switching of γ and β globin genes using a mini-construct"

Donna King, University of Chicago, Chicago, IL
"Regulated expression of the sheep juvenile β-globin gene in transgenic mice"

10.10 COFFEE BREAK

10.30 William Wood, University of Oxford, Oxford, England
"Developmental regulation of human α and β globin genes in transgenic mice"

10.50 Ken Peterson, University of Washington, Seattle, WA
"Gene order and developmental control of γ and β globin gene expression"

11.10 Steve Shapiro, University of Maryland, College, Park, MD
"Developmental control of the human ε-globin gene in transgenic mice"

11.30 Discussants:
"Regulation of ζ globin gene expression in transgenic mice"

Marc Pondel and Emma Whitelaw, Oxford University, Oxford, England and University of Sydney, Sydney, Australia
Dan Sabath, University of Washington, Seattle, WA
Stephen Liebhaber, University of Pennsylvania, Philadelphia, PA

SESSION II: TRANSCRIPTIONAL REGULATION I
Chairman: Gary Felsenfeld

12.00 Stephen Jane, NIH, Bethesda, MD
"Identification of a stage selector element in the human γ-globin gene"

12.30 Deborah Gumucio, University of Michigan, Ann Arbor, MI
"Phylogenetic footprinting"

12.45 BREAK FOR LUNCH

12.55 LUNCH – DISCOVERY HOUSE

2.30 – 6.00 POSTER SESSION I

6.00 – 7.30 DINNER – DISCOVERY HOUSE

SESSION III: TRANSCRIPTIONAL REGULATION II
Chairman: Alan Schechter

7.30 Paul Ney, NIH, Bethesda, MD
"Purification of NFE-2 from K562 cells"

7.50 Tim Townes, University of Alabama, Birmingham, AL
"Isolation and characterization of cDNA clones that bind to 5' HS2 sequences in the β-globin control region"

8.10 Nancy Andrews, Children's Hospital, Boston, MA
"Purification and characterization of NFE-2"

8.40 Sjaak Philipsen, MRC Mill Hill, London, England
"Characterization of the β locus LCR"

9.10 Sergio Ottolenghi, University of Milan, Milan, Italy
"Studies on GATA-1 and NFE 3"

9.30 Betty Peters, NIH, Bethesda, MD
"DNA-proteins binding to the ε-globin gene silencer"

9.50 Yuet Wai Kan, UCSF, San Franscisco, CA
"In vivo DNA footprinting in cells transcribing γ and β globin genes"

SUNDAY, MAY 31, 1992

7.30 – 8.15 BREAKFAST – DISCOVERY HOUSE

SESSION IV: GLOBIN LOCUS CHROMATIN AND LCR
Chairman: Jerry Lingrell

8.30 Gary Felsenfeld, NIH, Bethesda, MD
"Chromatin structure and chicken globin gene expression"

9.15 Mark Groudine, Fred Hutchinson Cancer Research Center, Seattle, WA
"Analysis of the human β globin LCR by homologous recombination"

9.45 Ron Shehee, University of North Carolina, Chapel Hill, NC
"Disruption of the mouse major adult β-globin gene causes perinatally lethal thalassemia"

10.00 James Shen, University of California at Davis, Davis, CA
"Transcriptional activation of human zeta globin promoter by its distal enhancer: modulation by specific nuclear factor-DNA complexes"

10.20 COFFEE BREAK

10.45 Doug Higgs, University of Oxford, Oxford, England
"The structure and function of the human a globin regulatory domain"

11.15 Tariq Enver, Institute of Cancer Research, London, England
"Lineage promiscuity in locus activation: chromatin structure of lineage affiliated cis-acting transcriptional regulators"

11.35 Ross Hardison, Pennsylvania State University, University Park, PA
"Comparative analyses of locus control regions of mammalian beta-globin gene clusters"

11.55 Tim Ley, Washington University, St. Louis, MO
a) "Structure and function of mouse b globin LCR"
b) "Local regulation of the g-globin gene promoter"

12.25 Dorothy Tuan, Harvard University, Cambridge, MA
"The tracking mechanism of HS2 enhancer"

12.45 BREAK FOR LUNCH

12.55 LUNCH – DISCOVERY HOUSE

2.30 – 6.00 POSTER SESSION II

6.00 – 7.30 DINNER – DISCOVERY HOUSE

SESSION V: GENE TRANSFER IN HEMOPOIETIC STEM CELLS
Chairman: Stuart Orkin

7.30 pm — Richard Jude Samulski, University of Pittsburgh, Pittsburgh, PA
"Development of parvovirus vectors for gene therapy"

7.50 — Arthur W. Nienhuis, NIH, Bethesda, MD
"Globin gene transfer with an AAV vector"

8.20 — Arthur Bank, Columbia University, New York, NY
"Transfer and expression of human genes in hematopoietic stem cells"

8.45 — Michel Sadelain, Whitehead Institute, Cambridge, MA
"Generation and characterization of recombinant retroviral genomes encoding the human b globin gene and associated regulatory sequences"

9.10 — Keith Humphries, British Columbia Cancer Res. Ctr, Vancouver, British Columbia, Canada and Phillip Lebuish, MIT, Boston, MA
"Studies of gene transfer to primitive human and murine hematopoietic cells"

9.30 — SESSION VI: PAPERS SELECTED FROM THE POSTERS
Chairman: A.W. Nienhuis

MONDAY, JUNE 1, 1992

7.30 – 8.15 — BREAKFAST – DISCOVERY HOUSE

SESSION VII: TRANSCRIPTIONAL REGULATION III
Chairman: Frank Bunn

8.30 — Stuart Orkin, Harvard Medical School, Boston, MA
"GATA-1: approaches to specificity of erythroid gene expression and development"

9.15 — Frank Costantini, Columbia University, New York, NY
"The effects of a GATA-1 mutation on hemopoiesis in the developing mouse"

9.30 — Douglas J Engel, Northwestern University, Evanston, IL
"GATA factor transcriptional regulation"

10.10 — COFFEE BREAK

10.30 — Beverly Emerson, Salk Institute, San Diego, CA
"Developmental regulation of β globin gene expression in vitro"

11.00 — Paul-Henri Romeo, INSERM, Paris, France
"h GATA-1 activity on erythroid regulating sequences: activation or derepression"

11.30 — David Martin, Fred Hutchinson Cancer Research Center, Seattle, WA
"Transcriptional activation by GATA"

11.50 Lee Wall, Institut du Cancer de Montreal, Quebec, Canada
"Transcriptional enhancement by the β-globin LCR can be regulated by distinct factors binding to the β-globin gene CAAT box"

12.10 Leonard Zon, Children's Hospital, Boston, MA
"Developmental regulation of hematopoietic transcription factors during Xenopus embryogenesis"

12.30 Roger Patient, Kings College, London, England
"GATA transcriptional factors and erythroid differentiation in Xenopus"

12.45 BREAK FOR LUNCH

12.55 LUNCH – DISCOVERY HOUSE

2.30 – 6.00 POSTER SESSION III

6.00 – 7.30 DINNER – DISCOVERY HOUSE

SESSION VIII: MANIPULATION OF HEMOGLOBIN SWITCHING
Chairman: George Stamatoyannopoulos

7.30 George Stamatoyannopoulos, University of Washington, Seattle, WA
"Introductory remarks"

7.40 George Dover, Johns Hopkins University, Baltimore, MD
"Update on pharmacologic induction of Hb F in man"

8.00 Susan Perrine, Children's Hospital, Oakland, CA
"Butyrate enhances γ globin gene expression in β globin disorders"

8.20 Gordon Ginder, University of Minnesota, Minneapolis, MN
"Mechanisms of developmental globin gene regulation and modulation by butyrate compounds"

8.40 Kevin McDonagh, NIH, Bethesda, MD
"Repression of the human γ-globin gene promoter by CCAAT displacement protein and reversal by sodium butyrate"

8.55 Discussant: Stuart Orkin

9.00 Griffin Rodgers, NIH, Bethesda, MD
"Treatment of hemoglobinopathies with hydroxyurea"

9.15 SESSION IX: PAPERS SELECTED FROM THE POSTERS
Chairman: Douglas J. Engel

TUESDAY, JUNE 2, 1992

7.30 – 9.00 BREAKFAST – MORAN ROOM – MANSION

Note: You might want to bring an umbrella just in case

***ATTENTION SPEAKERS*: ALLOCATED TIMES INCLUDE DISCUSSION**

PLENARY SESSIONS: SATELLITE HALL
POSTER SESSIONS: DISCOVERY HOUSE

PROGRAM
NINTH CONFERENCE ON HEMOGLOBIN SWITCHING
ROSARIO RESORT, ORCAS ISLAND, WASHINGTON
June 10 – June 14

FRIDAY, JUNE 10, 1994

1.00 – 8.00 pm REGISTRATION – DISCOVERY HOUSE

5.00 – 7.30 pm NO HOST COCKTAILS – DOLPHIN ROOM – DISCOVERY HOUSE

7.30 – 7.30 pm HORS D'OEUVRES DINNER

SATURDAY, JUNE 11, 1994

7.00 – 8.15 am BREAKFAST – DISCOVERY HOUSE

SESSION I. CONTROL OF GLOBIN EXPRESSION IN TRANSGENIC MICE, SYNKARYONS AND HETEROKARYONS
Chair: **George Stamatoyannopoulos,** University of Washington, Seattle, WA

8.30 George Stamatoyannopoulos, University of Washington, Seattle, WA
"Hemoglobin switching in transgenic mice and hybrids"

9.00 Simon Stanworth, Oxford University, Oxford, England
"Transgenic erythroblast X MEL cell hybrids in the analysis of globin gene switching"

9.15 Robert Broyles, University of Oklahoma, Oklahoma City, OK
"Hemoglobin switching in heterokaryons"

9.30 Ken Peterson, University of Washington, Seattle, WA
"Transgenic mice using β locus YACs"

9.50 Peter Fraser, Erasmus University, Rotterdam, The Netherlands
"The role of HS3 in γ-gene expression"

10.10 Marc Reitman, National Institutes of Health, Bethesda, MD
"Developmental regulation of the complete chicken β globin cluster in transgenic mice"

10.35 COFFEE BREAK

11.00 Doug Higgs, Oxford University, Oxford, England
"The relationship between long range chromatin structure and expression of the human α globin cluster in transgenic mice"

SESSION II. CONTROL OF EMBRYONIC GENES
Chair: **Alan Schechter,** National Institutes of Health, Bethesda, MD

11.30	Natacha Raich, INSERM, Creteil, France "Functional analysis of the human ε-globin gene silencer"
11.50	Margaret Baron, Harvard University, Boston, MA "Developmental regulation of the human embryonic β-like globin gene"
12.10	Constance Tom Noguchi, National Institutes of Health, Bethesda, MD "Transcriptional and post-transcriptional mechanisms of ε-globin gene silencing"
12.30	Marc Pondel, Oxford University, Oxford, England "Transcriptional regulation of the human α-globin gene cluster in transgenic mice and erythroid cell lines:
12.45	Emma Whitelaw, University of Sidney, Sidney, Australia "Transcription of the human zeta globin promoter in transgenic mice"
1.00	BREAK FOR LUNCH
1.15 – 2.45	LUNCH – DISCOVERY HOUSE
3.00 – 6.00	**POSTER SESSION I – DISCOVERY HOUSE**
6.00 – 7.30	DINNER – DISCOVERY HOUSE

SESSION III. MURINE MODELS OF DISEASE
Chair: **Bernard Forget**, Yale University, New Haven, CT

7.30	Oliver Smithies, University of North Carolina, Chapel Hill, NC "Some new procedures for gene targeting, and their application to various systems"
8.05	Roger Patient, King's College, London, England "Control of GATA factor expression during development in Xenopus and Zebrafish"
8.25	Leonard Zon, Children's Hospital, Boston, MA| "Induction of hematopoiesis during Xenopus and Zebrafish embryogenesis"
8.45	Discussant: Robert Broyles, University of Oklahoma, Oklahoma City, OK "Early erythropoiesis in developing *Rana catesbelana*"
8.50	Todd Evans, University of Pittsburgh, Pittsburgh, PA "Regulation of gene expression by GATA factors"
9.10	Elaine Dzierzak, National Institute of Medical Research, London, England "Hematopoietic stem cell development in the mouse embryo"
9.30	Andrew Thomson, Oxford University, Oxford, England "Globin gene expression in MPLV-transformed multi-potential progenitor cells from transgenic mice embryos"
9.50	Sergio Ottolenghi, University of Milano, Milano, Italy "Conditional immortalization of erythroid-myeloid progenitors by GATA-1 driven Sv40 ts A 58 gene, and expression of alternative GATA-1 promoters"

SUNDAY, JUNE 12, 1994

7.00 – 8.15 am BREAKFAST – DISCOVERY HOUSE

SESSION V. TRANSCRIPTIONAL REGULATION
Chair: **Stuart Orkin,** Children's Hospital, Boston, MA

8.30 Stuart Orkin, Children's Hospital, Boston, MA
"Layered regulation of globin gene expression"

9.10 Douglas Engel, Northwestern University, Evanston, IL
"GATA factor regulation of hematopoietic and other cell fates"

9.40 Stephen Jane, St Jude Children's Research Hospital, Memphis, TN
"The purification and characterization of the human stage selector protein complex"

10.10 James Bieker, Mt. Sinai Medical School, New York, NY
"Role of EKLF in erythroid-specific transcription"

10.30 COFFEE BREAK

10.55 Deb Gumucio, University of Michigan, Ann Arbor, MI
"Evolutionary approaches to the study of hemoglobin switching"

11.20 James Shen, University of California, Davis, CA
"Functional adaptability of nuclear factor-DNA complexes in human zeta globin promoter-HS-40 enhancer interaction"

11.40 Tim Townes, University of Alabama, Birmingham, AL
"LCR-FI: A bZIP transcription factor that activates erythroid-specific, human globin gene expression"

12.00 Jefferson Chan, University of California, San Francisco, CA
"Functional cloning of Nrf1, a member of the NFE2 multigene family"

12.20 Masi Yamamoto, Tohuku University, Japan
"Structure, expression and function of small Maf family protein Mafk"

Post transcriptional control of globin genes

12.40 Steve Liebhaber, University of Pennsylvania, Philadelphia, PA
"*Cis*- and *Trans*-acting determinants of globin mRNA stability"

1.00 BREAK FOR LUNCH

1.15 – 2.45 LUNCH – DISCOVERY HOUSE

3.00 – 6.00 **POSTER SESSION II**

6.00 – 7.30 DINNER – DISCOVERY HOUSE

SECTION VI. THERAPEUTIC INDUCTION OF FETAL HEMOGLOBIN SYNTHESIS
Chair: **Franklin Bunn,** Longwood Medical Research Center, Boston, MA

7.30 George Dover, Johns Hopkins University, Baltimore, MD
"Pharmacologic manipulation of fetal hemoglobin in man"

7.55 Tony Blau, University of Washington, Seattle, WA
"Feta hemoglobin induction using short chain fatty acids"

8.15 Susan Perrine, Boston University, Boston, MA
"Clinical trials of butyrate and isobutyramide in beta globin disorders"

8.35 Nancy Olivieri, Hospital for Sick Children, Toronto, Ontario
"Results of trials with intravenous arginine butyrate and recombinant human erythropoietin in thalassemia and sickle cell disease"

8.55 Dimitri Loukopoulos, University of Athens, Athens, Greece
"Treatment of β chain hemoglobinopathies with hydroxyurea and erythropoietin"

9.15 Griffin Rodgers, National Institutes of Health, Bethesda, MD
"Update on clinical trials to stimulate HbF levels"

9.35 Elieser Rachmilewitz, Hadassah Medical Organization, Jerusalem
"The effect of erythropoietin, hydroxyurea and the combination of the two, on γ chain synthesis in b thalassemia intermedia"

MONDAY, JUNE 13, 1994

7.00 – 8.15 BREAKFAST – DISCOVERY HOUSE

SESSION VII: GLOBIN CHROMATIN AND THE LCR
Chair: **Frank Grosveld,** Erasmus University, Rotterdam, The Netherlands

8.30 Gary Felsenfeld, National Institutes of Health, Bethesda, MD
"Chromatin structure and the expression of globin genes"

9.10 Beverly Emerson, The Salk Institute
"Transcriptional regulation of the chick beta-globin gene locus in chromatin and synthetic nuclei"

9.35 Frank Grosveld, National Institute of Medical Research, London, England and Erasmus University, Rotterdam, The Netherlands
"Looping or scanning"

10.00 Steve Fiering, Fred Hutchinson Cancer Research Center, Seattle, WA
"Analysis of the β-globin LCR by gene targeting"

10.15 Elliot Epner, Fred Hutchinson Cancer Research Center, Seattle, WA
"Replication of the human β-globin gene domain"

10.30 COFFEE BREAK

10.50 Ross Hardison, The Pennsylvania State University, University Park, PA
"Electronic genetic analysis as a guide to functions of globin gene promoters and locus control regions"

11.10 Sjaak Philipsen, Erasmus University, Rotterdam, The Netherlands
"Activation of model promoters by the human β-globin locus control region"

11.30 Christopher Lowrey, Dartmouth-Hitchcock Medical Center, Lebanon, NH
"Characterization of a DNase I hypersensitive site-forming element from the human β-globin locus control region.

11.50 David Martin, Fred Hutchinson Cancer Research Center, Seattle, WA
"In vitro studies of enhancer action"

12.10 Dies Meijer, Erasmus University, Rotterdam, Holland
"Functional definition of the 5' border of the β-globin domain"

12.30 James Ellis, National Institute for Medical Research, London, England
"LCR and enhancer activities in single-copy transgenic mice"

12.50 Dorothy Tuan, Medical College of Georgia, Augusta, GA
"Mapping the locus control region in erythroid progenitor cells"

1.10 BREAK FOR LUNCH

1.15 – 2.45 LUNCH – DISCOVERY HOUSE

3.00 – 6.00 **POSTER SESSION III**

6.00 – 7.30 DINNER – DISCOVERY HOUSE

7.30 **SESSION VIII. PAPERS SELECTED FROM THE POSTERS**
Co-Chairs:
Gary Felsenfeld, National Institutes of Health, Bethesda, MD
Douglas Engel, Northwestern University, Evanston, IL
George Stamatoyannopoulos, University of Washington, Seattle, WA

TUESDAY, JUNE 14, 1994

7.30 – 8.45 BREAKFAST – DISCOVERY HOUSE

SESSION IX. STEM CELL BIOLOGY
Chair: **David Williams,** Indiana University, Indianapolis, IM

9.00 Peter Lansdorp, Terry Fox Laboratory, Vancouver, BC
"Biology of purified stem cells"

9.25 Shelly Heimfeld, CellPro, Seattle, WA
"Ex-vivo expansion of CD34+ progenitor cells from bone marrow and cord blood"

9.50 Tariq Enver, Institute of Cancer Research, Chester Beatty Laboratories, London, England
"Function and regulation of the stem cell antigen CD34"

10.15 Ihor Lemischka, Princeton University, Princeton, NJ
"The developmental and molecular properties of hematopoietic stem cells"

10.40 COFFEE BREAK

11.00 Thalia Papayannopoulou, University of Washington, Seattle, WA
"Stem/progenitor cell traffic"

11.25 Keith Humphries, Terry Fox Laboratory, Vancouver, BC
"Selection and tracking of transduced long-term repopulating cells"

11.50 David Williams, Indiana University, Indianapolis, IN
"Molecular analysis of steel factor presentation in the hematopoietic microenvironment"

SESSION X. NEW GENE TRANSFER APPROACHES
Chair: **David Williams,** Indiana University, Indianapolis, IM

12.15 David Russell, Fred Hutchinson Cancer Research Center, Seattle, WA
"Viral transduction of non-dividing cells"

12.40 Nori Kasahara, University of California, San Francisco, CA
"Erythroid cell-specific targeting of retrovirus vectors"

1.00 BREAK FOR LUNCH

1.00 – 3.00 LUNCH

SESSION XI. ANIMAL MODELS
Chair: **Ronald Nagel,** Albert Einstein College of Medicine, Bronx, NY

3.30 John Dick, Hospital for Sick Children, Toronto, Ontario
"Genetic manipulation of human hematopoietic cells transplanted into SCID mice"

3.55 David Bodine, National Institutes of Health, Bethesda, MD
"Animal models for evaluating retrovirus mediated gene transfer protocols"

SESSION XII. GENE TRANSFER BIOLOGY, PRECLINICAL STUDIES, AND GLOBIN VECTORS
Chair: **Arthur W. Nienhuis,** St. Jude Children's Research Hospital, Memphis, TN

4.20 Arthur Nienhuis, St. Jude Children's Research Hospital, Memphis, TN
"Gene transfer into hematopoietic cells"

4.50 Friedrich Schuening, Fred Hutchinson Cancer Research Center, Seattle
"Gene transfer into human and canine hemopoietic cells"

5.15 Arthur Bank, Columbia University, New York, NY
"MDR gene transfer into human hematopoietic progenitors"

5.40 Michel Sadelain, Whitehead Institute, Cambridge, MA
"Generation of a high titer and stable retroviral vector conferring elevated and erythroid specific human β-globin expression"

5.55 Tim Townes, University of Alabama, Birmingham, AL
"Recombinant human hemoglobins designed for gene therapy of sickle cell disease"

6.10 BREAK FOR DINNER

6.30 – 8.00 DINNER

ATTENTION SPEAKERS: **ALLOCATED TIMES INCLUDE DISCUSSION**

PROGRAM

The Tenth Conference on

Hemoglobin Switching

June 14-18, 1996
Rosario, Orcas Island, Washington

FRIDAY, JUNE 14, 1996

2.00 – 8.00 pm REGISTRATION – DISCOVERY HOUSE

5.00 – 7.30 pm NO HOST COCKTAILS – DISCOVERY HOUSE

7.30 – 8.30 pm DINNER

SATURDAY, JUNE 15, 1996

7.00 – 8.15 am BREAKFAST – DISCOVERY HOUSE

8.30 – 12.25 pm **SESSION I: CONTROL OF HEMOGLOBIN SWITCHING**
Chairpersons: Sherman Weisman, Yale University, New Haven, CT
Alan Schechter, National Institutes of Health, Bethesda, MD

8.30 Qiliang Li and George Stamatoyannopoulos, University of Washington
"Binary system for studying hemoglobin switching in transgenic mice"

8.55 Kenneth Peterson, University of Washington, Seattle, WA
"Use of YACs for studies of switching"

9.15 Pat Navas, University of Washington, Seattle, WA
"Production of transgenic mice carrying a deletion of a 234 bp core sequence of hypersensitive site 3"

9.25 Karin Gaensler, University of California, San Francisco, CA
"β-globin YAC transgenic mice: Models for the analysis of human globin gene expression"

9.40 Douglas Engel, Northwestern University, Evanston, IL
"Regulatory elements controlling human β-globin locus transcription"

10.05 Deb Gumucio, University of Michigan, Ann Arbor, MI
"HS3-ε-γ constructs in transgenic mice: implications for silencing and fetal recruitment of the anthropoid γ gene"

10.25 COFFEE BREAK

10.45 Bernard Forget, Yale University, New Haven, CT
"High levels of γ-gene expression in adult mice with a deletion-type HPFH transgene"

11.05 Nick Proudfoot, University of Oxford
"Intergenic transcription across the human beta globin gene locus"

11.25 Sergio Ottolenghi, University of Milano, Milano, Italy
"Different DNA conformational changes induced by NF-Y/CP1 upon in vitro binding to HPFH and normal γ-globin CCAAT box region"

11.45 Connie Noguchi, National Institutes of Health, Bethesda, MD
"Transcription regulation by the epsilon-globin silencer and negative regulatory elements"

12.05 Bill Wood, Institute of Molecular Medicine, Oxford, England
"Epigenetic and *trans* regulation in switching"

12.25 – 1.00 pm **SESSION II: BLOOD EMBRYOGENESIS A**
Chairperson: Robert Broyles, University of Oklahoma, Oklahoma City, OK

12.25 Leonard Zon, Children's Hospital, Boston, MA
"Use of lower vertebrates to clone genes involved in stem cell induction and globin gene expression"

12.50 Todd Evans, Albert Einstein College of Medicine, Bronx, NY
"The regulation of embryonic erythropoiesis by BMP-4 and Rb: signalling upstream of GATA-1"

1.10 BREAK FOR LUNCH

1.10 – 2.45 LUNCH – DISCOVERY HOUSE

3.00 – 6.00 pm **POSTER SESSION A**

6.00 – 7.30 DINNER – DISCOVERY HOUSE

7.30 – 10.30 pm **SESSION III: STEM CELL AND GLOBIN GENE THERAPY**
Chairpersons: A.W. Nienhuis, St Jude Children's Research Hospital,
David Bodine, National Institutes of Health

7.30 David Bodine, National Institutes of Health, Bethesda, MD
"Retrovirus receptor levels and gene transfer to hematopoietic stem cells"

7.50 – 8.35 *The Question of In Vivo Selection*

7.50 Tony Blau, University of Washington, Seattle, WA
"Strategies for the selection of genetically modified progenitors and stem cells in vivo"

8.05 Brian Sorrentino, St Jude Children's Research Hospital, Memphis, TN
"Variants of the human dihydrofolate reductase gene for drug-selection of primitive hematopoietic cells"

8.20 Arthur Bank, Columbia University, New York, NY
"Gene transfer into murine and human hematopoietic progenitors"

8.35 GENERAL DISCUSSION

8.45 SHORT BREAK

8.55 – 9.35 *AAV Vectors*

8.55 A.W. Nienhuis, St Jude Children's Research Hospital, Memphis, TN
"Globin gene transfer by rAAV vectors"

9.20 Tim Townes, University of Alabama, Birmingham, AL
"Reactivation of silenced, virally transduced genes"

9.35 – 10.30 *Retroviral Vectors*

9.35 George Atweh, Mt. Sinai School of Medicine, New York, NY
"αLCR-based retroviral vectors for the gene therapy of β-globin disorders"

9.50 Michel Sadelain, Memorial-Sloan Kettering Cancer Centre, New York, NY
"Discordant human β-globin expression in MEL cells vs. long-term murine bone marrow chimeras"

10.05 Philippe LeBoulch, Harvard Medical School and Massachusetts Institute of Technology, Cambridge, MA
"Transfer of β-globin gene and β-LCR elements by classical retroviral transduction and by RCLI (Retrovirus and Cre/Lox-mediated integration)"

10.20 GENERAL DISCUSSION

SUNDAY, JUNE 16, 1996

7.00 – 8.15 am BREAKFAST – DISCOVERY HOUSE

8.30 – 12.30 **SESSION IV: TRANSCRIPTIONAL REGULATION**
Chairpersons: Stuart Orkin, Harvard Medical School, Boston, MA
James Shen, Academia Sinica

8.30 – 8.50 Steve Jane, The Royal Melbourne Hospital Research Foundation, Parkville, Australia
"Structure-function relationships of the SSP complex"

8.50 – 9.40 *Studies of EKLF*

8.50 James Bieker, Mount Sinai School of Medicine, New York, NY
"Functional analysis of the EKLF transcriptional activation domain"

9.10 Andrew Perkins, Children's Hospital, Boston, MA
"EKLF is required for competition of the human γ to βglobin switch"

9.25 Mark Wijgerde, Erasmus University, Rotterdam
"The role of EKLF in the β globin locus"

9.40 Cece Trainor, National Institutes of Health, Bethesda, MD
"Palindromic GATA sites in GATA-1 promoters: high affinity sites yield high expression levels"

9.55 John Cunningham, St Jude Children's Hospital, Memphis, TN
"Interactions of the enhancer binding protein NF-E2 with the transcription initiation complex"

10.10 Sjaak Philipsen, Erasmus University, Rotterdam, The Netherlands
"Transcription factors and erythropoiesis"

10.30 COFFEE BREAK

10.50 Mitch Weiss, Children's Hospital, Boston, MA
"Erythroid-specific properties of GATA-1"

11.10 Stuart Orkin, Harvard Medical School, Boston, MA
"Genetic manipulation of GATA-1 and its locus"

11.45 Frank Grosveld, Erasmus University, Rotterdam, The Netherlands
"Genetic manipulation of GATAs"

12.10 Masayuki Yamamoto, University of Tsukuba, Tsukuba, Japan
"Regulation of erythroid transcription factor genes"

12.30 – 1.10 pm **SESSION V: THERAPEUTIC INDUCTION OF FETAL HEMOGLOBIN BY HYDROXYUREA AND OTHER COMPOUNDS**
Chairperson: Frank Bunn, Harvard Medical School, Boston, MA

12.30 Griffin Rodgers, National Institutes of Health, Bethesda, MD
"Update on clinical trials of hydroxyurea in the severe beta-globin disorders"

12.50 Nancy Olivieri, Hospital for Sick Children, Toronto, Ontario, Canada
"Experience with hydroxyurea therapy in children with sickle cell disease"

1.00 GENERAL DISCUSSION

1.10 BREAK FOR LUNCH

1.10 – 2.45 LUNCH – DISCOVERY HOUSE

3.00 – 6.00 **POSTER SESSION B**

6.00 – 7.30 DINNER – DISCOVERY HOUSE

7.30 – 8.40 **SESSION VI: BLOOD EMBRYOGENESIS B**
Chairperson: Roger Patient, King's College, London, England

7.30 Roger Patient, King's College, London, England
"Regulation of haematopoiesis during embryogenesis in Xenopus and Zebrafish"

7.55 Elaine Dzierzak, National Institute of Medical Research, London, England
"Autonomous initiation of definitive hematopoiesis in the AGM region of the mouse embryo"

8.20 Margaret Baron, Harvard University
"Development and function of the embryonic yolk sac"

8.40 BREAK

8.55 – 9.45 pm **SESSION VII: THERAPEUTIC INDUCTION OF FETAL HEMOGLOBIN BY BUTYRATE AND OTHER SHORT CHAIN FATTY ACIDS**
Chairperson: Gordon Ginder, University of Minnesota, Minnesota, MN

8.55 Susan Perrine and George Atweh, Boston University Boston MA and Mt. Sinai Medical Centre, New York, NY
"Hematologic efficacy of pulse butyrate therapy: surpassing the 20% Hb F threshold"

9.15 Nancy Olivieri, Hospital for Sick Children, Toronto, Ontario, Canada
"Experience with sodium phenylbutyrate and hydroxyurea in thalassemia and experience with sodium valproate in sickle cell disease"

9.25 GENERAL DISCUSSION

MONDAY, JUNE 17, 1996

7.00 – 8.15 am BREAKFAST – DISCOVERY HOUE

8.30 am **SESSION VIII: GLOBIN CHROMATIN AND THE LCR**
Chairpersons: Frank Grosveld, Erasmus University, Rotterdam, The Netherlands
Mark Groudine, Fred Hutchinson Cancer Research Center, Seattle, WA

8.30 Gary Felsenfeld, National Institutes of Health, Bethesda, MD
"Establishing a transcriptionally active chromatin structure in the β-globin locus"

9.05 Peter Fraser, Erasmus University, Rotterdam, The Netherlands
"The LCR and transcription dynamics"

9.30 Steve Fiering, Fred Hutchinson Cancer Research Center, Seattle, WA
"Homologous recombination based analysis of murine-globin LCR function"

9.50 Elliott Epner, Fred Hutchinson Cancer Research Center, Seattle, WA
"Regulation of DNA replication in the β-globin locus"

10.10 Ross Hardison, The Pennsylvania State University, University Park, PA
"The domain opening activity of 5'HS3 of the human locus control region requires sequences outside the minimal core"

10.30 COFFEE BREAK

11.00 Doug Higgs, John Radcliffe Hospital, London, England
"Structural and functional analysis of the human α globin cluster"

11.25 Beverly Emerson, Salk Institute, San Diego, CA
"Transcriptional regulation of the β globin gene *in vitro*"

11.50 David Martin, Fred Hutchinson Cancer Research Center, Seattle, WA
"Enhancer action in globin gene regulation"

12.10 Emma Whitelaw, University of Sydney, Sydney, Australia
"Why do transgenes variegate?"

12.30 Chris Lowrey, Dartmouth-Hitchcock Medical Center, Lebanon, NH
"Manipulation of β-globin gene chromatin structure"

12.50 Emery Bresnick, University of Wisconsin-Madison, Madison, WI
"Requirements for long-range gene activation by the human beta-globin locus control region"

1.10 BREAK FOR LUNCH

1.15 – 2.45 LUNCH – DISCOVERY HOUSE

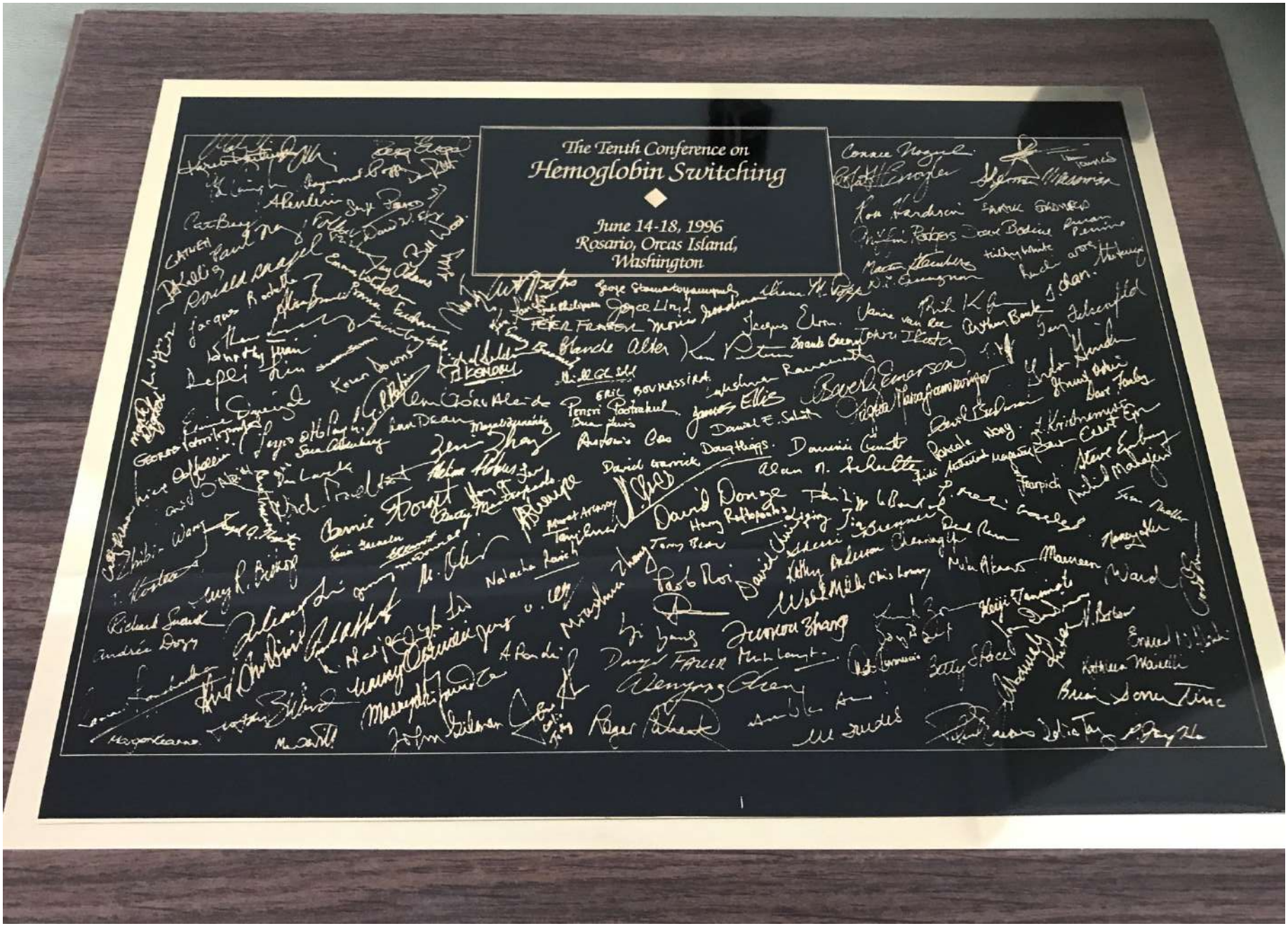
3.00 – 6.00 pm **POSTER SESSION III**

6.00 – 7.30 DINNER – DISCOVERY HOUSE

7.30 pm **SESSION X. PAPERS SELECTED FROM THE POSTERS**
Selection Committee:
Gary Felsenfeld, National Institutes of Health, Bethesda, MD
Stuart Orkin, Harvard Medical School, Boston, MA
Frank Grosveld, Erasmus University, Rotterdam, The Netherlands
Tariq Enver, Leukemia Research Fund Centre, London, England
George Stamatoyannopoulos, University of Washington, Seattle, WA

TUESDAY, JUNE 18, 1996

6.30 – 8.00 am BREAKFAST – DISCOVERY HOUSE


The Tenth Conference on
Hemoglobin Switching
June 14-18, 1996
Rosario, Orcas Island,
Washington

PROGRAM

The Eleventh Conference on

Hemoglobin Switching

October 2-6, 1998
Rosario, Orcas Island, Washington

FRIDAY, October 2, 1998

2.00 pm	DEPARTURE OF VICTORIA CLIPPER FROM PIER 69 IN SEATTLE
2.00 – 8.00 pm	REGISTRATION – DISCOVERY HOUSE
5.00 – 7.30 pm	NO HOST COCKTAILS – DISCOVERY CENTER
7.30 – 8.30 pm	DINNER

SATURDAY, OCTOBER 3, 1998

7.30 – 8.20 am	BREAKFAST – DISCOVERY CENTER
8.30	**SESSION I: BLOOD EMBRYOGENESIS** **Chairperson: Leonard Zon**
8.30	Leonard Zon, Children's Hospital, Boston, MA "Transcriptional factors that specify hematopoiesis during emrbyrogenesis"
8.45	*Discussion*
8.50	Alison Brownlie, Children's Hospital, Boston, MA "Using the zebrafish as a model to study globin gene expression"
9.00	*Discussion*
9.05	Shuo Lin, Medical College of Georgia, Augusta, GA "Systematic identification of novel hematopoietic genes using transgenic zebrafish"
9.25	*Discussion*
9.30	Roger Patient, King's College London, London, UK "Specification of blood mesoderm by GATA factors and SCL"
9.50	*Discussion*
9.55	Todd R. Evans, Albert Einstein College of Medicine, New York, NY "Regulation of embryonic erythropoiesis by BMPs"
10.10	*Discussion*

10.15 Margaret Baron, The Mount Sinai School of Medicine, New York, NY
"Induction of hematopoiesis and vasculogenesis by primitive endoderm signaling"

10.30 *Discussion*

10.35 COFFEE BREAK

11.00 SESSION II: ESTABLISHMENT OF HEMOPOIETIC LINEAGES
Chairperson: Thalia Papayannopoulou

11.00 Elaine Dzierzak, Erasmus University, Rotterdam, The Netherlands
"Emergence of the first hematopoietic stem cells from the AGM region of the mouse embryo"

11.20 *Discussion*

11.25 Mervin Yoder, University of Indiana, Indianapolis, IM
"Hematopoietic stem cell activity arises in the murine yolk sac prior to fetal liver hematopoiesis"

11.45 *Discussion*

11.50 Françoise Dieterlen-Lievre, College de France, France
"Developmental relationships of hemopoietic stem cells with endothelial cells in the embryo"

12.10 *Discussion*

12.15 Gordon Keller, National Jewish Center, Denver, CO
"Establishment of the primitive and definitive hematopoietic lineages"

12.35 *Discussion*

12.40 SESSION III: DEVELOPMENT OF GENE THERAPY FOR HEMOGLOBINOPATHIES
Chairperson: Arthur Nienhuis

12.40 David Bodine, National Institutes of Health, Bethesda, MD
"Stem cell gene therapy for hemoglobinopathies"

1.00 *Discussion*

1.05 BREAK FOR LUNCH

1.15 – 2.30 LUNCH – DISCOVERY HOUSE

2.30 – 6.00 pm POSTER SESSION I

6.00 – 7.30 DINNER – DISCOVERY HOUSE

7.30 pm SESSION III CONTINUES
Chairperson: Arthur Nienhuis

7.30 C. Anthony Blau, University of Washington, Seattle, WA
"In vivo selection using a cell growth switch"

7.45 *Discussion*

7.50 Brian Sorrentino, St Jude Children's Research Hospital, Memphis, TN
"In vivo selection of hematopoietic stem cells using DHFR-expressing vectors"

8.05 *Discussion*

8.10 David W. Russell, University of Washington, Seattle, WA
"Transduction of hematopoietic cells by foamy virus vectors"

8.25 *Discussion*

8.30 George Atweh, The Mount Sinai Medical School, New York, NY
"In vivo studies of HS-40-based globin retroviral vectors"

8.45 *Discussion*

8.50 James Ellis, Hospital for Sick Children, Toronto, Ontario, Canada
"Breaking the code of silence in retrovirus vectors"

9.05 *Discussion*

9.10 Philippe Leboulch, Harvard Medical School, Cambridge, MA
"High-level, long-term expression of human β-globin gene in mice following retroviral transfer: results and prospects"

9.25 *Discussion*

9.30 Keith Humphries, Terry Fox Laboratory, Vancouver, BC, Canada
"Analysis of gene transfer to in vivo repopulating cells"

9.45 *Discussion*

9.50 Michel Sadelain, Memorial Sloan-Kettering Cancer Center, New York, NY
"Strategies to overcome retroviral vector silencing"

10.50 *Discussion*

10.10 pm END OF SESSION

SUNDAY, OCTOBER 4, 1998

7.00 – 8.20 am BREAKFAST – DISCOVERY CENTER

8.30 am SESSION IV: TRANSCRIPTIONAL CONTROL OF HEMATOPOIESIS
Chairperson: Stuart Orkin

8.30 Ihor Lemischka, Princeton University, Princeton, NJ
"The molecular biology of hemopoietic stem cells and the microenvironment"

8.50 *Discussion*

8.55 Stuart Orkin, Children's Hospital, Boston, MA
"GATA-1: the first ten years"

9.20 *Discussion*

9.25 Gerd Blobel, Children's Hospital of Philadelphia, Philadelphia, PA
"Regulation of GATA-1 by CREB-binding protein (CBP)"

9.40 *Discussion*

9.45 Cece Trainor, National Institutes of Health, Bethesda MD
"The role of double GATA binding sites in hematopoiesis"

10.00 *Discussion*

10.05 Masayuki Yamamoto, University of Tsukuba, Tsukuba, Japan
"Regulation of GATA-1 gene expression"

10.20 *Discussion*

10.25 COFFEE BREAK

10.50 Paul-Henri Roméo, INSERM, Creteil, France
"Tal-1 binding motifs and target genes"

11.10 *Discussion*

11.15 Catherine Porcher, Children's Hospital, Boston, MA
"Structure/function study of the T-cell leukemia oncoproteins SCL/Tal-1"

11.30 *Discussion*

11.35 SESSION V: TRANSCRIPTIONAL CONTROL OF GLOBIN GENES I: EKLF FACTORS
Chairperson: Sherman Weissman

11.35 James J Bieker, Mount Sinai School of Medicine, New York, NY
"Modulation of EKLF activity by protein-protein interactions"

11.55 *Discussion*

12.00 Haruhiko Asano, University of Washington, Seattle, WA
"Cloning and characterization of a *Krüppel*-type factor activating ε and γ globin gene expression"

12.15 *Discussion*

12.20 John Cunningham, St Jude Children's Research Hospital, Memphis, TN
"Structure-function analysis of human EKLF"

12.35 *Discussion*

12.40 Sjaak Philipsen, Erasmus University, Rotterdam, The Netherlands
"EKLF and activation of the beta globin locus"

12.55 *Discussion*

1.00	Jay H. Chung, National Institutes of Health, Bethesda, MD "Studying in vivo recruitment of EKLF and chromatin remodeling complex BRG1 to beta-globin promoter by PIN*POINT"
1.10	*Discussion*
1.15	BREAK FOR LUNCH
1.30	LUNCH – DISCOVERY CENTER
2.30 – 6.00 pm	**POSTER SESSION II**
6.00 – 7.30	DINNER – DISCOVERY HOUSE
7.30 pm	**SESSION VI: TRANSCRIPTIONAL CONTROL OF GLOBIN GENES II: NFE2 AND OTHER TRANSCRIPTIONAL FACTORS** **Chairperson: YW Kan**
7.30	James Shen, Academia Sinica, Taipei, Taiwan "Modulation of an enhancer-promoter system during erythroid development"
7.45	*Discussion*
7.50	Emery Bresnick, University of Wisconsin-Madison, Madison, WI "Signaling mechanisms and coactivators that mediate β-globin locus control region function"
8.05	*Discussion*
8.10	Vincent Mignotte, INSERM, Creteil, France "Regulation of embryonic/fetal globin genes by nuclear hormone receptors: a novel perspective on hemoglobin switching"
8.25	*Discussion*
8.30	Steve Jane, Royal Melbourne Hospital, Parkville, Victoria, Australia "Identification of transcriptional regulators of γ gene expression using novel inducers of HbF"
8.45	*Discussion*
8.50	David O'Neill, Columbia University, New York, NY "Tissue- and developmental stage-specific DNA binding by a mammalian SWI/SNF complex at the human β globin locus"
9.00	*Discussion*
9.05 pm	**SESSION VII: FETAL HEMOGLOBIN SYNTHESIS** **Chairperson: George Dover**
9.05	Marie Trudel, Clinical Research Institute of Montreal, Quebec, Canada "Levels of fetal hemoglobin that affect in vivo sickling: insights from studies in transgenic mice"
9.20	*Discussion*

9.25 Susan Perrine, Boston University, Boston, MA
"Induction of fetal hemoglobin by butyrate and new derivatives of short chain fatty acids"

9.40 *Discussion*

9.45 Alan Schechter, National Institutes of Health, Bethesda, MD
"Results of screening for new classes of inducers of fetal hemoglobin synthesis"

10.00 *Discussion*

10.05 END OF SESSION

MONDAY, OCTOER 5, 1998

7.00 am BREAKFAST – DISCOVERY CENTER

8.30 am SESSION VIII: CONTROL OF THE α GLOBIN LOCUS
Chairperson: SL Thein

8.30 Bill Wood, John Radcliffe Hospital, Oxford, United Kingdom
"Expression of the human alpha globin cluster in transgenic mice"

8.50 *Discussion*

8.55 Doug Higgs, John Radcliffe Hospital, Oxford, United Kingdom
"Regulation of the alpha globin domain"

9.15 *Discussion*

9.20 J. Eric Russell, University of Pennsylvania, Philadelphia, PA
"Contribution of posttranscriptional mechanisms to efficient ζ- to ε-globin gene switching"

9.30 *Discussion*

9.35 am SESSION IX: GLOBIN GENE SWITCHING AND THE LOCUS CONTROL REGION I
Chairperson: George Stamatoyannopoulos

9.35 George Stamatoyannopoulos, University of Washington, Seattle, WA
"Studies of globin gene switching and the LCR"

9.55 *Discussion*

10.00 Frank Grosveld, Erasmus University, Rotterdam, The Netherlands
"LCR and position effects"

10.20 *Discussion*

10.25 COFFEE BREAK

10.50	Mark Groudine, Fred Hutchinson Cancer Research Center, Seattle, WA "What does the locus control region actually control?"
11.10	*Discussion*
11.15	Eric Bouhassira, Albert Einstein College of Medicine, Bronx, NY "The human β-globin promoter driven by LCR fragments is controlled by histone acetylation and methylation-dependent and independent regulatory mechanisms"
11.25	*Discussion*
11.30	Chris Lowrey, Dartmouth-Hitchcock Medical Center Lebanon, NH "Erythroid-specific chromatin structure reorganization within the human beta-globin locus"
11.45	*Discussion*
11.50	Adam C. Bell, National institutes of Health, Bethesda, MD "Insulators and boundaries in the chicken beta-globin locus"
12.05	*Discussion*
12.10	Emma Whitelaw, University of Sydney, Sydney, Australia "The inheritance of epigenetic modifications"
12.25	*Discussion*
12.30	David Martin, Fred Hutchinson Cancer Research Center, Seattle, WA "Autonomous and site-dependent effects of cis-acting control elements"
12.45	*Discussion*
12.50	Dorothy Tuan, Medical College of Georgia, Augusta, GA "An LTR of the human endogenous retrovirus Erv-9 is located in the 5' boundary area of the human β-globin locus control region"
1.05	*Discussion*
1.10	BREAK FOR LUNCH
1.15	LUNCH – DISCOVERY CENTER
2.30 – 6.00 pm	**POSTER SESSION III**
6.00 – 7.30	DINNER – DISCOVERY CENTER
7.30 pm	**SESSION X: GLOBIN GENE SWITCHING AND THE LOCUS CONTROL II** **Chairperson: Frank Grosveld**
7.30	Peter Fraser, Erasmus University, Rotterdam, The Netherlands "Globin switching in mouse and man"
7.50	*Discussion*

7.55	Tim Townes, University of Alabama, Birmingham, AL "Human γ-globin gene 5' flanking sequences essential for γ- to β-globin gene switching"
8.15	*Discussion*
8.20	Doug Engel, Northwestern University, Evanston, IL "Modulation of hemoglobin switching *in vivo*"
8.40	*Discussion*
8.45	Kenneth R. Peterson, University of Kansas, Kansas City, KS "*Cis*-control of globin gene switching resides in gene-specific sequences, as well as in gene order"
8.55	*Discussion*
9.00	Jorg Bungert, Northwestern University, Evanston, IL "Hypersensitive site 2 specifies a unique function within the human β-globin LCR to stimulate globin gene transcription"
9.10	*Discussion*
9.15	Karin Gaensler, University of California, San Francisco, CA "Deletion of putative regulatory sequence in the $^{A}\gamma$ to δ intergenic region in β globin YAC transgenic mice"
9.25	*Discussion*
9.30	Ann Dean, National Institutes of Health, Bethesda, MD "Transcriptional activation in chromatin: Structural and functional cross-talk between LCR HS2 and the ε-globin promoter"
9.40	*Discussion*
9.45	Ross Hardison, Pennsylvania State University, University Park, PA "Structure/function analysis of hypersensitive sites 2 and 3 of the beta-globin LCR"
10.00	*Discussion*
10.05	END OF CONFERENCE

TUESDAY, OCTOBER 6, 1998

6.30 – 7.30 am	BREAKFAST – DISCOVERY CENTER
7.30 am	DEPARTURE OF VICTORIA CLIPPER FOR SEATTLE

PROGRAM

The Twelfth Conference on
Hemoglobin Switching

June 9-13, 2000
Rosario, Orcas Island, Washington

FRIDAY, JUNE 9, 2000

1.00 pm	**DEPARTURE OF VICTORIA CLIPPER FROM PIER 69 IN SEATTLE**
1.00 – 8.00	REGISTRATION – DISCOVERY CENTER
5.00 – 7.30	NO HOST COCKTAILS – DISCOVERY CENTER
7.30 – 9.00 pm	**DINNER**

SATURDAY, JUNE 10, 2000

7.30 – 8.20 am	**BREAKFAST – DISCOVERY CENTER**
8.30 am	**SESSION I – GLOBIN GENE SWITCHING AND THE LCR** **Chairperson: George Stamatoyannopoulos**
8.30	Gary Felsenfeld, National Institutes of Health, Bethesda, MD *"Establishment and maintenance of chromatin boundaries"*
8.50	Discussion
8.55	Frank Grosveld, Erasmus University, Rotterdam, The Netherlands *"Globin chromatin and transcriptional activation"*
9.15	Discussion
9.20	Mark Groudine, Fred Hutchinson Cancer Research Center, Seattle, WA *"The β locus domain"*
9.40	Discussion
9.45	Tim Townes, University of Alabama at Birmingham, Birmingham, AL *Chromatin structure and transcription of the globin locus in HS1 to 4 knockout mice"*
10.00	Discussion
10.05	Michael McArthur, University of Washington, Seattle, WA *"Naturally occurring deletions within the LCR of β-thalassaemia patients"*
10.15	Discussion
10.18	Chris Lowrey, Dartmouth College, Hanover, NH *"Erythroid-specific chromatin structure reorganization within the human β-globin gene locus"*
10.30	Discussion

10.35	**COFFEE BREAK**
11.00 am	**SESSION I – GLOBIN GENE SWITCHING AND THE LCR (Continues)** **Chairperson: Gary Felsenfeld**
11.00	Peter Fraser, The Babraham Institute, Babraham, England *"Intergenic transcription and developmental remodelling of chromatin subdomains in the human β globin locus"*
11.15	Discussion
11.20	Nick Proudfoot, University of Oxford, Oxford, England *"LCR and intragenic transcripts in the human β-globin gene cluster"*
11.35	Discussion
11.40	Emery Bresnick, University of Wisconsin, Madison, WI *"Coactivator requirements for the enhancer function of the β-globin LCR"*
11.55	Discussion
12.00	Kenneth R. Peterson, University of Kansas Medical Center, Kansas City *"Cis-control of globin gene switching resides in gene-specific sequences, as well as in gene order"*
12.12	Discussion
12.15	Dorothy Tuan, Medical College of Georgia, Augusta, GA *"A transcription mechanism of LCR function: ERV-9 LTR and the HS2 enhancer in transcriptional regulation of cis-linked genes"*
12.30	Discussion
12.35 pm	**SESSION II – GENE SILENCING AND POSITION EFFECTS** **Chairperson: Ann Dean**
12.35	Gordon Ginder, Virginia Commonwealth University, Richmond, VA *"DNA methylation mediated gene silencing mechanisms in primary erythroid cells"*
12.47	Discussion
12.50	Eric E. Bouhassira, Albert Einstein College of Medicine, Bronx, NY *"Linker histones might mediate position effects that are dominant over the full LCR in transgenic mice"*
1.02	Discussion
1.05	Emma Whitelaw, University of Sydney, Sydney, New South Wales, Australia *"Epigenetic inheritance in mammals"*
1.20	Discussion
1.25	End of Session
1.30 – 2.45	LUNCH – DISCOVERY CENTER
3.00 – 5.30	POSTER SESSION I
6.00 – 7.15	DINNER – DISCOVERY CENTER

SATURDAY EVENING, JUNE 10, 2000

7.30 pm	**SESSION III – GENE THERAPY OF HEMOGLOBINOPATHIES** **Chairperson: David Bodine**
7.30	Dave Bodine, National Institutes of Health, Bethesda, MD *"Novel and not-so-novel vectors for gene therapy of hemoglobinopathies"*
7.45	Discussion
7.50	David W. Emery, University of Washington, Seattle, WA *"Chromatin insulators for globin gene vectors"*
8.05	Discussion
8.10	Michel Sadelain, Memorial Sloan-Kettering Cancer Center, New York, NY *"Therapeutic levels of hemoglobin produced in bone marrow chimeras expressing Lentivirus-encoded human β-globin"*
8.25	Discussion
8.30	James Ellis, Hospital for Sick Children, Toronto, ON, Canada *"Silencing of retro/lentivectors"*
8.45	Discussion
8.50	COFFEE BREAK

9.10 pm	**SESSION III – GENE THERAPY OF HEMOGLOBINOPATHIES (continues)** **Chairperson: Ron Nagel**
9.10	George Atweh, Mount Sinai School of Medicine, New York, NY *"Modifications to improve globin retrovirus vector"*
9.25	Discussion
9.30	Derek Persons, St Jude Children's Research Hospital, Memphis, TN *"In vivo selection strategies for treatment of β thalassemia"*
9.45	Discussion
9.50	Philippe Leboulch, Harvard Medical School and MIT, Cambridge, MA *"Globin retroviral and lentiviral vectors resistant to silencing and variegation"*
10.05	Discussion
10.10	End of Session

SUNDAY, JUNE 11, 2000

7.00 – 8.20 am **BREAKFAST – DISCOVERY CENTER**

8.30 am **SESSION IV – CONTROL OF α GLOBIN GENES**
Chairperson: Bill Wood

8.30 Douglas Higgs, University of Oxford, Oxford, England
"Differences in the regulation of α and β globin expression"

8.50 Discussion

8.55 Steve Liebhaber, University of Pennsylvania, Philadelphia, PA
"Role of mRNA stabilization in the expression and developmental control of the human α-globin gene cluster"

9.10 Discussion

9.15 am **SESSION V – FETAL HEMOGLOBIN**
Chairperson: George Dover

9.15 S.L. Thein, University of Oxford, Oxford, England
"Identification of factors regulating Hb F production: a genetic approach"

9.30 Discussion

9.35 Eva Skarpidi, University of Washington, Seattle, WA
"New inducers of fetal hemoglobin synthesis"

9.45 Discussion

9.50 Millicent Sutton, Mount Sinai School of Medicine, New York, NY
"Synergy between butyrate and hydroxyurea and reversal of end-organ damage in sickle cell disease

10.00 Discussion

10.05 Susan Perrine, Boston University, Boston, MA
"Fetal globin induction by short chain fatty acids in thalassemia"

10.20 Discussion

10.25 **COFFEE BREAK**

10.55 am **SESSION VI – STEM CELL BIOLOGY**
Chairperson: Thalia Papayannopoulou

10.55 Emanuela Gussoni, Children's Hospital, Boston, MA
"Isolation and characterization of stem cells from mouse skeletal muscle"

11.10 Discussion

11.15 Nobuko Uchida, Stem Cells Inc., Sunnyvale, CA
"Isolation and characterization of human central nervous system stem cell"

11.30 Discussion

11.35	Ihor Lemischka, Princeton University, Princeton, NJ *"The genetic program of hematopoietic stem cells and microenvironments"*
11.50	Discussion
11.55	Tony Blau, University of Washington, Seattle, WA *"Selection of transduced stem cells"*
12.10	Discussion
12.15	Brian Sorrentino, St Jude Children's Research Hospital, Memphis, TN *"A functional role for a novel ABC transporter in stem cells"*
12.30	Discussion
12.35	**Short Break**
12.45 pm	**SESSION VII – BLOOD EMBRYOGENESIS** **Chairperson: Roger Patient**
12.45	Elaine Dzierzak, Erasmus University, Rotterdam, The Netherlands *"De(re)constructing the AGM"*
1.00	Discussion
1.05	Gordon Keller, Mount Sinai School of Medicine, New York, NY *"Development of the hemangioblast"*
1.20	Discussion
1.25	End of Session
1.30 – 2.45	LUNCH – DISCOVERY HOUSE
3.00 – 5.30	**POSTER SESSION II**
6.00 – 7.15	DINNER – DISCOVERY HOUSE
7.30 pm	**SESSION VII: BLOOD EMBRYOGENESIS (continues)** **Chairperson: Len Zon**
7.30	Len Zon, HHMI, Children's Hospital, Boston, MA *"Dissecting hematopoiesis in the zebrafish"*
7.45	Discussion
7.50	Roger Patient, University of Nottingham, Nottingham, England *"Origins and programming of haematopoietic stem cells in fish and frog embryos"*
8.05	Discussion
8.10	Todd Evans, Albert Einstein College of Medicine, Bronx, NY *"Regulation of embryonic hematopoiesis by bmp signalling"*
8.25	Discussion
8.30	Shuo Lin, Medical College of Georgia, Augusta, GA *"Positive and negative regulation of erythropoiesis"*
8.45	Discussion

8.50 **COFFEE BREAK**

9.10 Thierry Jaffredo, College de France, Nogent-Sur-Marne, France
"Hemopoietic emergence into the embryo: a molecular morphogenetic study"

9.25 Discussion

9.30 Nancy Speck, Dartmouth College, Hanover, NH
"Definitive hematopoiesis: Runx1 marks the spot"

9.45 Discussion

9.50 Margaret Baron, Mount Sinai School of Medicine, New York, NY
"Endoderm-Mesoderm interactions in hematopoiesis and vasculogenesis"

10.05 Discussion

10.10 End of Session

MONDAY, JUNE 12, 2000

7.00 – 8.20 am **BREAKFAST – DISCOVERY CENTER**

8.30 am SESSION VIII – TRANSCRIPTIONAL CONTROL OF ERYTHROPOIESIS I
Chairperson: Stuart Orkin

8.30 Stuart Orkin, Children's Hospital, Boston, MA
"Modulation of GATA function"

8.50 Discussion

8.55 Masayuki Yamamoto, University of Tsukuba, Tsukuba, Japan
"Regulation of mouse GATA-1 and GATA-2 genes"

9.10 Discussion

9.15 Tariq Enver, Institute of Cancer Research, London, England
"Potentiation of GATA-2 activity"

9.30 Discussion

9.35 Cecelia Trainor, National Institutes of Health, Bethesda, MD
"GATA zinc fingers modulate transactivation"

9.50 Discussion

9.55 Mitchell Weiss, Children's Hospital of Philadelphia, Philadelphia, PA
"Identification of novel GATA-1 erythroid target genes"

10.10 Discussion

10.15 Gerd Blobel, Children's Hospital of Philadelphia, Philadelphia, PA
"Function of coactivators during erythroid gene expression"

10.30 Discussion

10.35 **COFFEE BREAK**

11.00 am	**SESSION IX – TRANSCRIPTIONAL CONTROL OF ERYTHROPOIESIS II** **Chairperson: Connie Noguchi**
11.00	Doug Engel, Northwestern University, Evanston, IL *"Small Maf regulation of hematopoiesis"*
11.15	Discussion
11.20	Paul-Henri Romeo, INSERM U.474, Paris, France *"Unexpected function of erythroblasts in the bone marrow"*
11.35	Discussion
11.40	Sjaak Philipsen, Erasmus University, Rotterdam, The Netherlands *"REDS, a signal regulating erythroid differentiation in the erythroblastic island"*
11.50	Discussion
11.55	James Shen, Academia Sinica, Taipei, Taiwan *"Novel coregulators interacting with erythroid specific DNA-binding transcription factors"*
12.15	Discussion
12.20	David O'Neill, Columbia University, New York, NY *"An Ikaros-containing chromatin remodelling complex in adult-type erythroid cells"*
12.30	Discussion
12.35 pm	**Short Break**
12.45 pm	**SESSION X – TRANSCRIPTIONAL CONTROL OF GLOBIN GENES: FETAL GLOBIN GENE FACTORS** **Chairperson: Jerry Lingrel**
12.45	Steve Jane, The Royal Melbourne Hospital, Parkville, Victoria, Australia *"Regulation of fetal globin expression by NF-E4"*
1.00	Discussion
1.05	Haru Asano, Nagoya University, Nagoya, Japan *"FKLF-2: A novel Krüppel-like transcriptional factor that activates globin and other erythroid lineage genes"*
1.20	Discussion
1.25	End of Session
1.30 – 2.45	**LUNCH – DISCOVERY CENTER**
3.00 – 5.30	**POSTER SESSION III**
6.00 – 7.15	**DINNER – DISCOVERY CENTER**

7.30 pm **SESSION XI – TRANSCRIPTIONAL CONTROL OF GLOBIN GENES: EKLF**
Chairperson: James Bieker

7.30 Shilpa Kadam, The Salk Institute, La Jolla, CA
"EKLF-dependent chromatin remodelling and transcriptional activation with recombinant SWI/SNF complexes"

7.45 Discussion

7.50 Jay Chung, National Institutes of Health, Bethesda, MD
"Differential recruitment of EKLF to γ- and β-globin promoters"

8.05 Discussion

8.10 Xiaoyong Chen, Mount Sinai School of Medicine, New York, NY
"Novel EKLF protein-protein interactions"

8.25 Discussion

8.30 Arthur van den Wijngaard, Erasmus University, Rotterdam, The Netherlands
"EKLF levels and globin gene switching: importance of gene order and distance to the LCR"

8.45 Discussion

8.50 **COFFEE BREAK**

9.10 pm **SESSION XI – TRANSCRIPTIONAL CONTROL OF GLOBIN GENES: EKLF (continues)**
Chairperson: Deborah Gumucio

9.10 Lee Wall, University of Montreal, Montreal, Quebec, Canada
"Where does EKLF act?"

9.25 Discussion

9.30 Andrew Perkins, Monash University, Clayton, Victoria, Australia
"A minimal domain upstream of the zinc fingers is sufficient for EKLF's activity in vivo"

9.45 Discussion

9.50 John Cunningham, St Jude Children's Research Hospital, Memphis, TN
"Studies of EKLF function at the endogenous β globin promoter"

10.05 Discussion

10.10 James Bieker, Mount Sinai School of Medicine, New York, NY
"EKLF regulation"

10.25 Discussion

10.30 End of Session

TUESDAY, JUNE 13, 2000

6.30 -7.30 am **BREAKFAST – DISCOVERY CENTER**

7.30 am **DEPARTURE OF VICTORIA CLIPPER FOR SEATTLE**


12 conference


12 conference

13th CONFERENCE ON HEMOGLOBIN SWITCHING
St John's College Oxford 2002

FINAL PROGRAMME

13TH Conference on Hemoglobin Switching
September 26 – 30, 2002
St. John's College, Oxford, United Kingdom

Thursday, September 26th

1.00 – 7.00 pm REGISTRATION – ST JOHN'S COLLEGE

6.00 – 7.00 pm NO HOST COCKTAILS – ST JOHN'S COLLEGE

7.00 pm DINNER – DINING HALL, ST JOHN'S COLLEGE

Friday, September 27th

7.30 – 8.30 am BREAKFAST – DINING HALL, ST JOHN'S COLLEGE

8.30 am **CHROMATIN AND THE LCR**
Chair: Bernie Forget / Margaret Baron

8.30 am Gary Felsenfeld
"Analysis of chromatin domain boundaries

9.00 am Michael Bender
"The activation of β-globin gene expression"

9.25 am Tim Townes
"Insertion of human HS3 in DHS1-4 mice restores wild-type β-globin gene expression"

9.50 am Peter Fraser
"Long-range contact between the LCR and globin genes *in vivo*"

10-15 – 10.35 COFFEE BREAK

Chair: Nick Proudfoot / Connie Noguchi

10.35 am Wouter de Laat
"Bidirectional activation of mouse genes surrounding an integrated human LCR"

10.50 am Eric Bouhassira
"Transcriptional oscillation, timing of replication and methylation. A unified theory of position effects"

11.05 am Jo Bungert
"Recruitment of transcription complexes to the human β-globin locus"

11.20 am Kenneth Peterson
"Role of γ-globin gene silencing and chromatin sub-domains in globin gene switching"

11.35 am	Qiliang Li "Development-specific epigenetic code alteration induced by mutations in the human γ-globin gene promoter"
11.50- 12.10	COFFEE BREAK
	Chair: Bill Wood / Ann Dean
12.10 pm	Frank Grosveld "Globin gene activation: a stochastic process"
12.35 pm	Stephen Liebhaber "Roles of LCR determinants in long-range gene activation"
1.00 pm	Niall Dillon "Heterogeneous organisation of LCRs and functional domains"
1.30 – 2.30 pm	LUNCH – DINING HALL, ST JOHN'S COLLEGE
2.30 – 6.00 pm	POSTER SESSION I
	BREAK-OUT SESSION – "RESEARCH FUNDING OPPORTUNITIES FROM NIDDK (Terry Bishop)
6.00 – 7.30 pm	DINNER – DINING HALL, ST JOHN'S COLLEGE
7.30 pm	**DEVELOPMENTAL HAEMATOPOIESIS** **Chair: Thalia Papayannopoulou / Tony Green**
7.30 pm	Elaine Dzierzak "AGM HSCS: Origins and genetic program"
7.55 pm	Margaret Baron "Embryonic induction of hematopoiesis and vasculogenesis"
8.15 pm	Leonard Zon "Haematopoietic stem cell induction in Zebrafish"
8.40 – 8.50 pm	COFFEE BREAK
8.50 pm	Roger Patient "The origins and programming of adult and embryonic blood in Xenopus and Zebrafish"
9.10 pm	Todd Evans "Regulation of embryonic erythropoiesis by the BMP signalling pathway"
9.25 pm	Tariq Enver "Transcriptional programming and reprogramming in haematopoietic stem cells"
9.50 pm	FINISH

Saturday, September 28th

7.30 – 8.30 am BREAKFAST – DINING HALL, ST JOHN'S COLLEGE

8.30 am **TRANSCRIPTIONAL CONTROL OF HAEMATOPOIESIS AND GLOBIN REGULATION**
Chair: Anna Rita Migliaccio / Paresh Vyas

8.30 am Stuart Orkin
"Transcriptional control of erythroid development"

9.00 am Masayuki Yamamotoj
"*In vivo* function of GATA-1 and GATA-2 – transgenic complementation rescue analysis of transcription factor function"

9.25 am Gerd Blobel
"Control of tissue-specific gene expression by GATA-1 and FOG-1: Role of Ets transcription factors"

9.45 – 10.05 am COFFEE BREAK

Chair: Stuart Orkin / Jon Frampton

10.05 am Cecelia Trainor
"The actions and interactions of GATA zinc fingers"

10.20 am John Strouboulis
"Characterization of GATA-1 protein complexes"

10.35 am Paul-Henri Roméo
"bHLH dependent and independent functions of TAL-1 in adult hematopoiesis"

11.00 am Catherine Porcher
"Molecular dissection of SCL helix-loop-helix domain"

11.15 am John Crispino
"MTB, a novel co-repressor of hematopoietic bHLH proteins that promotes erythroid cell differentiation"

11.30 – 11.50 am COFFEE BREAK

Chair: Jim Bieker / Elaine Dzierzak

11.50 am Doug Engel
"The DRED Repressor"

12.15 pm Claire Francastel
"Compartmentalization of NF-E2 subunits during erythroid differentiation"

12.30 pm Merlin Crossley
"Basic Krüppel-like factor recruits multiple co-repressors to silence gene expression"

12.45 pm Haruhiko Asano
"Identification of a new Krüppel-type zinc finger protein that enhances expression of embryonic/fetal globin genes from the endogenous locus"

1.00 pm Stephen Jane
"The role of NF-E4 in fetal globin activation and silencing"

1.30 – 2.30 pm LUNCH – DINING HALL, ST JOHN'S COLLEGE

2.30 – 6.00 pm POSTER SESSION II

BREAK-OUT SESSION "EC, NETWORK OF EXCELLENCE"
(Sjaak Philipsen)

6.00 – 7.00 pm DINNER – DINING HALL, ST JOHN'S COLLEGE

7.30 pm **CO-REGULATORS OF GENE EXPRESSION**
Chair: Gary Felsenfeld / Cecelia Trainor

7.30 pm Tony Kouzarides
"Histone modifications in transcriptional control"

8.00 pm Emery Bresnick
"Native nucleoprotein structure of the endogenous murine β-globin locus"

8.20 – 8.30 pm COFFEE BREAK

8.30 pm Chao-Zheng Song
"Functional interplay between CBP and PCAF in acetylation and regulation of transcription factor FKLF2 activity"

8.45 pm Ann Dean
"Recruitment of chromatin modifying complexes to a globin promoter"

9.00 pm John Cunningham
"ALY, a component of the stage selector protein (SSP) provides a link to the transcriptional machinery at the γ-globin gene promoter"

9.15 pm Shilpa Kadam
"Selective gene regulation by chromatin remodelling complexes during differentiation"

9.30 pm FINISH

Sunday, September 29th

7.30 – 8.30 am BREAKFAST – DINING HALL, ST JOHN'S COLLEGE

8.30 am **THE ROLE OF KLFs IN HAEMOPOIESIS AND GLOBIN REGULATION**
Chair: Gordon Ginder / Sjaak Philipsen

8.30 am James Bieker
"Protein interactions play a crucial role in modulating EKLF activity"

8.55 am	C-K. James Shen "Multiple protein-DNA complex(es) and globin gene regulation"
9.15 am	Patrick Gallagher "Decreased mRNA expression and altered chromatin configuration of non-globin erythroid Krupple-like factor (EKLF) target genes in EKLF-deficient mice"
9.35 am	Andrew Perkins "Novel insights into the role of EKLF and related factors in haemoglobin switching using EKLF null cell lines"
9.55 – 10.15 am	COFFEE BREAK
	REGULATION AND MODIFICATION OF α GLOBIN GENE EXPRESSION **Chair: Doug Higgs / Ross Hardison**
10.15 am	Eduardo Anguita "Deletion of the mouse α globin regulatory element (HS -26) has an unexpectedly mild phenotype"
10.30 am	Paul Ney "Role of Nfe2 binding sites in alpha-globin gene regulation"
10.45 am	Cristina Tufarelli "RNA mediated silencing and methylation of the α globin gene"
11.05 am	Mitchell Weiss "Protecting haemoglobin"
11.25 – 11.40	COFFEE BREAK
	THE CONTROL OF FETAL HEMOGLOBIN **Chair: George Dover / Swee Lay Thein**
11.40 am	Hua Cao "Histone deacetylase inhibitors are strong inducers of γ globin gene expression"
12.00 noon	Betty Pace "Short chain fatty acid derivatives induce fetal globin expression and erythropoiesis *in vivo*"
12.15 pm	Millicent Sutton Pharmacologic induction of hemoglobin F in sickle cell disease and beta thalassemia"
12.30 pm	Joseph DeSimone "Subcutaneous 5-AZA-2'-deoxycytidine is well tolerated and produces robust increases in fetal haemoglobin"
12.45 pm	Nick Anagnou "Molecular mechanisms of fetal globin gene activation and silencing"
1.00 – 2.30 pm	LUNCH – DINING HALL, ST JOHN'S COLLEGE

GENE THERAPY FOR HEMOGLOBINOPATHIES AND THALASSEMIA
Chair: Arthur Nienhuis / Ron Nagel

2.30 pm David Bodine
"New strategies to develop gene transfer therapy for hemoglobinopathies"

2.50 pm David Emery
"Oncoretrovirus vectors for human gamma globin"

3.10 pm James Ellis
"Retrovirus silencing, memory and insulation by cHS4"

3.30 pm Michel Sadelain
"Cure of murine β-thalassemia intermedia and lethal β^o-thalassemia by Lentivirus-mediated globin gene transfer"

3.50 – 4.10 pm COFFEE BREAK

Chair: Griffin Rodgers / Alan Schechter

4.10 pm Philippe Leboulch
"Pan-erythroid beta-globin expression at therapeutic levels by multiple lentiviral integration or insulation"

4.30 pm Derek Persons
"Development of selectable, gamma-globin lentiviral vectors for gene therapy of the hemoglobin disorders"

4.50 pm Tony Blau
"Pharmacologically regulated cell therapy"

GENOMICS AND GLOBIN GENE REGULATION
Chair: Sherman Weissman / Jeffery Miller

5.10 pm Ross Hardison
"Lessons from the alignment of human and mouse genomes: finding candidate functional sequences despite variation in conservation"

5.25 pm Sjaak Philipsen
"Comparative analysis of globin loci in pufferfish and man suggests a common origin of vertebrate globin loci and reveals a novel mammalian globin locus"

5.40 pm FINISH

6.30 pm DRINKS RECEPTION

7.30 pm OFFICIAL DINNER – DINING HALL, ST JOHN'S COLLEGE
Guest Speaker – Sir David Weatherall

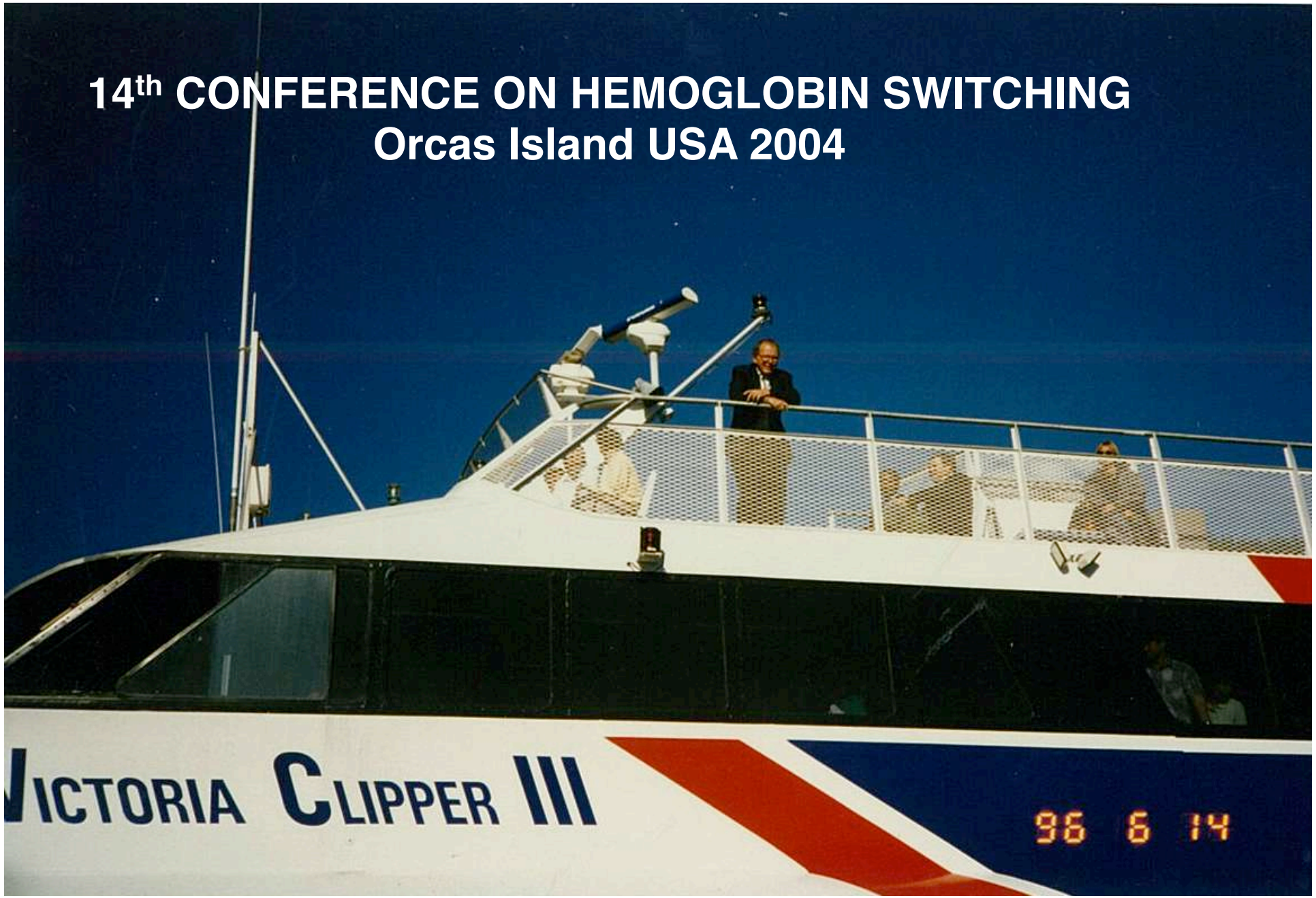
Monday, September 30th

7.30 – 8.30 am BREAKFAST – DINING HALL, ST JOHN'S COLLEGE

DEPART

The 13th Conference Moved to St John's College Oxford UK

14th CONFERENCE ON HEMOGLOBIN SWITCHING
Orcas Island USA 2004



PROGRAM

The Fourteenth Conference on
Hemoglobin Switching

September 10-14, 2004
Rosario, Orcas Island, Washington

FRIDAY, SEPTEMBER 10, 2004

1.00 PM	**DEPARTURE OF VICTORIA CLIPPER FROM PIER 69 IN SEATTLE**
100 – 8.00	REGISTRATION – DISCOVERY CENTER
5.00 – 7.30	NO HOST COCKTAILS – DISCOVERY CENTER
7.30 – 9.00	**DINNER**

SATURDAY, SEPTEMBER 11, 2004

7.15 – 8.20 AM **BREAKFAST**

8.30 AM **SESSION I – DEVELOPMENTAL HEMATOPOIESIS**
Chairperson: Elaine Dzierzak

8.30-8.50 Roger Patient, University of Nottingham, Nottingham, England
"Adult red cells are programmed completely independently of embryonic red cells during development"

8.55-9.15 Leonard Zon, HHMI, Children's Hospital, Boston, MA
"Dissecting erythropoiesis using the zebrafish"

9.20-9.40 Elaine Dzierzak, Erasmus University, Rotterdam, The Netherlands
"Genes, cytokines and the AGM microenvironment"

9.45-10.00 James Palis, University of Rochester, Rochester, NY
"Primitive erythropoiesis: An orphan lineage"

10.05 AM **Coffee Break**

10.30 AM **SESSION II – STEM CELLS**
Chairperson: Thalia Papayannopoulou

10.30-10.50 Daniel Kaufman, University of Minnesota, Minneapolis, MN
"Human embryonic stem cells as a model for hematopoiesis"

10.55-11.15 Gerald de Haan, University of Groningen, Groningen, The Netherlands
"Genetics of variation in genome-wide gene expression in hematopoietic stem cells"

11.20-11.40 Tariq Enver, University of Oxford, United Kingdom
"Development impact of leukaemia-associated chimaeric transcription factors on stem cell fate"

11.45-12.05 Keith Humphries, Terry Fox Laboratory, Vancouver, BC, Canada
"Emerging methods for large-scale expansion of hematopoietic stem cells"

12.10 PM Coffee Break

12.30 PM SESSION III – TRANSCRIPTIONAL CONTROL OF HEMATOPOIESIS
Chairperson: Stuart Orkin

12.30-12.50 Stuart Orkin, Children's Hospital, Boston, Massachusetts
"Studies of GATA-1 function"

12.55-1.15 Paul-Henri Romeo, INSERM U.474, Paris, France
"The erythropoietin signaling is acting on the GATA-1 transcriptional activity"

1.20 PM Break for Lunch

3.00 – 6.00 PM POSTER SESSION I

6.00 – 7.30 PM Dinner

7.30 PM SESSION III – TRANSCRIPTIONAL CONTROL OF HEMATOPOIESIS (continues)
Chairperson: Stuart Orkin

7.30-7.45 Gerd Blobel, Children's Hospital of Philadelphia, Philadelphia, PA
"Transcriptional regulation by GATA-1 and FOG-1"

7.50-8.05 Paresh Vyas, University of Oxford, United Kingdom
"Transcriptional regulation of GATA-1 expression"

8.10-8.25 John Strouboulis, Erasmus University, Rotterdam, The Netherlands
"Characterization of GATA-1 complexes"

8.30-8.45 Mitchell Weiss, Children's Hospital of Philadelphia, Philadelphia, PA
"Global regulation of erythroid gene expression by transcription factor GATA'1"

8.50 PM Coffee Break

9.10 PM SESSION III – TRANSCRIPTIONAL CONTROL OF HEMATOPOIESIS (continues)
Chairperson: Cecelia Trainor

9.10-9.25 Catherine Porcher, University of Oxford, United Kingdom
"The bHLH protein SCL/TAL-1 interacts with the co-repressor ETO-2 in erythroid cells and megakaryocytes"

9.30-9.45 Hozumi Motohashi, University of Tsukuba, Tsukuba, Japan
"Identification of a novel functional domain conferring positive and negative regulatory properties of MafG"

9.50-10.05 Paul Ney, St Jude Children's Research Hospital, Memphis, TN
"Mechanisms of erythroid differentiation: Lessons from the friend virus model"

10.10-10.25 Patrick Gallagher, Yale University, New Haven, CT
"Multiple defects in erythroid gene expression in erythroid Kruppel-like factor (EKLF) target genes in EKLF-deficient mice"

SUNDAY, SEPTEMBER 12, 2004

7.15 – 8.20 AM Breakfast

8.30 AM SESSION III – TRANSCRIPTIONAL CONTROL OF HEMATOPOIESIS (continues)
Chairperson: Sergio Ottolenghi

8.30-8.50 Emery Bresnick, University of Wisconsin, Madison, WI
"Transcriptional control via GATA switches"

8.55-9.15 Masayuki Yamamoto, University of Tsukuba, Tsukuba, Japan
"Fine regulation of GATA-1 and GATA-2 gene expression in vivo"

9.20 AM SESSION IV – GENOMICS
Chairperson: Doug Higgs

9.20-9.40 Doug Higgs, University of Oxford United Kingdom
"Comparison of the structure and function of the alpha globin cluster throughout evolution"

9.45-10.05 Ross Hardison, Pennsylvania State University, University Park, PA
"Genome-wide prediction and validation of erythroid cis-regulatory modules"

10.10-10.30 John Stamatoyannopoulos, Regulome, Seattle, WA
"Large scale identification and computational prediction of DNaseI HSs"

10.35 AM Coffee Break

11.05 AM SESSION V – CHROMATIN, LCR, SWITCHING
Chairperson: Gary Felsenfeld

11.05-11.30 Gary Felsenfeld, National Institutes of Health, Bethesda, MD
"Division of labor at chromatin boundaries"

11.35-11.50 Ann Dean, National Institutes of Health, Bethesda, MD
"Enhancers and insulators: intertwined functions"

11.55-12.15 Frank Grosveld, Erasmus University, Rotterdam, The Netherlands
"Regulation of the human beta globin locus"

12.20 PM Coffee Break

12.40-1.00 Tim Townes, University of Alabama at Birmingham, Birmingham, AL
"LCR regulation of globin gene expression"

1.05-1.20 Michael Bender, Fred Hutchinson Cancer Research Center, Seattle, WA
"The role of beta-globin locus hypersensitive sites"

1.25 PM **Brea for Lunch**

3.00 – 6.00 PM **POSTER SESSION II**

6.00 PM **Dinner**

7.30 PM **SESSION V – CHROMATIN, LCR, SWITCHING (continues)**
Chairperson: Frank Grosveld

7.30-7.45 Wouter de Laat, Erasmus University, Rotterdam, The Netherlands
"Spatial organization of gene expression"

7.50-8.05 Qiliang Li, University of Washington, Seattle, WA
"Hemoglobin switching and the chromatin facilitated looping mechanism"

8.10-8.25 Dorothy Tuan, Medical College of Georgia, Augusta, Georgia
"Functional mechanism of the ERV-9 LTR and the HS2 enhancers in the human β-globin gene locus"

8.30-8.45 Kenneth R. Peterson, University of Kansas Medical Center, Kansas City
"LCR HS specificity for globin gene activation"

8.50 PM **Coffee Break**

9.20 PM **SESSION V – CHROMATIN, LCR, SWITCHING (continues)**
Chairperson: Claire Francastel

9.20-9.35 Jorg Bungert, University of Florida, Gainesville, FL
"In vitro and in vivo characterization of the adult beta-globin downstream promoter region"

9.40-9.55 Keiji Tanimoto, University of Tsukuba, Tsukuba, Japan
"Genomic imprinting recapitulated in the human beta-globin locus"

10.00-10.15 Steven Fiering, Dartmouth University, Lebanon, NH
"Transcriptional interference/gene competition in the murine β-globin locus"

MONDAY, SEPTEMBER 13, 2004

7.15 – 8.20 AM **Breakfast**

8.30 AM **SESSION V – CHROMATIN, LCR, SWITCHING (continues)**
Chairperson: Tim Townes

8.30-8.50 Peter Fraser, The Babraham Institute, Babraham, United Kingdom
"Globin gene transcription: What's the Hubbub?"

8.55-9.10 Depei Liu, Chinese Academy of Medical Sciences and Peking Union Medical College, PR China
"Erythroid-specific active chromatin hub forms in a clustered housekeeping-gene compartment"

9.15-9.30 David Bodine, National Institutes of Health, Bethesda, MD
"The chromatin domain of the erythroid ankyrin promoter"

9.35-9.50 Christopher Lowrey, Dartmouth College, Hanover, New Hampshire
"Regulation of the epigenetic structure of the human beta-globin gene locus"

9.55-10.10 Gordon Ginder, Virginia Commonwealth University, Richmond, VA
"DNA methylation and maintenance of embryonic globin gene silencing"

10.15 AM Coffee Break

10.45 AM SESSION VI – TRANSCRIPTIONAL CONTROL OF GLOBIN GENES
Chairperson: Doug Engel

10.45-11.05 Doug Engel, University of Michigan, Ann Arbor, MI
"DRED repression of globin gene transcription"

11.10-11.30 James Bieker, Mount Sinai School of Medicine, New York, NY
"EKLF's journey from synthesis to cellular localization"

11.35-11.50 Sjaak Philipsen, Erasmus University, Rotterdam, The Netherlands
"Novel aspects of the EKLF knockout phenotype"

11.55 AM Coffee Break

12.15 PM SESSION VI – TRANSCRIPTIONAL CONTROL OF GLOBIN GENES (Continues)

12.15-12.30 James Shen, Academia Sinica, Taipei, Taiwan
"Cofactor and chromatin interaction of NF-E2 and EKLF"

12.35-12.50 Steve Jane, The Royal Melbourne Hospital, Parkville, Victoria, Australia
John Cunningham, St Jude Children's Research Hospital, Memphis, TN
"The of the SSP in fetal globin gene regulation in humans and primates"

12.55 PM SESSION VII – FETAL HEMOGLOBIN
Chairperson: George Dover

12.55-1.10 Susan Perrine, Boston University, Boston, MA
"Small molecule gamma globin inducers: Prediction of structure and binding site through computational modeling"

1.15 PM Break for Lunch

3.00 PM SESSION VII – FETAL HEMOGLOBIN (continues)
Chairperson: George Dover

3.00-3.15 Tohru Ikuta, Medical College of Georgia, Augusta, GA
"Human gamma-to-beta-globin switching mediated by the cAMP-signaling pathway"

3.20-3.35 Cesare Peschle, Thomas Jefferson University, Philadelphia, PA
"The Kit ligand/receptor complex: role in perinatal Hb switching and effect in beta-thalassemia culture"

3.40-3.55 Martin Steinberg, Boston University, Boston, MA
"Polymorphisms in genes modulating HbF expression"

4.00-4.15 Swee Lay Thein, GKT School of Medicine, London, UK
"Genetic modulation of fetal hemoglobin levels"

4.20 PM Coffee Break

4.40 PM SESSION VII – FETAL HEMOGLOBIN (continues)
Chairperson: Marie Trudel

4.40-4.55 Betty Pace, University of Texas at Dallas, Dallas, TX
Role of nitric oxide and reactive oxygen species in drug-induced γ-globin activation"

5.00-5.15 Connie Noguchi, National Institutes of Health, Bethesda, MD
"Hypoxia and histone deacetylase inhibitors alter expression of transcription factors in erythroid progenitor cells and induces γ-globin gene expression"

5.20-5.35 Donald Lavelle, VA Medical Center, Chicago, Illinois
"The role of DNA methylation and covalent histone modifications of the ε-, γ- and β-globin promoters in globin gene expression during development and following decitabine treatment in P. Anubis"

5.40 PM SESSION VIII – GENE THERAPY
Chairperson: Arthur Nienhuis

5.40-5.55 Punam Malik, Children's Hospital Los Angeles, Los Angeles, CA
"Gene therapy for red cell disorders using lentiviral vectors"

6.00 PM Dinner

7.30 PM SESSION VIII – GENE THERAPY (continues)
Chairperson: Arthur Nienhuis

7.30-7.50 Hans-Peter Kiem, Fred Hutchinson Cancer Research Center, Seattle, WA
"Stem cell gene transfer and selection: implications for the treatment of genetic diseases"

7.55-8.10 Dmitry Shayakhmetov, University of Washington, Seattle, WA
"Development of high-capacity gutless adenovirus vectors for gene transfer into human hematopoietic cells"|

8.15-8.30 Derek Persons, St Jude Children's Research Hospital, Memphis, TN
"Development of therapeutically consistent gamma-globin lentiviral vectors and evaluation of their insertion genotoxicity"

8.35 PM SESSION IX – PAPERS SELECTED FROM THE POSTERS
Chairperson: Ross Hardison

TUESDAY, SEPTEMBER 14, 2004

6.00 – 7.00 AM Breakfast

7.00 AM Boat leaves for Seattle

PROGRAM

15TH CONFERENCE ON HEMOGLOBIN SWITCHING
ST JOHNS COLLEGE, OXFORD, UNITED KINGDOM
SEPTEMBER 14 – 18, 2006

Thursday, September 14th

1.00 - 7.00 pm	REGISTRATION - ST. JOHN'S COLLEGE
6.00 - 7.00 pm	NO HOST COCKTAILS - ST. JOHN'S COLLEGE - RECEPTION
7.00 pm	**DINNER - DINING HALL, ST. JOHN'S COLLEGE**

Friday, September 15th

7:30 - 8:20 am **BREAKFAST - DINING HALL, ST. JOHN'S COLLEGE**

SESSION I: Developmental Hemopoiesis and Stem Cells

Chair: Thalia Papayannopoulou

8.30 – 8.50 am **Roger Patient**
Programming of HSCs during development

8.55 – 9.15 am **Leonard Zon**
A high-throughput chemical genetic screen in Zebrafish establishes that Prostaglandin E2 is a potent regulator of hematopoietic stem cell formation

9.20 – 9.40 am **Elaine Dzierzak**
Positional information in mouse HSC development

9.45 – 9.55 am **Thierry Jaffredo**
Somite-derived cells replace ventral aortic hemangioblasts and provide aortic smooth muscle cells of the trunk

9.58 – 10.08 am **Eric Bouhassira**
New insights into early human erythropoiesis and globin gene switching from differentiation of human ES cells

10.11 – 10.21 am **Toru Nakano**
Analysis of GATA and its related factors using in vitro differentiation of mouse ES cells

10.25 – 10.45 am **COFFEE BREAK**

SESSION II: Transcriptional control of erythropoiesis and globin gene expression

(Session 1, GATA proteins)

Chair: Connie Noguchi

10.45 – 11.03 am **Masayuki Yamamoto**
Regulation of mouse Gata1 gene expression in erythroid progenitors

11.06 – 11.24 am **Sjaak Philipsen**
Dynamic regulation of Gata factor levels is more important than their identity

11.27 – 11.45 am **Emery Bresnick**
Diverse modes of GATA factor function

11.50 –12.10 pm COFFEE BREAK

12.10 – 12.20 pm **Paresh Vyas**
Transcriptional regulation of GATA1

12.23 – 12.33 pm **Christopher Lowrey**
Targeting GATA-1 to binding sites in nuclear chromatin

12.36 – 12.56 pm **Paul-Henri Romeo**
TAL-1 and GATA-1 coupled cell proliferation and differentiation during terminal erythroid differentiation

1.01 – 1.19 pm **James Bieker**
Novel role for EKLF in megakaryocyte-erythroid differential lineage commitment

1.30 - 2.30 pm LUNCH - DINING HALL, ST. JOHN'S COLLEGE

2.30 - 6.00 pm POSTER SESSION I

BREAK-OUT SESSION – TERRY BISHOP
LARKIN ROOM

6.00 - 7.30 pm DINNER - DINING HALL, ST. JOHN'S COLLEGE

SESSION II : Transcriptional control of erythropoiesis and globin gene expression (Session 2, Various proteins)

Chair: Doug Engel

7.30 – 7.48 pm **Tim Townes**
Differential binding of EKLF to embryonic/fetal globin gene promoters during development: model for globin gene switching

7.51 – 8.01 pm **John Cunningham**
Co-ordinate high level expression of the murine α- and β-globin genes is regulated in a context-specific manner by erythroid Krüppel-like factor (EKLF)

8.04 – 8.14 pm **Osamu Tanabe**
Stage-specific, gene-selective regulation of the embryonic and fetal β-type globin genes by the orphan nuclear receptors TR2 and TR4

8.17 – 8.27 pm **David Garrick**
A role for both histone deacetylases and the PRC2 polycomb complex in repressing alpha-globin gene expression in non-erythroid tissues

8.30 – 8.50 pm **COFFEE BREAK**

8.50 – 9.00 pm **Andrew Perkins**
The transcription factor, Ikaros, plays a key role in the γ-β globin gene switching

9.03 – 9.13 pm **Katarzyna Kolodziej**
Characterization of nuclear orphan receptor TR2/TR4 complexes in erythroid cells

9.16 – 9.26 pm **David Bodine**
Erythroid specific activation of the Ankyrin-1E promoter by the formation of a chromatin loop

9.30 pm **FINISH**

Saturday, September 16th

7.30 - 8.20 am **BREAKFAST - DINING HALL, ST. JOHN'S COLLEGE**

SESSION II : Transcriptional control of erythropoiesis and globin gene expression

(Session 3, KLF proteins)

Chair: Elaine Dzierzak

8.30 – 8.50 am **Frank Grosveld**
Do Ldb1 complexes mediate long range DNA interactions?

8.55 – 9.05 am **Merlin Crossley**
The regulation of gene repression by BKLF

9.08 – 9.18 am **Joyce Lloyd**
EKLF and KLF2 have compensatory roles in embryonic globin gene expression and primitive erythropoiesis

9.21 – 9.31 am **Patrick Gallagher**
Failure of definitive erythropoiesis in EKLF-deficient mice

9.34 – 9.44 am **Mitchell Weiss**
Multiple functions for alpha hemoglobin stabilizing protein (AHSP) in hemoglobin synthesis and homeostasis

9.47 – 9.57 am **Jon Crispino**
Cyclin D/CDK4/6 kinase activity, regulated by GATA1, is required for megakaryocyte polyploidization

10.00 - 10.20 am COFFEE BREAK

SESSION III : Cis Regulation and Epigenetic control of gene expression in erythropoiesis

Chair: Nick Proudfoot

10.20 – 10.40 am **Doug Higgs**
The mechanism of alpha globin activation during erythropoiesis

10.45 – 11.05 am **Job Dekker**
Regulation of gene expression through chromatin interaction networks

11.10 – 11.30 am **Lyubomira Chakalova**
Preferential associations between actively transcribing genes reveal transcriptional networks

11.35 – 11.53 am **Wouter de Laat**
Nuclear organization revealed by 4C technology

11.56 – 12.11 am **Gerd Blobel**
Regulation of higher order chromatin organization by GATA-1

12.15 - 12.35 pm COFFEE BREAK

12.35 – 1.00 pm **Gary Felsenfeld**
Epigenetic regulation at the chicken beta globin locus

1.05 – 1.15 pm **Dorothy Tuan**
Long-range function of the ERV-9 LTR in transcriptional regulation of the globin genes

1.18 – 1.28 pm **Ann Dean**
Chromatin structure and epigenetic modification in the human β-globin locus

1.35 - 2.30 pm LUNCH - DINING HALL, ST. JOHN'S COLLEGE

2.30 - 6.00 pm POSTER SESSION II

BREAK-OUT SESSION – SJAAK PHILIPSEN
LARKIN ROOM

6.00 - 7.30 pm DINNER - DINING HALL, ST. JOHN'S COLLEGE

7.30 – 9.00 pm

QUICK FIRE SESSION

Chair : Roger Patient

1. Jim Hughes
2. Alan Cantor
3. David Emery
4. Peter Fraser
5. Laura Guttierrez
6. Dan Kaufman
7. Veronica Buckle
8. Natalia Meier
9. Connie Noguchi

9.00 pm **FINISH**

Sunday, September 17th

7.30 - 8.20 am **BREAKFAST - DINING HALL, ST. JOHN'S COLLEGE**

SESSION III : Cis Regulation and Epigenetic control of gene expression in erythropoiesis

(Session 2)

Chair: Ann Dean

8.30 – 8.45 am **Stephen Jane**
The protein methyltransferase PRMT5 links histone H4 methylation to Dnmt3a-dependent DNA methylation and transcriptional silencing

8.48 – 8.58 am **Ken Peterson**
Silencing of $^{A}\gamma$-globin gene expression during adult definitive erythropoiesis is mediated by GATA-1 binding

9.01 – 9.11 am **Jorg Bungert**
Dynamic regulation of transcription complex recruitment to the β-globin gene locus

9.14 – 9.24 am **Gordon Ginder**
The role of methyl binding domain protein 2 (MBD2) in developmental globin gene regulation

9.27 – 9.37 am **M.A. Bender**
Dynamics of the beta-globin locus

9.40 – 9.50 am **Stephen Fiering**
Analysis of DNA methylation patterns of murine β-like globin genes in primitive and definitive erythroid cells reveals a large primitive cell specific hypomethylated domain

10.00–10.25 am **COFFEE BREAK**

SESSION IV : Systems biology to study hemopoiesis

Chair: Bernie Forget

10.25 -10.45 am **Stuart Orkin**
Protein interaction network for pluripotency of ES cells: possible clues to organization of self-renewal machinery in other stem cells

10.50 – 11.08 am **John Stamatoyannopoulos**
Large-scale analysis of erythroid chromatin structure

11.11 – 11.21 am **Bertie Gottgens**
Transcriptional networks controlling blood stem cell development

11.24 – 11.34 am **Ross Hardison**
Comparative genomics to find function in noncoding DNA

11.37 – 11.47 am **FREE**

11.50–12.10 pm COFFEE BREAK

SESSION V : Fetal globin expression *in vivo*

Chair : Alan Schechter

12.10 – 12.20 pm **Swee Lay Thein**
A major quantitative trait locus on chromosome 6q23 for HbF levels – an update

12.23 – 12.33 pm **Jeffery Miller**
Silencing and reactivation of gamma-globin expression in humans

12.36 – 12.46 pm **Jim Vadolas**
In vivo model systems for therapeutic approaches to β-thalassemia

12.49 – 12.59 pm **Don Lavelle**
The pattern of covalent histone modifications throughout the β-globin gene locus in fetal liver and adult bone marrow erythroblasts pre- and post-decitabine

1.02 – 1.12 pm **Susan Perrine**
γ-Globin promoter activation by a new generation of short-chain fatty acid derivatives

1.15 – 1.25 pm **Betty Pace**
Histone deacetylase inhibitors induce γ-globin expression by p38 MAPK-mediated CREB and ATF-2 activation

1.30 - 2.30 pm LUNCH - DINING HALL, ST. JOHN'S COLLEGE

SESSION V : Fetal globin expression *in vivo*

Chair: Bill Wood

2.30 – 2.40 pm **Tohru Ikuta**
Roles of cyclic nucleotides in β-like globin gene expression during development

2.43 -2.53 pm **Judy Chang**
Treatment of sickle cell anemia using the murine embryonic stem cell model

2.56 – 3.11 pm **Arthur Nienhuis**
Genotoxicity of retroviral integration

3.16 – 3.26 pm **Punam Malik**
Elements that result in high titers and expression from globin cassettes

3.30 – 3.50 pm **COFFEE BREAK**

SESSION V : Fetal globin expression *in vivo*

Chair: Arthur Nienhuis

3.50 – 4.05 pm **Michel Sadelain**
The expanding application of lentivirus-mediated erythroid-specific gene therapy

4.10 – 4.25 pm **Philippe Leboulch**
Study design of the first phase I/II clinical trial of lentivirus-mediated gene therapy of the β-hemoglobinopathies and future strategies for selection of transduced cells

4.30 pm

QUICK FIRE SESSION

Chair : Marie Trudel

1. Melanie Stumpf
2. Jim Palis
3. Cristina Pina
4. Keiji Tanimoto
5. Michelle Souyri
6. Claire Guillemin
7. Hsiao Voon

5.30 pm FINISH

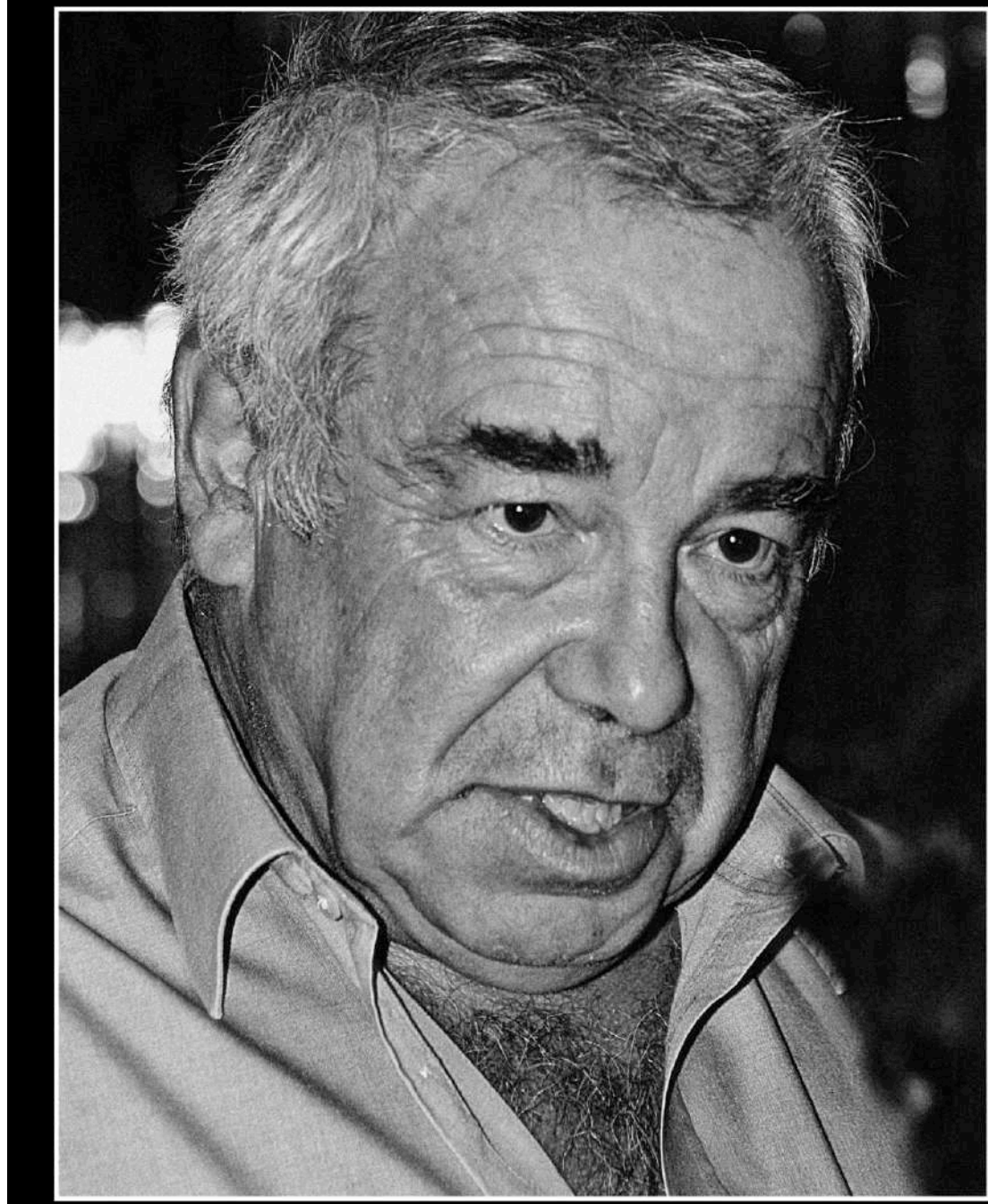
6.30 pm **DRINKS RECEPTION**

7.30 pm **OFFICIAL DINNER - DINING HALL, ST. JOHN'S COLLEGE**
Guest Speaker – Sir David Weatherall

Monday, September 18th

7.30 - 8.20 am **BREAKFAST - DINING HALL, ST. JOHN'S COLLEGE**


HEMOGLOBIN SWITCHING




16th Hemoglobin Switching Conference 2008
Asilomar Conference Center, Monterrey,


16th Hemoglobin Switching Conference 2008
Asilomar Conference Center, Monterrey,

PROGRAM

16th Hemoglobin Switching Conference October 11–14, 2008
Asilomar Conference Center, Monterrey, California

Saturday, October 11th

13:00-20:00	REGISTRATION – front desk, Main building
17:00-18:00	NO HOST COCKTAILS - RECEPTION
18:00-19:00	DINNER

Sunday, October 12th

7:30 - 8:25	BREAKFAST
SESSION I:	Developmental Hemopoiesis and Stem Cells Chairs: Thalia Pappayanopoulou + Stu Orkin (Merrill Hall)
8:30-8:50	Dzierzak- To be or not to be.....a hematopoietic stem cell
8:55-9:10	Patient- Differential programming of adult and embryonic blood cells
9:15-9:30	Francastel- Epigenetic signatures of multipotent and committed human hematopoietic progenitors
9:35-9:50	Baron- Development of embryonic red blood cells
9:55-10:10	Palis- Early ontogeny of erythropoiesis
10:15-10:45	COFFEE BREAK
10:45-11:00	Choi- ER71 in hematopoietic and vascular development
11:05-11:15	Townes- iPS cell gene replacement for sickle cell disease
11:25-11:35	Bouhassira- Erythroid cell production from human ES and iPS Cells
11:45-12:05	J. Stamatoyannopoulos- Digital analysis of chromatin structure in erythroid cells
12:10-12:20	Brief Break
SESSION II :	Haemoglobin Switching I Chairs: Tim Townes + Marie Trudel
12:20-12:40	Orkin- Genetic approaches to globin switching
12:45-12:55	Tuan- The ERV-9 LTR retrotransposon in the regulation of globin gene switching
13:00-13:10	Peterson- Transactivation of fetal globin gene expression
13:15-13:25	Lavelle- DNA Methylation and Globin Gene Expression
13:30–14:45	LUNCH
14:45 - 15:15	Bishop-Funding Opportunities at NIDDK (Merrill Hall)

14:45 – 17:00 POSTER SESSION I (Heather Hall)

18:00 – 19:00 DINNER

SESSION III: Control of erythropoiesis and globin gene expression Chairs: Ann Dean + Masi Yamamoto

19:05-19:25 Grosveld- Transcription factor networks
19:30-19:50 Zon- Use of the zebrafish to study globin gene expression
19:55-20:10 Gallagher-Transcription factor binding in erythroid cells: ChIP-chip and ChIP-Seq

20:10-20:20 Brief Break

20:20-20:30 Bungert- The role of USF and NF-E2 in the recruitment of transcription complexes to the LCR and to the beta-globin gene promoter
20:35-20:45 Noordermeer- Long range gene activation by an ectopic beta-globin LCR
20:50-21:00 Tanimoto- Regulation of beta-like globin gene expression in primitive erythroid cells of human beta-globin YAC transgenic mice

Monday, October 13th

7:30 - 8:25 BREAKFAST

SESSION IV : Transcription factors and co-factors controlling globin gene expression Chairs: Doug Higgs + Cecelia Trainor

8:30-8:50 Yamamoto- GATA factor switching in the regulation of erythroid gene expression
8:55-9:10 Bresnick- GATA factor-dependent transcriptional mechanisms
9:15-9:25 Vyas-Transcriptional regulation of GATA-1
9:30-9:40 Hardison: Biological functions of DNA occupied by the erythroid transcription factor GATA1: evolutionary history and current events
9:45-10:00 Blobel- Co-activators and co-repressors in erythroid/megakaryocytic transcription

10:00-10:30 COFFEE BREAK

10:35-10:50 Bieker- Novel aspects of EKLF epigenetic and transcriptional control of erythroid gene expression
10:55-11:05 Lloyd- Interactions between KLF genes in erythroid and cardiovascular development
11:10-11:20 Zhou- Role of EKLF in human gamma- to beta-globin gene switching
11:25-11:35 Perkins- EKLF, the cell cycle and chromatin
11:40-11:50 Crossley- A network of Klfs
11:55-12:05 Cunningham- Mechanisms of EKLF action in vivo

12:10-12:20 Brief Break

SESSION V : Transcription factors/accessory factors Chairs: Swee Lay Thein + Bill Wood

12:20-12:30 Ginder- The role of methyl CpG binding proteins in globin gene switching
12:35-12:45 Huang- Methylation of H4R3 mediates long-range chromatin interaction and beta-globin transcription
12:50-13:00 Milot- Ikaros nucleates a GATA-1-containing repressosome in erythroid cells
13:05-13:15 Shen- Activation by Post-translational Modifications of Erythroid Transcription Factors During Erythroid Differentiation

13:20-14:45 LUNCH
14:45-17:00 Poster Session II
18:00- 19:25 Dinner – BANQUET ON THE BEACH

SESSION VI: Quick Fire Chair: Roger Patient

19:30 – 20:45 Powerpoint presentation of 8 posters (7 minutes each; 2 minutes for Q&A) selected by the organizers and session chairs from the two poster sessions; only work that has not been presented by lab PIs is eligible for the quick fire session

SESSION VII: Chromatin Chair: Jim Bieker

20:45-20:55 Liu- SATB1
21:00-21:20 Higgs- Long-range effects of globin gene activation

Tuesday, October 14th

7:30 - 8:25 BREAKFAST

SESSION VIII : Epigenetic control of gene expression during erythropoiesis Chairs: Doug Engel + Claire Francastel

8:30-8:50 Felsenfeld- Dissection of a complex boundary element in the chicken beta-globin locus
8:55-9:10 Li- Distinctive chromatin structures of the beta-globin LCR in embryonic and definitive erythroid cells
9:15-9:25 Bodine- Identification and Characterization of Insulator Elements in Loci Active in Red Blood Cells
9:30-9:40 Fiering- Chromatin structure of the b-globin locus in primary human erythroblasts
9:45-9:55 Brand- Dual role for the H3K9 methyltransferase G9a in regulating stage-specific transcription at the ß-globin locus
10:00-10:10 Engel: DRED species and subunits
10:15-10:30 Dean- Contribution of Enhancer and Insulator Loops to Long Range Gene Regulation

10:30-11:00 COFFEE BREAK

SESSION IX : Erythroid regulation beyond transcription Chairs: Frank Grosveld + Sherman Weissman

11:00-11:10	Weiss- Structural determinants of alpha hemoglobin stabilizing protein function
11:15-11:25	Ney- NIX and autophagy in programmed mitochondrial clearance
11:30-11:45	Romeo- Red blood cells: from the beginning to the end
11:50-noon	Noguchi- Disregulated erythrocytosis associated with SCL/Tal1 and EpoR expression
12:05-12:10	Brief Break
12:10-12:20	Shimizu- Induction of hyperproliferative fetal megakaryopoiesis by an N-terminally truncated GATA1 mutant
12:25-12:35	Philipsen- An shRNA “bookshelf” screen aimed at reactivation of g-globin

SESSION X : Haemoglobin Switching II: Fetal globin expression in vivo Chair: G. Stamotoyannopoulos

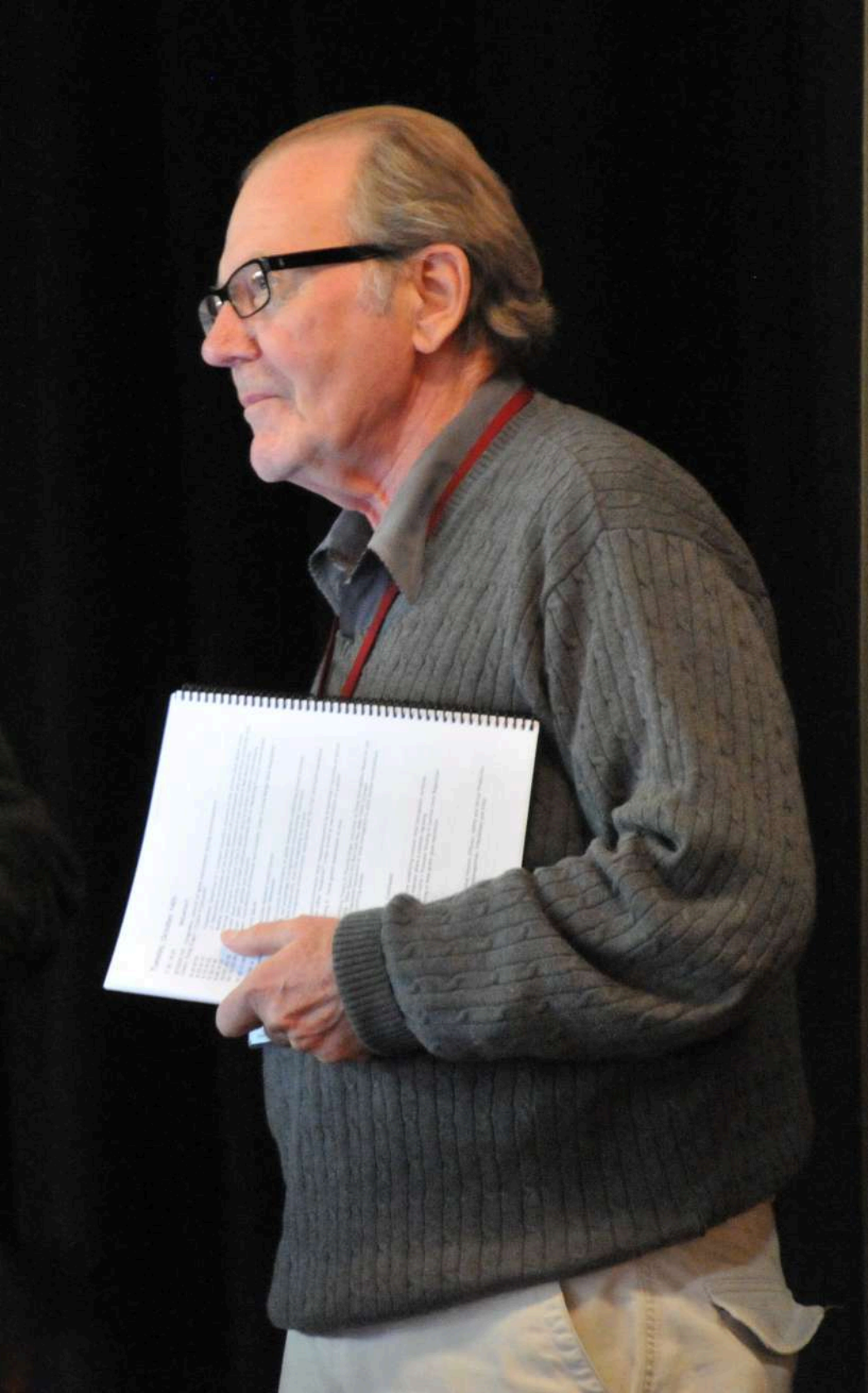
12:40-12:50	Lowrey-A Unifying Theory of Pharmacologic Induction of Fetal Hemoglobin Based on Cell Stress Signaling - What Doesn't Kill Red Cells May Make Them Stronger
12:55-13:05	Miller: Signaled expression of fetal hemoglobin in adult human erythroblasts: transcriptome profiling studies
13:05– 14:05	LUNCH
18:00 – 19:00	DINNER

SESSION XI : Haemoglobin Switching II: Continued Chair: G. Stamotoyannopoulos

19:05-19:20	Thein- Genetic architecture underlying common fetal hemoglobin variation
19:25-19:35	Ikuta- Fetal hemoglobin inducers share a common signaling
19:40-19:50	Pace- Competitive Stat3/GATA-1 Promoter Binding in Gamma Gene Regulation
19:55-20:05	Jane- Epigenetic silencing of fetal globin gene expression
20:10-20:20	Brief Break

SESSION XII: Gene Therapy Chair: Y.W. Kan

20:25-20:40	Persons- Gamma-Globin Lentiviral Vectors: Efficacy, Safety and Vector Production
20:45-21:00	Malik- Gene Therapy for Hemoglobinopathies: Tribulations and trials
21:05	End of Conference



PROGRAM
17th Hemoglobin Switching Conference
September 2nd – 6th, 2010
St. John's College, Oxford, UK

Thursday 2nd September

12.00 – 18.00 REGISTRATION

18.00 NO-HOST DRINKS

19.00 DINNER

Friday 3rd September

07.30 – 08.25 BREAKFAST

SESSION I: Developmental hematopoiesis and models of hematopoiesis
CHAIR: Marella de Bruijn

8.30 – 8.50 **Roger Patient**
Maturation of the erythroid cell fate switch during development

8.55 – 9.15 **Elaine Dzierzak**
Hemogenic endothelium, hematopoietic stem cells and hematopoietic clusters

9.20 – 9.35 **Kyunghee Choi**
Hemangiogenic vefsus cardiogenic mesoderm development regulated by ER71 inhibition of Wnt signaling

9.40 – 9.55 **James Palis**
Yolk sac-derived definitive erythropoiesis: maturation in the fetal liver with a unique pattern of globin gene expression

10.00 – 10.25 COFFEE BREAK

SESSION II: Analysis of hematopoiesis/erythropoiesis
CHAIR: Thalia Papayannopoulou

10.25 – 10.45 **Len Zon**
Signaling pathways and transcriptional control of erythropoiesis

10.50 – 11.05 **Paul-Henri Romeo**
Hematopoiesis and erythropoiesis in mice deficient for TIF1γ

11.10 – 11.25 **Xiaoying Bai**
Role of TIF1γ in hematopoiesis

11.30 – 11.42 **Paul Ney**
Mechanism of programmed mitochondrial clearance in erythrocytes

11.45 – 11.57 **Catherine Porcher**
Structural and functional characterisation of the SCL transcriptional protein complex

12.00 – 12.10 BREAK

SESSION III: Genomics
CHAIR: Ross Hardison

12.10 – 12.30 **John Stamatoyannopoulos**
Genome-scale profiling of regulatory factor occupancy

12.35 – 12.55 **Peter Fraser**
Nuclear genome organisation in erythroid gene expression

13.00 – 13.12 **Eric Soler**
Genome-wide dynamics of Gata1 complexes

13.15 – 13.27 **Pat Gallagher**
Barrier insulators in erythroid cells

13.30 – 14.30 LUNCH

15.00 – 18.00 POSTER SESSION I

15.00 – 18.00 BREAK-OUT SESSION – LARKIN ROOM
Terry Bishop
Late-Breaking news from the NIH

18.00 – 19.00 DINNER

SESSION IV: Cis control
CHAIR: Doug Higgs

19.05 – 19.25 **Gary Felsenfeld**
Containing the spread of heterochromatin at the chicken β-globin locus

19.30 – 19.45 **Suming Huang**
Chromatin boundaries require the functional collaboration between hSET1 and NURF complexes

19.50 – 20.05 **David Garrick**
A SNF2 protein targets variable copy number repeats and thereby influences allele-specific expression

20.10 – 20.25 **De-Pei Liu**
SATB2 contributes to transcriptional regulation of human fetal beta-like globin genes

20.30 – 20.55 COFFEE BREAK

SESSION V: Networks and long range interactions
CHAIR: Sherman Weissman

20.55 – 21.15 **Frank Grosveld**
Transcription factor networks and long-range interactions

21.20 – 21.35 **Emery Bresnick**
Chromosomal transitions driven by multiprotein complexes that control erythropoiesis

Saturday 4th September

07.30 – 08.25 BREAKFAST

SESSION V: Networks and long range interactions, contd...
CHAIR: Alan Schechter

8.30 – 8.45 **Ann Dean**
Mechanisms underlying long range β-globin gene regulation

8.50 – 9.05 **Jörg Bungert**
The role of TBP, CBP/p300, and BRG1 in the recruitment of RNA polymerase II to the β globin gene locus

SESSION VI: GATA-1
CHAIR: John Strouboulis

9.10 – 9.30 **Masi Yamamoto**
SUMO-conjugated GATA1 and GATA factor switching

9.35 – 9.50 **Gerd Blobel**
Acetylation-dependent interaction of GATA-1 with a potential mitotic "bookmarking" protein

9.55 – 10.10 **John Crispino**
GATA1, Trisomy 21, and MPL: Model of oncogenic cooperation in AMKL

10.15 – 10.40 COFFEE BREAK

SESSION VII: Control of Hb Switching I
CHAIR: Griffin Rodgers

10.40 – 10.55 **Chris Lowrey**
The role of cell stress signaling in the pharmacologic induction of human fetal hemoglobin

11.00 – 11.15 **Betty Pace**
Role of p38 MAPK/CREB1/ATF-2 Signaling in γ−Globin Gene Regulation

11.20 – 11.35 **Swee Lay Thein**
Impact of HbF QTLs on hemoglobin disorders

11.40 – 11.55 **Guillaume Lettre**
Sequencing and fine-mapping within known loci identify newly associated common and rare DNA variants and increases the explained heritable variation in fetal hemoglobin levels

12.00 – 12.15 BREAK

12.15 – 12.30 **Jian Xu**
Control of hemoglobin switching by BCL11A

12.35 – 12.50 **Vijay Sankaran**
The molecular basis of persistent fetal hemoglobin expression in human trisomy 13

12.55 – 13.10 **Kai Hsin Chang**
Hemoglobin switching in human embryonic stem cells – derived hybrids

13.15 – 13.27 **Don Lavelle**
Regulation of gamma-globin expression in P. anubis in vivo and ex vivo

13.30 – 14.30 LUNCH

15.00 – 18.00 POSTER SESSION II

18.30 – 21.30 RIVERBOAT CRUISE ON THAMES

Sunday 5th September

07.30 – 08.25 BREAKFAST

QUICK FIRE SESSION
CHAIRS: Bender & Mohandas Narla

8.30 – 10.30 8 x 10 mins QUICK FIRE SESSION
10:30 – 10.55COFFEE BREAK

SESSION VIII: Control of Hb Switching II
CHAIR: George Stamatoyannopoulos

10.55 – 11.15 **Stuart Orkin**
Control of Hb switching and γ-globin gene silencing

11.20 – 11.35 **Sjaak Philipsen**
New tricks of an old friend: regulation of globin switching by KLF1

11.40 – 11.55 **Tim Townes**
KLF1 regulates BCL11A expression and γ- to β-globin gene switching

12.00 – 12.15 **Doug Engel**
TR2/TR4: Complexes and activities

12.20 – 12.32 **Dorothy Tuan**
The active and inactive proximal γ-globin promoter complexes assembled by NF-Y during erythroid development

12.35 – 12.47 **Gordon Ginder**
The role of Methylcytosine Binding Domain protein 2 (MBD2) and its associated co-repressor complex in developmental globin gene silencing

12.50 – 13.02 **Ken Peterson**
Induction of fetal hemoglobin by MTF-1

13.05 – 14.05 LUNCH

SESSION IX: iPS cells CHAIR: Connie Noguchi

14.10 – 14.30 **Michel Sadelain**
Therapeutic β-globin expression in thalassemia patient induced pluripotent stem cells from genomic safe harbors

14.35 – 14.55 **Y-W Kan**
iPS cell Therapy Following Prenatal Diagnosis

SESSION X: Development of new therapeutic approaches
CHAIR: Bill Wood

15.00 – 15.15 **Stephen Jane**
In search of novel epigenetic therapies for the β-hemoglobinopathies

15.20 – 15.35 **Andrew Wilber**
Towards clinical gene transfer trials for beta-thalassemia and sickle cell disease

15.40 – 15.55 **Punam Malik**
The long and the short of chromatin insulators

16.00 – 16.12 **Giuliana Ferrari**
Preclinical assessment of gene therapy for beta thalassemia

16.15 – 16.35 **Philippe Leboulch**
Transfusion independence and HMGA2 activation after gene therapy of human beta-thalassemia, and comparison with autologous iPS transduction

16.40 – 17.05 COFFEE BREAK

SESSION XI: EKLF
CHAIR: Cece Trainor

17.05 – 17.20 **James Bieker**
A novel EKLF-mediated mechanism of severe anemia

17.25 – 17.40 **Dave Bodine**
Relocation of EKLF occupancy during erythropoiesis

17.45 – 18.00 **Andrew Perkins**
KLF1/EKLF regulatory networks in primary erythroid cells

18.05 – 18.20 **Joyce Lloyd**
Roles of EKLF and KLF2 in Embryonic Globin Gene Regulation and Erythropoiesis

18.25 – 18.40 **Merlin Crossley**
Investigations into the biological functions of Bklf/Klf3

18.45 DRINKS

19.30 CONFERENCE BANQUET

Monday 6th September

07.30 – 08.25 BREAKFAST

DEPARTURE


2010

18th Annual Conference

Hemoglobin Switching

7-11 June 2012 ~ Monterey , California, USA

PROGRAM

18th Hemoglobin Switching Conference June 7 – 11, 2012

Asilomar Conference Center, Monterey, California

Thursday, June 7

12noon Check In
5:00 Beach Banquet
7:00 Cash Bar

Friday, June 8

7:30 BREAKFEST

SESSION I: Embryonic Erythropoiesis (Chair: Stu Orkin)

8:30 Roger Patient - Building Blood Programmes

8:50 Len Zon - Pathways Regulating Blood Stem Cell Self-Renewal and Engraftment

9:10 Kunghee Choi - ER71 in hematopoietic and vascular development

9:25 Jim Palis - Embryonic Erythropoiesis- Role of Erythropoietin

9:40 Elaine Dzierzak - Program of the endothelial to hematopoietic stem cell transition

10:00 COFFEE BREAK

SESSION II: Transcription (co-) Factors (Chair: Cece Trainor)

10:25 Tim Towns - Human Globin Gene Regulation During Development

10:40 John Crispino - Cofactor-mediated Restriction of GATA-1 Chromatin Occupancy Coordinates Lineage-specific…

10:55 Alan Cantor - In Vivo Role Of ZBP-89 In Hematopoiesis

11:10 Joeva Barrow - Neutralizing the Function of a Beta-globin Associated cis-Regulatory DNA Element Using Artificial… 11:25 Suming Huang - The role of hSET1 complex in regulating transcription and insulator activities during hematopoiesis 11:40 Paul–H. Romeo - TIF1γ (TRIM33) function and mode of action during adult hematopoiesis

12:00 Merlin Crossley - Unexpected effects of Kruppel-like Factor 3 (KLF3)

12:15 LUNCH

2-4PM Poster Session 1 – Heather Hall

6:00 DINNER

7:00 Masi Yamamoto - The Keap1-Nrf2 System and Hematopoiesis

7:00 A. Ronchi - The dual role of Sox6 in erythropoiesis: inducer of erythroid differentiation and direct regulator of…

7:35 Eric Milot - Control of transcription elongation during erythroid cell differentiation

SESSION III: KLFs (Chair: George Stamatoyannopoulos)

7:50 Andrew Perkins - Novel roles for Klf1 in erythropoiesis revealed by mRNA-seq

8:05 Joyce Lloyd - Complementary and opposing roles of KLF1 and KLF2 in erythropoiesis

8:20 Jim Bieker - Integration of Chromatin Alteration And Transcription By EKLF/KLF1

8:40 COFFEE BREAK

9:00 Sjaak Philipsen - Role of KLF1 In Globin Regulation And Erythroid Homeostasis

9:20 Vip Viprakasit - Variable clinical phenotypes and management outcomes in patients with KLF-1 mutations

9:35 Peter Fraser - Nuclear organization, chromosome structure and transcription

9:50 Extended discussion

Saturday, June 9

7:30 BREAKFEST

SESSION IV: Chromatin (Chair: Ann Dean)

8:30 Gary Felsenfeld - Further lessons from the chicken β-globin insulator

8:50 Emery Bresnick - Cis-Element Requirements for Establishing the Definitive Hematopoietic Compartment in Mouse and Man

9:05 M. Bender - Structural and Functional Studies Lead to a Model of β-Globin Activation That Suggests Distinct…

9:20 F. Recillas-Targa - Genetic and epigenetic regulatory complexity of the chicken alpha-globin genes domain

9:35 M. Sokolovsky - An S phase-dependent switch initiates erythroid transcription and genome-wide loss of DNA methylation

9:50 Mohandas Narla - Human Erythropoiesis

10:05 COFFEE BREAK

SESSION V: Complexes (Chair: Doug Engel)

10:20 Frank Grosveld - Networks of transcription factors and chromatin looping

10:40 Marie Trudel - KLF1, KLF2 and Myc control a regulatory network essential for embryonic erythropoiesis

10:55 Ann Dean - Functional organization of chromatin around the β-globin locus

11:10 Marjorie Brand - Changes in the methylation status of histones are critical for the regulation of b-globin gene…

11:25 Gordon Ginder - Regulation of Fetal/Embryonic Globin Gene Silencing by the MBD2/Mi-2/NuRD Complex

11:40 Jian Xu - Comparative Genomic Analysis of Human Fetal and Adult Erythropoiesis

11:50 James Hughes - Identifying distal regulators using chromatin profiles and Capture C

12:05 Gerd Blobel - Manipulating higher order chromatin structure at the β-globin locus by targeted tethering of a…

12:20 LUNCH

2-4PM Poster Sessions 2 - Heather Hall

6:00 DINNER

SESSION VI: Genomics (Chair: Doug Higgs)

7:00 Mike Snyder - Adventures in Personal Genomics and Whole Omics

7:30 John Stamatoyannopoulos - Footprinting the Human Genome

7:45 Eric Soler - Transcriptional repression mediated by Eto2 and the Gata1/Ldb1/Tal1 complex

SESSION VII: Epigenomics (Chair: Connie Noguchi)

8:00 Stu Orkin - BCL11A in hemoglobin switching

8:15 Dorothy Tuan - Molecular assembly of the proximal gamma-globin promoter complex during erythroid development

8:45 Betty Pace -Identification of γ-Globin Gene Regulators During Normal Erythropoiesis

9:00 COFFEE BREAK

9:20 Jared Ganis - A Screen for Regulators of Globin Switching in the Zebrafish Embryo

9:30 Dan Bauer - Functional evaluation of HbF-associated region of BCL11A locus

9:40 S.-L. Thein - HBA2 Levels in Adults are Influenced by Two Distinct Genetic Mechanisms

10:00 Extended discussion

Sunday, June 10

7:30 BREAKFEST

SESSION IX: Quickfire Session (Chair: Roger Patient)

8:30 – 10.40

9:47 COFFEE BREAK

SESSION X: Drug Discovery (Chair: Emery Bresnick)

10:43 Doug Engel - Inhibition of LSD1 stimulates γ -globin synthesis

11:00 Steve Jane - Development of novel small molecules for reactivation of fetal hemoglobin

11:20 James Shen - A New Generation of Chemical Compounds Elevating the Human gamma-Globin Gene Transcription…

11:40 Don Lavelle - Dynamic Regulation of 5-Hydroxymethylcytosine at the Gamma-Globin Promoter During Erythroid…

11:55 Eric Bouhassira - Zinc-Finger Neclease Mediated correction of α-Thalassemia in IPS

12:10 LUNCH

6:00 DINNER

SESSION XI: Therapy (Chair: Thalia Papayannopoulou)

7:00 P. Leboulch - Five year outcome of lentiviral gene therapy for a human beta-thalassemia patient, lessons and prospects

7:20 M. Sadelain - Globin gene transfer for the treatment of thalassemia and sickle cell disease

7:40 Giuliana Ferrari - Interaction of globin vectors with the human genome: implications for gene therapy of beta-thalassemia

SESSION XII: Humans (Chair: Masayuki Yamamoto)

7:50 Mitch Weiss - Protein Quality Control in Erythropoiesis and Beta Thalassemia

8:05 Chris Lowrey - Role of Cell Stress Signaling in Gamma-Globin and HbF Induction

8: 20 Rob Paulson - Analysis of signals regulating stress erythropoiesis

8:35 COFFEE BREAK

9:00 A. Migliaccio - The role of the glucocorticoid receptor polymorphism in human erythroid stress signaling

9:10 E. Vichinsky - Fetal Hemoglobin And Its Relationship To CNS Disease In Hemoglobinopathies

9:25 S. Perrine - A growing pipeline for fetal globin reactivation: epigenetic and

9:40 P. Malik - Gene Therapy for Hemaglobinopathies

9:55 Late discussions

PROGRAM

19th Hemoglobin Switching Conference

September 4th – 8th 2014

St. John's College, Oxford, UK

Thursday 4th September

12.00 – 18.00	REGISTRATION
18.00	NO-HOST DRINKS
19.00	DINNER

Friday 5th September

07.30 – 08.25 BREAKFAST

SESSION I: Developmental hematopoiesis
CHAIR: Marella De Bruijn

8.30 – 8.45 **Elaine Dzierzak**
Responsiveness to developmental signalling pathways defines two HSC types

8.48 – 9.00 **Bertie Göttgens**
Transcriptional network control of blood cell development

9.03 – 9.15 **Suming Huang**
LincRNA *HOTSET* regulates Hox gene expression and promotes hematopoietic fates

9.18 – 9.33 **Roger Patient**
Building HSC circuitry during development

9.36 – 9.51 **Len Zon**
Pathways regulating stem cell induction, self-renewal and engraftment

10.00 – 10.30 COFFEE BREAK

SESSION II: Primitive and Definitive Erythropoiesis
CHAIR: Thalia Papayannopoulou

10.30 – 10.42 **Jim Palis**
Differential stat signaling in embryonic erythropoiesis

10.45 – 10.57 **Mohandas Narla**
Dynamic changes in gene expression during erythroid differentiation of human stem cells

11.00 – 11.12 **Merav Socolovsky**
S phase and the commitment to the erythroid transcriptional program

11.15 – 11.30 BREAK

SESSION III: Cis-acting regulation
CHAIR: John Strouboulis

11.30 – 11.50 **Frank Grosveld**
Targeted Chromatin Capture (T2C) to unravel the spatial organization of the genome

11.55 – 12.07 **Jim Bieker**
Co-ordination of BMP4 induction and enhancer-directed regulation of EKLF/KLF1 expression

12.10 – 12.22 **Jorg Bungert**
Transcription complex recruitment to the β-globin locus control region: structural and functional analysis of a stable footprint associated with locus control region hypersensitive site 2

12.25 – 12.45 **Gary Felsenfeld**
Roles for RNA in expression of erythroid genes

13.00 – 14.30 LUNCH

15.00 – 18.00 POSTER SESSION

15.00 – 18.00 BREAK-OUT SESSION – LARKIN ROOM - NIH FUNDING OPPORTUNITIES

Terry Bishop & Pankaj Qasba

18.00 – 19.30 DINNER

SESSION IV: Cis-acting regulation (Contd.)
CHAIR: Doug Higgs

19.30 – 19.42 **Deborah Hay**
Long range regulation of globin gene expression

19.45 – 19.57 **Jim Hughes**
Linking *cis*-acting elements and analyzing how variants of such elements may influence the chromosomal landscape

20.00 – 20.12 **Gerd Blobel**
Activation of fetal globin expression by forced chromatin looping

20.15 – 20.27 **Ann Dean**
LDB1 contributions to enhancer chromatin looping and erythroid gene activation

20.30 – 20.42 **Emery Bresnick**
Dissecting cis-element mechanisms in hematopoietic stem/progenitor cells and erythroid cells

Saturday 6th September

07.30 – 08.25 BREAKFAST

SESSION V: Key Transcription Factors
CHAIR: Catherine Porcher

8.30 – 8.42 **Merlin Crossley**
Single nucleotide variants and hereditary persistence of fetal hemoglobin

8.45 – 8.57 **Takahiro Maeda**
LRF functions as a repressor of embryonic/fetal globin in adult erythroblasts

9.00 – 9.10 **Joyce Lloyd**
Roles of KLF1 and KLF2 in globin gene regulation

9.13 – 9.25 **Andrew Perkins**
KLF1 mutations and disease

9.28 – 9.40 **James Shen**
Regulation of the nuclear import of EKLF during erythroid differentiation – cell culture and animal studies

9.43 – 9.55 **Swee Lay Thein**
Genetic variation at the erythroid key regulator gene *KLF-1* contributes to high HbF levels in some patients with sickle cell disease

10.00 – 10.30 COFFEE BREAK

SESSION VI: Key Transcription Factors
CHAIR: John Crispino

10.30 – 10.50 **Stu Orkin**
BCL11A as a central regulator of HbF silencing and a prime target for HbF reactivation

10.55 – 11.07 **Vijay Sankaran**
Human genetics of fetal hemoglobin regulation and erythropoiesis

11.10 – 11.25 **Dan Bauer**
Functional characterization of the HbF associated BCL11A enhancer

11.28 – 11.40 **Fyodor Urnov**
Genome editing for blood disorders

11.45 – 12.00 BREAK

SESSION VII: Key Transcription Factors
CHAIR: Marjorie Brand

12.00 – 12.12 **Sjaak Philipsen**
Genetic analysis of potential modifiers of hemoglobin switching

12.15 – 12.27 **David Wiley**
Thyroid regulation of globin switching

12.30 – 12.42 **Masi Yamamoto**
Erythropoietin production in neural and neural crest cells during primitive erythropoiesis

12.45 – 12.57 **Doug Engel**
Activation and repression by the orphan nuclear receptors, TR2 and TR4

13.00 – 14.30 LUNCH

15.00 – 18.00 POSTER SESSION II

18.00 – 19.30 DINNER

SESSION VIII: Genomic Approaches to Hematopoiesis
CHAIR: David Bodine

19.30 – 19.42 **Jian Xu**
Epigenomics of genetic switches during human fetal and adult erythropoiesis

19.45 – 20.00 **Ross Hardison**
Insights into hematopoietic lineage choice from functional genomics

20.05 – 20.25 **John Stamatoyannopoulos**
To be confirmed

Sunday 7th September

07.30 – 08.25 BREAKFAST

SESSION IX: Gene Editing
CHAIR: Frank Grosveld

8.30 – 8.45 **Tim Townes**
CRISPR-Cas enhanced gene replacement for sickle cell disease and severe combined immune deficiency

8.50 – 9.05 **Kai-Hsin Chang**
Development of a treatment of Cooley's anemia by precise genome editing

9.10 – 9.25 **Tom Ryan**
Gene editing of stem cells to correct humanized mouse models of Cooley's anemia

SESSION X: Gene Therapy
CHAIR: George Stamatoyannopoulos

9.30 – 9.45 **Punam Malik**
Gene therapy for sickle cell disease using a gamma globin lentivirus vector

9.50 – 10.05 **Giuliana Ferrari**
Engineering the hematopoietic stem cell for gene therapy of beta-thalassemia

10.10 – 10.40 COFFEE BREAK

SESSION X: Gene Therapy (contd.)
CHAIR: George Stamatoyannopoulos

10.40 – 10.55 **Philippe Leboulch**
Outcomes (June 12, 2014) of gene therapy for β-thalassemia major (β^E/β^0) via transplantation of autologous hematopoietic stem cells transduced ex vivo with a lentiviral $\beta^{A\text{-}T87Q}$-globin vector

SESSION XI: New Approaches to therapy of thalassemia
CHAIR: David Nathan

11.05 – 11.17 **Steve Jane**
Selective inhibitors of Protein Arginine Methyl Transferase 5 (PRMT5) as a novel treatment for β-thalassemia and sickle cell disease

11.20 – 11.30 **Ken Peterson**
A cell-based high-throughput screen for novel inducers of fetal hemoglobin

11.33 – 11.43 **Angela Rivers**
The LSD-1 inhibitor RN-1 induces γ-globin expression in sickle cell mice and baboons (*P. Anubis*)

11.46 – 11.58 **Betty Pace**
Tecfidera (Dimethyl Fumarate): A novel inducer of fetal hemoglobin in human primary erythroid progenitors

12.01 – 12.13 **Olivier Hermine**
GDF-11 induced ineffective erythropoiesis in beta-thalassemia and is a potential therapeutic target

12.30 – 14.00 LUNCH

SESSION XII: Quick Fire Session – Introduced by Doug Higgs
CHAIR: Len Zon

14.00 – 16.30 10 x 10 mins

17.00 COACHES TO BLENHEIM PALACE (FOR TOUR)

18.15 DRINKS

19.00 CONFERENCE BANQUET

Monday 8th September

07.30 – 08.25 BREAKFAST

DEPARTURE

2014


10


19th Hemoglobin Switching Conference - Oxford, Sept 2014
Doug Vernimmen

PROGRAM

20th Biennial Hemoglobin Switching

Conference September 14---18, 2016

Asilomar Conference Center, Pacific Grove, California, USA

Wednesday, 14th September

3:00 – 5:00	REGISTRATION @ Chapel Hall
4:00---6:00	Open reception in Chapel Hall near registration
6:00 – 7:00	DINNER

Thursday, 15th September

7:30–8:15 BREAKFAST

8:20 Welcome and opening remarks--- Doug Engel

SESSION I: Developmental hematopoiesis (Chair: Gerd Blobel)

8:30 Roger Patient --- Programming globin expression during development and evolution (20', including 5'intro)

8:52 Christina Eich ---Dynamic expression of Gata2 during HSC development (12')

9:06 James Palis ---Role of Myb in the emergence of HSC---independent hematopoiesis (15')

9:20 Leonard Zon --- Stem Cell Clonal Biology Using the Zebrafish (15')

SESSION II: Erythropoiesis (Chair: Thalia Papayannopoulou)

9:37 Vijay Sankaran --- Regulation of BCL11A During Human Development (15')

9:55 Merav Socolovsky --- Reconstructing Early Erythroid development in vivo using single---cell RNA---seq (15')

10:05 COFFEE BREAK

SESSION II: Erythropoiesis (cont.) (Chair: Tim Townes)

10:35 Rob Paulson --- Regulation of stress erythropoiesis by macrophages during the recovery from acute anemia (15')

10:52 Marjorie Brand --- Proteomic Modeling of Erythropoiesis (15')

11:10 Johan Flygare --- Direct Erythoid Lineage Conversion is a Novel Platform for Studying Factors Regulating Globin… (15')

11:27 Paul–H. Romeo ---The yin and yang effects of low doses of irradiation on hematopoietic stem cells (15')

11:45 David Bodine --- Overlapping transcriptional profiles in Diamond Blackfan Anemia patients with ribosomal protein… (15')

12:00 LUNCH

2---4PM Poster Session 1 – Heather Hall

4:30--- 6 Reception on the Beach

6:00 DINNER --- BBQ on the Beach

SESSION III: Cis regulation (Chair: Sjaak Philipsen)

7:15 Mitch Weiss --- Genome editing to recapitulate hereditary persistence of fetal hemoglobin (15')

7:33 Merlin Crossley --- Analysis of naturally occurring point mutations in the foetal globin promoters (15')

7:51 Dan Bauer --- Genome editing approaches to reactivate fetal hemoglobin (15')

8:09 Ann Dean --- Insights into the function of erythroid gene enhancers (15')

8:25 Extended discussion

Friday, 16th September

7:30 BREAKFAST

SESSION IV: Chromatin (Chair: Doug Engel)

8:30 Frank Grosveld --- The 3D genome and transcription factors in early hemopoiesis (20')

8:51 Jorge Bungert --- Modulation of Globin Gene Expression via Direct Delivery of Synthetic Zinc Finger DNA---Binding… (15')

9:07 Lars Hanssen --- The role of CTCF in directing tissue---specific enhancer activity (15')

9:23 Gerd Blobel --- Chromatin Readers and Nuclear Architecture

9:39 James Hughes ---Dissection of the alpha globin interaction compartment using Next Generation Capture---C (15')

9:55 Gary Felsenfeld ---Triple helix formation and globin gene expression (15')

10:10 COFFEE BREAK

SESSION V: Key Transcription Factors (Chair: Joyce Lloyd)

10:40 James Bieker --- Erythroid transcriptional control by EKLF/KLF1 (15')

10:56 Bryan Venters --- Epo---driven Pol II binding dynamics during murine erythropoiesis (15')

11:12 Andrew Perkins --- Human and mouse neomorphic and hypomorphic KLF1 mutations: mechanisms underlying … (15')

11:28 C.K. Shen --- Regulation of Longevity/ Juvenescence by a Genetically Modified Hematopoietic System (15')

11:44 Sjaak Philipsen --- Genetic and epigenetic regulation of hemoglobin switching (15')

12:00 LUNCH

2---4PM Poster Session 2 --- Heather Hall

6:00 DINNER

SESSION V: Key Transcription (cont.) (Chair: Roger Patient)

7:05 Stuart Orkin --- Approaches to drugging "undruggable" targets for HbF induction (20')

7:27 Emery Bresnick --- Controlling Hemoglobin Synthesis Via Multiple Heme---sensing Mechanisms (15')

SESSION VI: Omics (Chair: Masi Yamamoto)

7:43 John Stamatoyannopoulos – TBD (20')

8:05 Ross Hardison --- ValIdated Systematic IntegratiON: A VISION for epigenomics in hematopoietic gene regulation (15')

8:22 Jian Xu --- Elucidating the Rules and Roles of Erythroid Transcriptional Enhancers (15')

8:39 Narla Mohandas --- Human Erythropoiesis: Gene and Protein Expression (15')

8:54 Extended discussion

Saturday, 17th September

7:30 BREAKFAST

SESSION VII: Genome editing (Chair: Frank Grosveld)

8:35 Andreas Reik --- CLINICAL---SCALE GENOME EDITING OF BCL11A FOR TREATMENT OF THE HEMOGLOBINOPATHIES (15')

8:52 Tom Ryan --- Hemoglobin switching in humanized mouse models (15')

9:04 Kai---Hsin Chang --- Genome editing of BCL11A for treatment of sickle cell disease (15')

9:21 Tim Townes --- CRISPR/Cas Gene Correction for Sickle Cell Disease and Severe Combined Immunodeficiency (15')

9:40 COFFEE BREAK

SESSION IX: Gene Therapy (Chair: George Stamatoyannopoulos)

10:15 David Williams --- Targeting BCL11A using shRNA embedded miRNAs (shRNAmiRs) in lentivirus vectors for treatment… (15')

10:32 Punam Malik --- Mechanisms of Human Hematopoietic Stem Cell Loss during Ex Vivo Manipulation and Gene Transfer (15')

10:49 Philippe Leboulch --- Update on clinical outcomes of gene therapy for beta---thalassemia and sickle cell disease (15')

11:07 John Tisdale --- Progress in gene therapy in sickle cell disease (15')

11:25 Giuliana Ferrari --- Gene Therapy for beta---thalassemia: update on Italian trial (15')

11:45 LUNCH

SESSION X: Quickfire Session (Chair: Leonard Zon)

2:00 – 4.00

4:00 COFFEE BREAK

6:00 DINNER

SESSION XI: New Approaches to therapy of SCD and thalassemia (Chair: Dover)

7:15 Yogen Saunthararajah --- PHASE 1 EVALUATION OF ORAL THU---DECITABINE FOR NON---CYTOTOXIC EPIGENETIC… (15')

7:33 Betty Pace --- Expression of miR---144 regulates Nrf2 and fetal hemoglobin levels in sickle cell disease (15')

7:50 Angela Rivers --- RN---1, an LSD---1 inhibitor, induces Hb F in the baboon(P. anubis) and reduces ROS in a SCD mouse model (15')

8:08 Masayuki Yamamoto --- Amelioration of inflammation and tissue damage in sickle cell disease by Nrf2 activation (15')

8:23 Extended discussion

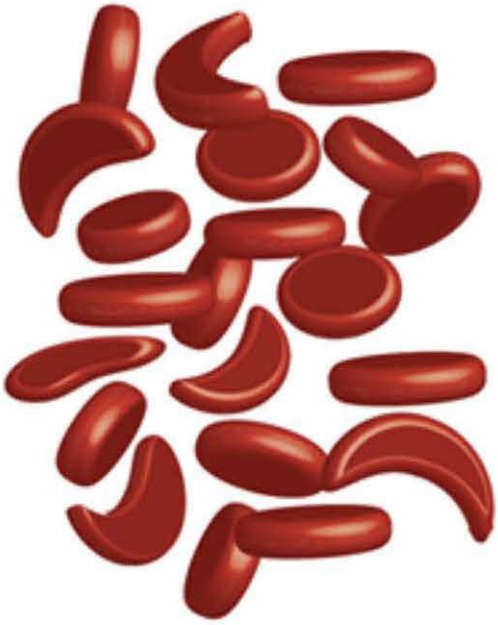
Sunday, 18th September

7:30--- 9:00 BREAKFAST DEPARTURE

PROGRAM

21st Hemoglobin Switching Conference

September 20th – 24th 2018
Pembroke College, Oxford, UK



Thursday 20th September

12.00 – 18.00 REGISTRATION

19.00 DINNER

Friday 21st September

07.30 – 08.10 BREAKFAST

8.15 – 8.30 **Doug Higgs**
Tribute to George Stamatoyannopoulos

SESSION 1: Development of the Hematopoietic System
Chair: Len Zon

8.30 – 8.45 **Catherine Porcher**
Transcriptional and epigenetic control of blood specification

8.48 – 9.03 **Marella de Bruijn**
Gene regulatory interactions underlying the endothelial-to-hematopoietic transition

9.06 – 9.21 **Elaine Dzierzak**
Single cells transitioning to hematopoietic fate during development show pulsatile Gata2 expression

SESSION 2: Primitive Hematopoiesis
Chair: Marieke von Lindern

9.24 – 9.39 **Jim Palis**
STAT3 uniquely regulates the terminal maturation of primitive erythroid cells

9.42 – 9.57 **Marlies Rossmann**
tif1γ regulates primitive erythropoiesis through nucleotide metabolism

10.00 – 10.30 COFFEE BREAK

SESSION 3: Definitive Hematopoiesis
Chair: Cristina Pina

10.30 – 10.45 **Paresh Vyas**
Heterogeneity of human stem and early lympho-myeloid progenitors

10.48 – 11.03 **Claus Nerlov**
Heterogeneity of hematopoietic stem cells

11.06 – 11.21 **David Bodine**
The erythroid lineage is the last to emerge during hematopoiesis

11.25 – 11.40 BREAK

SESSION 4: Erythropoiesis
Chair: Saghi Ghaffari

11.40 – 11.55 **Mohandas Narla**
Heterogeneity of human erythroid progenitors

11.58 – 12.13 **Marjorie Brand**
Understanding erythropoiesis using quantitative proteomics and single-cell mass cytometry

12.16 – 12.31 **Merav Socolovsky**
Specialized cell cycles in early erythropoiesis

12.34 – 12.49 **Margaret Baron**
Stimulation of the proliferation of mouse definitive erythroid progenitors by activation of the Vitamin D receptor transcription factor

13.00 – 14.30 LUNCH

15.00 – 17.00 POSTER SESSION

15.00 – 16.00 BREAK-OUT SESSION – HAROLD LEE ROOM

Terry Bishop
Funding opportunities from the NIDDK at NIH

SESSION 4: Erythropoiesis (Contd..)
Chair: Anupama Narla

17.00 – 17.15 **Jan Frayne**
Creation and applications of immortalized adult erythroid cell lines

17.18 – 17.33 **Tolulope Rosanwo**
Optimized beta-globin expression and enucleation from induced red blood cells for *in vitro* modeling of sickle cell disease

17.36 – 18.00 Discussion of HUDEP led by Stuart Orkin

18.00 – 19.30 DINNER

SESSION 5: *Cis*-Regulation of Globin Gene Expression and Switching
Chair: Merlin Crossley and Doug Vernimmen

19.30 – 19.45 **Sjaak Philipsen**
Evolutionary conserved regulation of oxygen-carrying hemoglobins in jawless and jawed vertebrates

19.48 – 20.03 **Jian Xu**
in situ CAPTURE of the structure-function of β-globin LCR enhancers

20.06 – 20.21 **Alister Funnell**
In situ functional mapping of globin regulatory elements at single nucleotide resolution

Saturday 22nd September

07.30 – 08.25 BREAKFAST

SESSION 5: ***Cis*-Regulation of Globin Gene Expression and Switching (Contd..)**
Chair: Mira Kassouf

8.30 – 8.45 **Merlin Crossley**
Mutations in the proximal fetal globin promoters disrupt repressor or create de novo activator sites to DRVE HPFH

8.48 – 9.03 **Jorg Bungert**
Regulation by the locus control region and a γ-globin associated chromatin opening element

9.06 – 9.21 **Ann Dean**
Fetal γ-globin genes are regulated by a long non-coding RNA locus

9.24 – 9.39 **Marieke Oudelaar**
How regulatory domains form and how elements within them interact

9.42 – 9.57 **Andy King**
Cis-factors governing ζ-globin expression and silencing

10.00 – 10.30 COFFEE BREAK

SESSION 6: **The erythroid transcriptional and co-factor program and Switching**
Chair: John Strouboulis and Suming Huang

10.30 – 10.45 **Bertie Gottgens**
Defining Tal1 function using a molecular roadmap of early mouse organogenesis

10.48 – 11.03 **Frank Grosveld**
Dynamics of the LBD1 complex and the activation of hematopoietic development and 3D genome interactions

11.06 – 11.21 **Gordon Ginder**
The MBD2-NuRD chromatic remodeling complex mediates strong gamma globin gene silencing in human erythroid cells

11.25 – 11.40 BREAK

11.40 – 11.55 **John Crispino**
Global chromatin occupancy and epigenetic signature analysis reveal new insights into the function of GATA1 N-terminus in erythropoiesis

11.58 – 12.13 **Emery Bresnick**
GATA/heme multi-omics reveals a trace metal-dependent erythrocyte developmental mechanism

12.16 – 12.31 **Andrew Perkins**
KLF1 acts as a pioneer transcription factor to open chromatin and facilitate recruitment of GATA1

12.34 – 12.49 **Jim Bieker**
KLF1/EKLF and its variants in aberrant erythroid gene regulation

13.00 – 14.30 LUNCH

15.00 – 17.00 POSTER SESSION II

18.00 – 19.30 DINNER

SESSION 7: Genomics of Erythropooiesis
Chair: Marieke Oudelaar and Doug Higgs

19.30 – 19.45 **Johan Flygare**
Identifying factors for direct reprogramming of fibroblasts to adult definitive erythroid progenitor cells

19.48 – 20.03 **Ross Hardison**
Systematic integration of epigenomes via IDEAS paints the regulatory landscape of hematopoiesis

20.06 – 20.21 **Jeff Vierstra**
Cis-regulatory determinants of erythropoiesis

20.24 – 20.39 **Len Zon**
Transcriptional signaling centers govern human erythropoiesis and harbor genetic variations of red blood cell traits

20.42 – 20.57 **John Stamatoyannopoulos**
Cis-acting regulatory network of a ~2Mb region encompassing the human beta-like globin genes

Sunday 23rd September

07.30 – 08.25 BREAKFAST

SESSION 8: Therapeutic Pathways for Altering Globin Gene Expression
Chair: Constance Noguchi and Stephen Jane

8.30 – 8.45 **Stuart Orkin**
BCL11A as a target for therapeutic reactivation of HbF

8.48 – 9.03 **Nan Liu**
Direct promoter repression by BCL11A controls the fetal to adult hemoglobin switch

9.06 – 9.21 **Woojin Kim / Victoria Hargreaves**
Structure of BCL11A DNA-binding domain

9.24 – 9.39 **Kai-Hsin Chang**
ssODN-aided genome editing of HbF-inducing hotspot revealed by a CRISPR-Cas9-mediated saturated mutagenesis leads to robust HbF induction in erythroid progeny of adult hematopoietic stem and progenitor cells

9.42 – 9.57 **Gerd Blobel**
HRI kinase represses fetal hemoglobin expression in adult human erythroid cells

10.00 – 10.30 COFFEE BREAK

10.30 – 10.45 **Vijay Sankaran**
Control of human hemoglobin switching by LIN28B-mediated regulation of BCL11A translation

10.48 – 11.03 **Betty Pace**
Role of miR-144 in γ-globin expression under oxidative stress conditions

11.06 – 11.21 **Mitch Weiss**
Unc 51-like autophagy-activating kinase (ULK1) mediates clearance of free α-globin in β-thalassemia

SESSION 9: Lentiviral Gene Therapy for Hemoglobinopathies
Chair: Dan Bauer and Olivier Hermine

11.24 – 11.39 **Giuliana Ferrari**
Hematopoietic stem cell gene therapy for adult and pediatric patients affected by transfusion dependent beta-thalassemia

11.42 – 11.57 **Philip Gregory**
Lentiviral vector gene therapy for sickle cell disease

12.00 – 12.15 **Philippe Leboulch**
Gene therapy of the β-hemoglobinopathies: new vectors for ex vivo selection and correction of α:β chain imbalance

12.18 – 12.33 **Punam Malik**
Gene therapy for sickle cell anemia using a modified gamma globin lentivirus vector and reduced intensity conditioning transplant

12.36 – 12.54 **David Williams**
A novel lentiviral vector driving lineage-specific BCL11A knockdown, γ-globin induction and simultaneous repression of β-globin for the treatment of sickle cell disease

13.00 – 14.30 LUNCH

SESSION 10: Genome Editing for Hemoglobinopathies
Chair: Vijay Sankaran

14.30 – 14.45 **Michelle Lin**
CRISPR/Cas9 genome editing to treat sickle cell disease and β-thalassemia by fetal hemoglobin upregulation appears well-tolerated, effective and durable

14.48 – 15.03 **Annarita Miccio**
Induction of fetal hemoglobin synthesis by CRISPR/Cas9-mediated editing of the human β-globin locus

15.06 – 15.21 **Dan Bauer**
Highly efficient therapeutic gene editing of human hematopoietic stem cells

15.24 – 15.39 **Tim Townes**
Modified Cas9 for safe and effective sickle gene correction

15.42 – 16.15 Discussion on Genome Editing led by Vijay Sankaran

17.00 COACHES FOR BANQUET

Monday 24th September

07.30 – 08.25 BREAKFAST

DEPARTURE


21st Hemoglobin Switching Conference
Oxford - September 2018
Doug Vernimmen


21st Hemoglobin Switching Conference 2018
Medieval Banquet - Warwick Castle
Doug Vernimmen

June 21, 2018 |

George Stamatoyannopoulos, pioneer of blood-disease research, dies

The professor of medicine was UW's chief of medical genetics from 1989 to 2005.

Photo credit: American Society of Gene and Cell Therapy

George Stamatoyannopoulos conceptualized and helped found the American Society of Gene and Cell Therapy.

[Editor's note: Dr. George Stamatoyannopoulous, a University of Washington professor of medicine who pioneered the study of blood diseases, died June 16, 2018. This remembrance was submitted by the UW's Department of Medicine and Division of Medical Genetics.]

George Stamatoyannopoulos was born in Athens, Greece, on March 11, 1934. His childhood was shaped by the cataclysmic events that engulfed Greece between 1939-49, where a brutal Nazi occupation, famine, and ensuing bloody civil war scattered his family. Following the war he completed a classical education, studying science at night. He entered medical school in Athens at age 17, graduating top in his class.

Following his medical training, he pursued thesis research on inherited blood disorders, particularly anemias. He performed the first large-scale molecular geographical survey of a genetic trait, which strikingly revealed the relationship between malaria and both thalassemia and sickle cell traits. He also discovered that the fetal form of hemoglobin, which was re-awakened in some thalassemia patients, could ameliorate the effects of the disease. His theory that thalassemia and sickle cell anemia could be generally treated by re-activating fetal hemoglobin has underpinned decades of international effort to cure these disorders with drugs, gene therapies, and now gene editing.

As a young investigator he expanded genetic studies of blood diseases in Greece, where his work drew the attention of medical genetics pioneer Arno Motulsky, who recruited him to the University of Washington in 1964 with his wife and collaborator, Thalia Papayannopoulou. A full professor since 1973, he founded the Markey Molecular Medicine Center and was chief of medical genetics from 1989 to 2005.

Among his many lasting contributions was the creation of organizations and institutions to catalyze the advance of science. In 1978 he established a biennial meeting attracting hundreds of scientists at all levels involved in efforts to understand and cure red blood cell diseases using cutting-edge molecular approaches, and continued to serve as its co-organizer for nearly 40 years.

Foreseeing that genetic therapies represented a fundamentally new paradigm for treating disease that would escalate in importance as technologies progressed, he conceptualized and organized the founding of the American Society of Gene and Cell Therapy, now the pre-eminent scientific forum for a field numbering thousands of scientists spanning academia and biotechnology. His contributions were recognized by establishment of the Stamatoyannopoulos lecture, the society's highest award.

He had an abiding concern for the careers of young investigators, and was a long-time mentor to many leading scientists around the world.

Dr. Stamatoyannopoulos received many honorary degrees and awards, including the Henry M. Stratton Medal for Distinguished Research in Hematology, the William Dameshek Prize of the American Society of Hematology, the Philip Levine Award of the American Society of Clinical Pathologists, and he was elected to numerous honorary organizations and academies. He also served as president of the American Society of Hematology (1992), president of the American Society of Gene and Cell Therapy (1996), and held leadership positions in national and international medical and scientific societies.

He authored over 420 scientific papers and 14 books, including *The Molecular Basis of Blood Diseases*, the first book of its kind to unite molecular advances across an entire field of medicine. His discoveries span many fundamental contributions to the study of blood diseases, gene regulation, gene therapy, and population genetic history. His industry and consistency of top-tier scientific output were remarkable; indeed, his first and last scientific papers were published in *Nature*, 55 years apart.

Dr. Stamatoyannopoulos was a scholar at heart with an enduring love of history and philosophy. He had passionately assembled one of the largest private collections in the world of early printed books comprising Renaissance and post-Renaissance editions of classical Greek and Byzantine authors.

He is survived by his wife and close collaborator of over 50 years, Thalia, a professor of medicine and internationally-recognized hematologist; two sons, one of whom is a professor of genome sciences and medicine and was a scientific collaborator in recent years; and three grandchildren.

He requested to be buried in his ancestral village near the Homeric town of Kyparissia, Greece.

My reminiscences of George – J. Doug Engel

George Stamatoyannopoulos stands out as one of the most influential mentors that I never directly worked with, much like my relationship with Gary Felsenfeld, both of whom were and are legends in our field. Like all of us, I believe that my career has been profoundly, positively influenced by some inspirational scientists that I have been privileged to directly work with: Jim McGhee, Pete von Hippel, Norman Davidson, Tom Maniatis, Hal Weintraub and Mark Groudine to name but a few. My relationship with George was different. We collaborated for more than a decade with Doug Higgs to put together the programs for the Hemoglobin Switching Conferences, with flurries of inconveniently timed telephone calls and teleconferences as the deadlines for fixing the final programs approached, and it is from these interactions that I grew to know George best. This was always an exciting endeavor since we got to talk to our friends, and people who would become our friends, about their latest and greatest data, and the three of us would argue patiently (correction: Doug and I were patient) for why certain individuals should or should not be included in the final program. I can say with authority that Higgs and I never, ever won those arguments.

George and I also interacted in many other ways over the past 30 years. One was when George invited me to first attend HIS Hemoglobin Switching Conference in 1988 and present our model for one aspect of hemoglobin switching, which at the time we referred to as "dueling lollipops" (and that was published later as the much more mundane promoter competition model). Another was when he first decided to move to the University of Michigan (with Art Neinhuis) to Chair the Department of Human Genetics after Jim Neel stepped down. George had decided that when he moved he would recruit Mark Groudine and me to Michigan, and I was excited at the prospect, only to be disappointed by Georges' first coronary, death and resurrection by the skill of cardiologists at the University of Washington. A third time was when George tried to recruit me to UW (actually a couple of times). On the final occasion, George led the charge for my recruitment as a potential Chair of Biochemistry at UW at the same time as I was being recruited to my current home. Since I am not a biochemist, and while my interactions with the few youngsters in the UW Biochemistry Department were all very positive, the very vocal old guard senior faculty there were dismayed (to put it kindly) when I told them that the biochemistry they practiced half a century ago was no longer at the cutting edge of their discipline, so they lobbied the dean to kill my candidacy, much to Georges' and my disappointment at the time. In hindsight, of course, it turned out best for all concerned.

Finally, one initially negative interaction over one topic in particular led eventually to our much deeper and mutually respectful relationship. In the mid-1990s, my lab and many (!) others were interested in how the human and mouse β-globin LCRs functioned, and we had recently converted from analysis of the function of the chicken globin genes, for which there was superior embryology at the time, to employing transgenic mouse studies to explore human β-globin gene regulation. This subdiscipline was really crowded, with some stellar individual laboratories taking different approaches to dissecting essentially the same problem. I decided that we should do something that differed (both from our traditional work and from the work of other people in this field), so we set out to use yeast targeted recombination to make mutations in human yeast artificial chromosomes bearing the entire human β-globin locus, and then introduce these mutated YACs back into the germ line of mice to study the effects of the mutations on hemoglobin switching *in vivo*. The appropriate YACs had already been generated by Karin Gaensler and Rick Myers a few years earlier, and with the advent Georges' and Ricks' lab independently demonstrating how to properly generate and analyze YAC transgenic mice, the stage for success seemed set. I vividly remember an early telephone call with George telling me that his YAC transgenic manuscript had just been accepted for publication in *Science* (an acceptance letter that was

shortly thereafter withdrawn by one of the stellar *Science* "professional" editors), and asking me how I would go about generating mutations in such large segments of DNA. I told him all about our entire proposed strategy using targeted recombination in yeast that I had recently submitted in a grant proposal, a strategy to which we had contributed absolutely nothing and that had been carefully and completely documented in a decade of outstanding work from yeast geneticists, including the creation of all manner of auxotrophic strains and specialized recombination vectors that would be required to execute the experiments. In addition to being an exceptional innovator, George was also an outstanding student, and so he immediately grasped the advantages of utilizing this recombination strategy to create YAC mutations and proceeded to employ it for their own YAC studies, which were subsequently executed and published in a series of careful analyses conducted primarily by Ken Peterson.

Needless to say, I was completely nonplussed by George's explosive reaction when I presented the first of our own preliminary studies at a Red Cells Gordon Conference. As it turns out, Ken and George had generated essentially identical mutations in a different YAC, but had not yet analyzed the consequences of the mutations on globin gene expression. In retrospect, I realized that was because George and Ken had done a much more careful job than Joerg and I had of analyzing the integrity of the integrated YAC transgenes, and so they were slightly slower to publish. Georges' antagonism persisted for several meetings over the next few years, and at every opportunity he would harangue me about how the superior results from his lab were at odds with our conclusions (once with George shouting at me at the top of his lungs from about an inch away), but I think we both gradually began to appreciate how similar our results were. The fervor and mutual animosity gradually led to an armistice about five years later since we both, in the final analysis, reached very similar concordant conclusions from the execution and careful analysis of these experiments. For both of us, the rift was completely healed by 2002, when George asked Doug Higgs and me to assist with the organization of the next Hemoglobin Switching Conference.

The things I learned uniquely from George were several. First, be passionate about your science. Those of us who choose to pursue an occupation as scientists must understand what a privilege it is to be able to pursue our intellectual interests as academics with all of the freedoms that that lifestyle affords, but that it also comes with great responsibility. We must communicate with passion what a unique calling our profession is to the next generation of young scientists, and to treasure our common beliefs in holding discovery, fairness and work ethic to a standard without compromise. Second, we must instill in our scientific progeny that their most important goal should be discovery, and not in getting a piece of work published in one or another tabloid. Finally, and probably the most difficult for all of us, insofar as possible we need to respect the work of both our friends and our competitors, because over the course of a career in science it will turn out that we will cross paths many, many times, and we all should remember that if we exhibit bias in reviewing the grant or manuscript of a competitor, we are not only failing to fulfil our professional responsibility, we are begging for the same treatment for our manuscripts and grant applications at some point in the future.

In the final analysis, I must say that George earned all of the love and respect that our profession affords to the legacy of a giant in our field. His intellect, passion, creativity and work ethic were notably heroic, and earned him the admiration of colleagues, students and competitors alike. He was a man for his time, and we shan't see another like him ever again.

Dear George, I wasn't able to meet you,
but the memory of you is beautiful
& inspiring. Thank you for
your contributions. - K Hartwell

Sept 23, 2018.
The passing away of George is like passing away of an era. We will always remember his passion for hemoglobinopathies, for leading the field, for stirring up controversies, of strong opinions (right or wrong) and the ability to identify youngsters and inspire them into this field. We will miss him. This hemoglobin switching meeting is just not the same without him. However, carrying out your passion, George, is the best tribute we can give you. May God give strength to Thalia, John and his entire family to bear his loss and celebrate the great life he lived.

Punam
(PUNAM MALIK).

Dear George, I thank you for inspiring much of my work. You would be happy to see that finally we made it! Our popo little patient is not transfused from almost 2 years and he is happily swimming in the Sardinian sea. I will miss your suggestions and challenge. Giuliana (Giuliana Ferrari).

DEAR GEORGE, YUO WERE NOT HERE ANYOLORE, BUT WE ALL FELT AS YOU WERE STILL AROUND KEEPING ALIVE YOUR CREATURE, THE Hb SWITCH MEETING, FOR THE YEARS TO COME. THANKS FOR ALL YOU HAVE DONE.

Paolo Mag

Dear George (Thalia)

Thank you for all the years of enthusiastic support of this meeting, and the field! You were/are always a great inspiration!

DAN Weiss

Thalia

I will always remember the conversations & arguments that accompanied our visits to your lab in Seattle (when working on BCL11a with Stefano). It is (and was) an honor to work with both you and George. An inspiration. No other word will do.

Philip (GREGORY)

Dear Thalia

We all missed you and George here. Your absence is acutely felt throughout the conference. We missed how you continuously pushing people to think deeper and do better. Hope to see you in the next switchy conference. Please know that you have our deepest sympathy for your loss.

Best regards. Kaihui.

Hi George,

We miss you so much at the conference this year. Thank you for supporting so many scientits in the field. I will always remember my first conference in Orcas Island.

Yaqiong.

George,
I wish I had the chance to talk to you! Your mentorship and experience are an inspiration for the field and you will be missed by every one.

Deepest sympathies,

Jens Lichtenberg

George
Have a good sleep in heaven!..

JR.

I am now in this 'secret society' I have heard rumors about. There are amazing people here, friendly too. The mission and spirit lives on. Thank you ♡ / Johan

George, you were a great friend, mentor and role model. Your encouragement always meant a lot to me. You are missed already.

Pat Gallagher

George was a great friend and role model. He was passionate about his family, work and country (probably in that order) I will miss him and not forget him

MITCH WEISS

Hello George,

It is my first time in this meeting & have heard so much about you. I wish, I had a chance to know you! I hope to work hard and come up with newer discoveries in this field. Thankyou for paving the way.

Aishwarya Gurumurthy.

George -

I was fortunate enough to meet you once and was glad that I had that opportunity. Your reputation was well deserved and I will be forever grateful for your contributions to the field

Crew Smith

George,

I have been so inspired by your legacy and commitment to this field & others.

John R

Dear George,

It is a great meeting I really learnd lot and having good contacts and experts in the field of Hemoglobin Switching research.

Thank you so much for your great contribution to this field.

Thank you

Ramasamy Jayadeeswara
University of Illinois
Chicago
IL – U.S.A

Dear Thalia,

Geraldine and I send our regards to you, John and the remainder of your family on the loss of George. For me as for so many George was the colleague, friend, critic and so much else in all ways – hemoglobin research and beyond.

We hope you will continue with your work and all and that we will see you again soon.

Alan + Geraldine
Schechter

Hope ~~to~~ to see you at ASH, Thalia,
Gerry

Dear Thalia,

Phil, Patti and I are sending you our best wishes and thoughts. we will miss George and his continuing ~~encouragement~~ encouragement and advice for science and friendship - particularly for motivating young investigators and sharing his generous nature and support.

We look forward to seeing you at ASH.

Connie + Phil + Patti Noguchi

Dear Thalia,

George was a great mentor who encourage me to explore Hemoglobin research field. Yi and I sent our regards and best wishes to you. We miss him a lot.

Best wishes,

Sun Hug

Dear Thalia,

I first met you and George at the '94 Oracs Island meeting. Your passions for science was obvious! Miss you this year!

But,

best wishes,

Utpal Dave

Dear Thalia

I truly enjoyed serving with you and George on study section. You are both passionate about globin gene research and support of young investigators Best wishes

Jörg Bungert

Dear George, and Thalia,

Thank you for everything you have done.
Broadening my horizons
Showing that the most unlikely corner is sometimes the place to be
And that without a sense of humor you get nowhere in life.

Sjaak Philipsen.

Dear George & Thalia,

Following your work has brought me over to the other side of the world & changed the course of my life. You've made a tremendous and inspiring contribution to the field. George - I'm sorry to not have the chance to discuss that paper with you anymore & finally get it out. You had true passion to the end.

Sincerely Alister Frewell

Thalia,

Your and George's support has meant the world to me. I am glad I have had the chance to work and get to know you both.

Jeff Vierstra

George has always been and will continue to be an inspiration. He was a true physician-scientist who wanted to help patients and push forward the field of hemoglobin switching.

-Vijay Sankaran

An inspirational leader and scientist, role model — devoted to pushing the boundaries of knowledge for the ultimate benefit of thousands of people afflicted worldwide with hemoglobinopathies.

Ο θεος να αναπαυσει την ψυχη του.

Jim Palis

George Stem was passionately devoted to our fields, and he made the incredible effort to BUILD a community of scientists, encouraging newcomers and maintaining interest in what we were doing. — Ross Hardison

My attempt to "immortalise" George was through photography. I had to set most to him at lunch to engage conversation, and he always showed interest in what I was doing. He may be gone now, but his name will remain on his publications and his spirit on the photographs. Doug Vermeulen

I was fortunate to know George and his passion for the field of hemoglobin switching for almost 40 years. He was a larger than life figure and a major force in moving this field forward. He had a major positive impact on my career and that of dozens of other new investigators.

George was a great influence on me, as a role model, mentor, and most importantly a friend. I know that he ~~[illegible]~~ filled the same roles for many others as well. I miss George and I am grateful to have had him in my life. - Dave Bodine

George was a giant in the field. He was a source of great inspiration.

George was a true friend and an inspirational scientific colleague. I am very fond of his inspiration, work in India and he truly enjoyed his time in India. When we were together in Hematology study section he reminded me that hemoglobin research is very important and needs support. He is a giant in hematology research and I will miss him greatly. My only regret is we that we were unable to accomplish our plans of visiting India together.

Nalini Das

George is a monumental figure in the field. His review articles were my introduction to the field. He was always encouraging and supportive to me. He was instrumental to my two favorite meetings, Hb Switching and ASGCT. In addition Thalia and John has been great role models, mentors, and colleagues.

-Daniel Bauer

George you have been inspiration to me and the best mentor ever. You will forever be remembered and missed. Always Betty Pace

George thankyou for inviting me to my first Switching meeting "young man, you should come to this important meeting" and I got hooked ever since. miss you, ~~and~~ thankyou for putting in motion field that will help a great number of patients!! Globin Switching, Gene therapy and lots more!

Thalia,
I'm so grateful to you and George for the wonderful field of science that you both have built. I've attended two Hemoglobin switching meetings, and have learned so much. Seeing the excellent science has made me determined to be a better scientist myself. Best, Vikram Sankaran

George was our leader. He was a great inspiration. He made all the Hemoglobin Switching Conferences fun, particularly there when I was a postdoc, with his wonderful and insightful commentaries.

Don Lawler

I met George at the 1st Switching Meeting in 1978, and I was grateful to him for asking me to make a presentation there. For the last 40 years, George was always very kind to me, inspired me and even supported me to be elected to the AAP. We will miss him dearly. DAVID CHOI, Boston

George and Thalia were wonderful mentors early in my career. They were co-authors on the paper published from my PhD thesis. I will always be thinking of them.

Warmly,
Ann Dean

"Andrew, please speak up"
from George
(Andrew Perkins)

As a young scientist it was always uplifting to have had your confidence, support, + encouragement over the years ... it remains an inspiration even now.

Jim Bieker

I have not had the pleasure of direct interaction with George but have benefited tremendously from being part of the Switching Conference community throughout my D. Phil and Postdoc training. George's legacy transcends his physical presence or immediate interaction/Collaboration. His science and impact on the switching community/science will perpetuate through his mentees and all the people he had supported and interacted with over the years. Personally, this meeting has and continues to inspire and motivate me to commit to an academic path; the scientific rigour as well as collegiate environment and warmth of the switching community will always be at the heart of my academic path and training. All my thoughts and respect to George's legacy and my condolescences to his family and Thalia.

Mira Kassouf.
Higgs Lab - Oxford

As a new investigator attending my first Hemoglobin Switching Conference I remember how exciting it was for me. But most of all I remembered how George was so encouraging, to even the likes of me. With passing years I came more and more to appreciate all that George -- and you -- did to advance our field of research. It is no exaggeration to say that without that enthusiastic love of science and advocacy, our field would be nowhere near where it is today, and many important discoveries would likely not have occurred. I and a multitude of others in our field will be forever grateful.

He is and will be greatly missed.

With sympathy and great admiration,

Gordon Ginder

Being Relative new to the globin switching field, I've only had the pleasure to meet George once. I had just worked @ CRISPR Therapeutics for about a year ~~on~~ developing CRISPR/Cas9 based gene therapy to treat β-hemoglobinopathies. We had arranged to consult with George at ASH 2016 and I remember being quite intimidated in his presence, or rather humbled. But after our CSO described the basis of our therapy and showed him some pre-clinical work, he took one look and simply said "it's good". I remembered being in that moment feeling a huge sign of relief and knew that the work that I was doing was somehow validated by someone like George. It was very memorable. And I am saddened that I didn't get a chance to know him more. He will be sorely missed.

Michelle Lin
~~CRISPR~~ CRISPR Therapeutics.

Thalia and George,

Thank you for mentorship + kind friendships over the year. Your leadership + contributions to the field are very much appreciated. Forever grateful for what you do + wisdom.

Betty Pace

George Stam is memorable for many things, but the main one for me is his support for and cultivation of a community of scientists tackling fundamental issues in erythropoiesis, gene regulation, and hemoglobin switching. He took the time to engage with all of us, find out what we were doing, and encourage to continue — and do better. The Hb Switching meetings turned into wonderful meetings - times to renew friendships, learn cutting-edge developments and plan exciting new research. All this happened through George's leadership. He was truly a remarkable man.

- Ross Hardison

Thalia,

So Sorry for your loss.

George was a towering figure in the field. I have to admit he scared me when I first came to the Switching Meeting. But after the first meeting I realized he was full of sage advice. He will be missed.

Bob Paulson

Dearest Thalia,

I'll really miss George and am so sad for you — he was such a dynamic force in life and he will remain so to me and the field of Hb switching forever.

As I think back to my first Airlee House meeting (I think it was '88), it was the first time I met George — BUT — I never would have met him and been involved in this amazing group of researchers without YOU! You did that amazing immunostaining of the mouse cells expressing human globin in my BMT mice. Behind every good mouse is a good woman."

Thanks to you BOTH — what a team!

All the best,

Elaine

Jim Lowrey

My first Switching meeting was in 1982 at Orcas Island. I was a postdoc in Jerry Lingrel's lab. Before the first session of the meeting George Asked me what I was working on. I couldn't believe that he talked to me! We had a 1 hour conversation about the possible mechanism(s) directing the switch from fetal to adult hemoglobin. This one conversation stimulated my interest in the field more than any other conversation with anyone. I am eternally grateful for George and consider him as a mentor even though I never worked in his lab. Finally, I am very thankful for my conversations with Thalia as well. The Stamatoyannopoulos family is incredible!!!

Jörg Bungert

I was lucky to serve with George on study sections and I know him as a passionate supporter of globin research, especially with respect to young investigators.

George made a unique contribution to our field. For me he was a wonderful friend, colleague and mentor: A great inspiration.

Doug Heggs.

George was a superb role model for many, including myself. I was honored to have the privilege of interacting with him and learning from him. He will be greatly missed.

Emery Bresnick

Oxford sept. 21st, 2018.

Small Dialogue on the bus to Oxford.

P: have you heard about George? It is going to be so sad to have a meeting without him.

AR: Please stop, it is sad but we do not want three old days with this feelings around.

AR: Are you Indu?

P: Yep I am.

AR: Do you believe in reincarnation?

P: well may be I do.

AR: Then you know what George will reincarnate himself into. He is going to reincarnate himself into the best retrovirus for Gene Therapy of hemoglobinopathies. He is going to say: I am sick and tired of how slow you are working on it. I will take directly charge of this job and make ~~it happen~~ personally sure that it happens.

I miss George being at the switching meeting. He was a force in science, a great friend, and wonderful mentor. The ISSCR would have never happened without his help.

Seems to be less arguing at the meeting, and that's too bad!

Lee Zou

Thalia & John.

I am enjoying the Switching reading. As always, the science is very exciting and the entire community is here.

But it is not the same, and I fear it never will be again. I miss George. He was a great role model, leader and mentor. I am grateful that I still have you, Thalia, to fill those roles.

Dave Bodeau

The Hemoglobin Switching conferences have driven a whole field over the past 40 yrs. George's imprint on this field and all medical science has been permanently secured by this legacy. Personally I have found that the conferences have been a focal point of my career. Indeed, I believe I am the only investigator to have attended all conferences, including the first at the Batelle center in Seattle. We will miss George. He is not replaceable!

Stuart Orkin

DEAR THALIA,

My Deepest sympathies. George WAS our leader and inspiration. He made all the meetings great fun. I have twonderful memories of the exciting discussion he led at the 1ST meetings I atlended in the 1980s.

Sincerely,

DON LAVELLE
UIC

George:

Still want to say thank you to you for all your helps. God Bless!

Shuaiying Cui

Boston.

Hi George,
I never met you but I have read several papers written by you. I hear you were a wonderful guy and an inspiration. Good luck! I wish I had met you!

Ankit

Dear George
I will always remember your passion, energy, support of young faculty and love of a good fight.
You are missed Rocky

Gail

Dear Thalia,

I cannot begin to know the feelings of loss you must be feeling.

With Sympathy
as you say good-bye
to the man
who shared your life.

My thoughts and prayers go to you and your family. With deepest sympathy,

Terry Bishop

P.S. We miss you here at the Switching Conference in Oxford!

A Fond Salute to George Stamatoyannopoulos – Scholar Leader Mentor Colleague Friend

George Stam, as the world came to know him, slipped away from us on June 16 of this year. This marked over half a century of major achievements that revolutionized our understanding of the science of genetics and hematology. His unique and persistent, typically impatient, approach to make progress was surpassed by none. He will also be remembered for his lifelong leadership and commitment to the pursuit of truth, to the creation of a deeper understanding of how blood cells are normally generated, and the development of better treatments for diseases that arise when this process goes awry. Driven by an insatiable curiosity and attachment to collegial exchange, George, nevertheless, had principles and expectations that were sometimes challenging to live up to. But he was personally never out to win, the goal was always just to resolve a problem and find the best solution. The American Society of Hematology was his community; the American Society of Gene Therapy his brainchild, and the International Society of Experimental Hematology a special intellectual home. His departure leaves a unique vacancy softened only by his enormous legacy of contributions and deep personal ties.

Many an outstanding and interesting obituary has already been written describing George's unusual and impressive academic history and his rapid rise to prominence in every endeavour that captured his interest (1-3). Thus, for this tribute, we sought to use a different approach - one that might better convey his many special qualities through shared personal reflections drawn from a wide circle of colleagues. Below is a handful of such insightful contributions commemorating and celebrating the unique and remarkable George Stam.

Art Nienhuis, Former Chief of the Clinical Hematology Branch and Deputy Clinical Director at the National Institutes of Health's Heart, Lung and Blood Institute, an Editor of Blood and subsequently 4th Director and CEO of St. Jude Children's Research Hospital, was one of George's early acquaintances in science after George moved to the US in 1964. Art soon became a close lifelong colleague working on many of the same scientific questions and related issues. Who better to be the first to describe the essence of George's ability to inspire a lifelong admiration as follows; "My association and friendship with George began in 1976 when we organized the first Hemoglobin Switching Conference which was held in Seattle in 1978 and which has been held bi-annually ever since. I found George to be a stimulating friend and colleague; we spoke telephonically or in person daily for a period of more than 20 years."

John Adamson was another giant in the early development of modern hematology in Seattle and first hand observer of the novel ideas that George and Thalia Papayannopoulou (George's wife and scientific partner for over 50 years), were generating decades ago. John, now a Professor of Hematology and Oncology at the University of San Diego, remembers "We met shortly after George and Thalia came to the University of Washington. We were early collaborators, occasionally competitors, but always collegial. George was a polymath. He was preeminent whether studying long range regulatory elements on gene expression or the origins of modern populations in the Mediterranean region, and a lover of the classic writings. He was one of a kind and is sorely missed."

Stuart Orkin, now the David G Nathan Distinguished Professor at Harvard University and Chair of the Department of Pediatric Oncology at the Dana-Farber/Harvard Cancer Center in Boston is another star in the discipline of hematology known for parallel discoveries of many of the genes and mechanisms that determine how red cells are created. Stuart has written: "I will remember George Stam fondly as he exuded passion for science and life and a commitment to hematology in all his activities. George was a guiding light to the entire hemoglobin field through his own research and through his forward-thinking establishment of the biannual hemoglobin switching conference. George was just genuine in all respects. As a junior faculty member many years ago, I drove George to a Red Cell Gordon conference in NH. Ever since, he would always ask about how my family was doing. There was great warmth beneath his sometimes imposing façade. I will miss George. He was unique."

Leonard Zon, Grousbeck Professor of Pediatric Medicine at the Harvard Medical School and Director of the Stem Cell Program, Children's Hospital Boston is one of the next generation of internationally recognized pillars of innovation and discovery in the discipline of hematopoiesis. Len was also keen to add his thoughts to a tribute intended to be meaningful to all generations – old and new alike. He writes: "George was a major force in science. He was a superb scientist, providing the evidence that looping of enhancers occurs as a method to induce globin gene expression. His work on the globin locus control region defined its role in transcription. George ran the Hemoglobin Switching meeting, and this meeting set up the field to be productive in basic science and has ultimately translated the field into therapies for patients with thalassemia and sickle cell anemia. George was a natural leader and organizer. He had a great method of telling his fellow scientists exactly what he thought of their work, and gently pushing them to do even more. He pushed me to ask Harold Varmus for a zebrafish genome project. He helped me

personally on many occasions with scientific advice, and was absolutely my coach for setting up the International Society for Stem Cell Research. He had started the American Society of Gene Therapy, and had a lot of experience to help me. I am eternally grateful for George - he was a fantastic scientist, a superb mentor, and a great friend."

This tribute would also not be complete without input from **Marshall Horwitz**, one of George's lead recruits to the University of Washington in Seattle and now Associate Dean, Physician-Scientist Education Director and Medical Scientist Training Program Professor. Marshall writes;"I am honored to be asked to contribute a few words: Beyond science and medicine, George was a humanitarian in every sense of the word and inspired others to excel. It is hard to believe he is gone, yet he will always be with us through the discoveries he pioneered, the programs he initiated, the values he championed, the discipline of his scientific approach, the students he mentored, and his exemplary life."

Tariq Enver was one of George's early postdoctoral fellows and is now Professor of Stem Cell Biology and Interim Director at the University College London Cancer Institute, and also Vice Dean for Research of the UCL Faculty of Medical Sciences. Only from a former trainee do you get the direct unadulterated message! "Where do you start? A lot is a bit too personal. One thing though that he insisted upon with me was the business of supporting a field. He was ferociously competitively as you know – 'Tariq - you don't understand , we have to beat the bastards' - this is what he would say to me while gently thumping the table with his clenched fist - head in hand... But when it came to reviewing 'the bastards', his disposition was rather different. 'You have to support the field Tariq- that is the important thing' - even though, and it goes without saying- they remain bastards!"

Doug Engel, Elizabeth C. Crosby Professor at the University of Michigan and co-author of the highly downloaded and beautifully written commemorative piece on George published in the July-August issue of *The Hematologist* (2), highlights another side of George that reminds us all of how a powerhouse mind can be encased in such an approachable and caring individual. In Marshall's own words, he says "Although George and I had a few pretty fierce battles over experimental interpretations from time to time, I initially thought that this was just an aspect of George's naturally combative Greek personality. With time and as our professional relationship matured, I learned that he defended his ideas so vociferously because he felt so deeply that we had a responsibility as scientists to always get it right. George was profoundly, unerringly in search of truth, which is the underlying reason he was so universally loved and admired."

Doug Higgs, Director of the MRC Molecular Haematology Unit of the MRC Weatherall Institute of Molecular Medicine at the University of Oxford, UK, was the co-author with Doug Engel of the obituary in *The Hematologist* (2). In a few words, Doug has summed up what so many of his closest colleagues remember best; "George was a wonderful friend, mentor and supporter throughout my career and I found his leadership of our field to be inspirational. His legacy is that he led globin research from the early days of observation and hypothesis through to the application of the subsequent experimental data to transform the management of patients with haemoglobinopathies."

Anna Rita Migliaccio, Professor of Histology at the University of Bologna, Italy, became a close friend and colleague of both George and Thalia. She reminisces that when she and her scientific partner and husband, Giovanni, met George and Thalia for the first time in 1988 as fellows in the Adamson laboratory in Seattle, “It was a mesmerizing experience for us because we knew their seminal papers on hemoglobin switching by heart from previous work in Italy but had never met them. It was scientific love at first sight and the beginning of a 30-year collaboration. For us collaborating with one of the most famous scientific couples in the world has been inspiring and always instructive. George was a volcano of ideas and a pusher for realization. George‘s scientific inheritance is so broad and deep that it will not be lost. As a person George is irreplaceable, but his legacy will stay for years to come, taking form from the numerous students and collaborators he has promoted during his long-lasting career.”

The world also needs to hear from those whose lives were profoundly affected by George although their work and interactions were not so close. **Keith Humphries**, Professor of Medicine at the University of British Columbia in Canada, Distinguished Scientist in the Terry Fox Laboratory at the BC Cancer Research Centre and its Director for almost a decade and recent Editor of Experimental Hematology, fits this role perfectly. Here is what Keith wanted you to hear; “Reflecting on my career, I realize that George was a constant positive force throughout. External examiner on my PhD defense; provider of countless letters of support over the years; sage career advice on many occasions; wise counsel when I took on executive roles with ISEH and then as Editor of Experimental Hematology; co-organizer of important scientific meetings that I was privileged to attend and that continuously shaped my research directions. It is staggering to imagine how many others can say similar things and appreciate the larger than life impact that George had on the field of experimental hematology.”

In a more abbreviated capsule, **Cynthia Dunbar**, Senior Investigator at the NIH and also a former Editor of Blood and first author of the insightful and detailed obituary of George published in the August issue of Molecular Therapy (3), writes the following: “George always expected progress yesterday - tomorrow was never sufficient! This passionate impatience benefitted mentees, colleagues and patients with serious genetic diseases.”

Ron Hoffman, Director, Myeloproliferative Disorders Research Program and Professor of Medicine, at the Mount Sinai School of Medicine in New York also reflects on the huge impact George had on his development as a physician-scientist. “George Stam was one of my role models. He was the real McCoy. He was a no nonsense scientist who always reached for excellence. He was all business and he wanted to get there in a hurry. I respected this approach and to this day I emulate it. There was also, however, a kindness and humanity to this man which I also valued. When I was entering this field he always said hi to me and encouraged me to do what I was doing. He invited me to meetings and was interested in my work. This was an invaluable gift because it made me feel that I was on the right track. George and I both attended a small meeting two decades ago with our wives (Thalia and Nan) that I will always remember fondly. During that trip we all discovered Grappa and I learned that George also knew how to have a good time. This showed me another facet of his enormous personality. George was a founder of the field of molecular hematology. His legacy is his numerous contributions to this discipline which serve as a foundation for the continued healthy marriage between hematology

and genetics. I will always miss his inevitably referring to me jokingly at meetings as ‘a young man’. This always made me feel like I was in part his student. To me George was larger than life.”

Even those who did not feel part of George’s inner circle had seminal comments. In this vein, **Mike Milsom**, Head of the Division of Experimental Hematology at the Deutsches Krebsforschungszentrum in Heidelberg, Germany writes, “Unfortunately I didn’t personally know George very well at all. But having started working on hematopoiesis focused on gene therapy, he was obviously an internationally prominent figure who I looked up to as a trainee (both for his scientific contributions to gene therapy/globin regulation and his leadership in setting up the American Society of Gene Therapy). I’m not sure it’s great material for a memorial piece, but the one time I had an extended discussion with him was when I interviewed for a postdoc position at the Fred Hutch. As part of the visit, I got shipped up to the University to meet with George and I was pretty much in awe of him at the time. We had a really stimulating discussion, which wound up with George asking me why I wanted to come to the USA to carry out a postdoc. I thought this was a pretty standard interview question, and I duly reeled off all the opportunities it would present me with from a training perspective. I was then somewhat surprised that George went on to trying to persuade me that it would probably be in my own interests to stay in Europe, given the issues with decreased research funding and restrictive legislation on moving gene therapy into the clinic. I came out of the interview a bit confused, but in retrospect, I really admired the fact that he gave advice that he felt prioritized the trainee over the interests of the institution. I think that is a great teaching point for academics who are put in leadership positions.”

Narla Mohandas, former Director of Hematopoiesis at Lawrence Berkeley National Laboratory and 3-year Interim Director of the Human Genome Project is now the Vice President for Research of the New York Blood Center. By way of farewell to a longstanding colleague and friend, he wrote, “a few sentences about my admiration about George. He was truly a remarkable individual and a giant in Hematology research.”

Clearly George was an inspiring scientist, thoughtful leader and universal colleague whose efforts in many areas continue to have an indelible impact. His contributions were also noteworthy in part through the connections he made and recognized, because of and occasionally in spite of the uncompromising high ideals and goals he shared with his beloved wife, Thalia Papayannopoulou, and their family. The world is a better place for his having helped it along. May we all continue to remember and learn from his amazing example.

1. University of Washington Newsroom. Postscript June 21, 2018**.** George Stamatoyannopoulos, pioneer of blood-disease research, dies.
2. Engel D, Higgs D. George Stamatoyannopoulos, MD (1934-2018). The passing of a true believer. The Hematologist 15 (4):2018.
3. Dunbar CE, Bodine DM, Nienhuis AW. George Stamatoyannopoulos, MD (1934-2018). Molec Ther 26(8) 1871-1872.

IMAGES IN HEMATOLOGY

Airlie House Legend

Martin H. Steinberg and Alan N. Schechter

1.Department of Medicine, Boston University School of Medicine, Boston, MA 02118

2 Molecular Medicine Branch, NIDDK, National Institutes of Health, Bethesda, MD 20892

Correspondence to

Dr. Martin H. Steinberg
Department of Medicine,
Boston University School of Medicine,
72 East Concord Street
Boston, MA 02118
Email: mhsteinb@bu.edu

or

Alan N. Schechter, M.D., Chief
Molecular Medicine Branch, NIDDK
Senior Historical Consultant
Building 10; Room 9N-314
National Institutes of Health
Bethesda, MD 20892
Email: alans@intra.niddk.nih.gov

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In the late 1980's (probably in 1988), the National Heart, Lung and Blood Institute convened a "think tank" at Airlie House in Northern Virginia to discuss the developmental therapeutic landscape for sickle cell disease. The participants, most of whom are shown in the accompanying photograph, included in Row 1 (left to right), William Eaton, Marilyn Gaston, Ronald Nagel, Samuel Charache, H. Franklin Bunn, Clarice Reid, Yves Beuzard, Max Perutz, Donald Abraham, Jean Smith and Alan Schechter, and in Row 2, Bernard Forget, Herbert Meiselman, Eugene Orringer, Martin Steinberg, Charles Wells, Mohandas Narla, Robert Josephs, Arthur Nienhuis and George Stamatoyannopoulos. David Nathan also participated. John Hercules from NHLBI largely planned and organized the meeting but died in March 1988.

These clinicians, investigators and NIH leaders were responsible for establishing much of the groundwork in basic, translational and clinical science that have led to treatments for sickle cell disease, some now approved and others likely to be approved. By the time of this meeting Perutz had established the basis of many of the functions of hemoglobin and shared a Nobel Prize in1962 for determining the molecular structure of this molecule. His work provided an understanding of how hemoglobin variants cause disease and how they might be therapeutically targeted. Studies stimulated by this meeting include the effective use of a fetal hemoglobin inducing agent, hydroxyurea, that has decreased morbidity and mortality of sickle cell anemia patients, the continuing development of agents that modulate intercellular adhesive interactions, a deepening appreciation of the effects of red cell hydration on disease pathophysiology and the beginnings of gene therapy for hemoglobinopathies.

George has been, and will continue to be, an inspiration to me in that he epitomized a researcher who is driven to solve a scientific mystery and improve the lives of patients. I'll always be grateful for his advice and support of my career.

John Crispino

George's passion, energy and drive have always been an inspiration to me and he was always there to provide help and support whenever needed. He has served as a role model and a mentor to scientists from Greece, even in fields extending beyond globin research. He will be sorely missed by everyone...

John Strouboulis

As a young investigator, I am very grateful to George and all his efforts in welcoming, training, and supporting the next-generation of investigators. George's legacies and inspirational work will be forever remembered by everyone working with hemoglobin regulation and switching, hematology, and beyond.

Best,
Jian Xu
UT Southwestern

Dear Thalia
This is just a short note to say how much George and you have been an inspiration throughout my career. Your passion to understand to biology and improve health is a very noble virtue. The drive for excellence and integrity was very clear in all that you both did and is an important principle to always remember. Your humanity and compassion, especially to younger people taking their first steps, was so helpful to so many. Thank you and we will all miss George.
Yours,
Paresh

"The globin switching field has lost a leading light. George is dearly missed."
Dorothy Tuan

Eulogy for George
From Roger Patient

I first properly met George when visiting Tariq Enver who was postdocking with him and Thalia, after doing his PhD with me. It was the beginning of an extremely stimulating relationship. I have many memories of exciting conceptual chats over dinner. This would often involve diagrams on napkins to clarify what he was talking about. I fondly remember one occasion when Tariq and I were focussing on the pen on the napkin and started to get a creeping feeling that he was just doodling and that the movement of the pen was irrelevant to what he was saying! I also remember being totally floored by a word he kept using, which I heard as 'broccoli'. I couldn't see what relevance this vegetable had to globin switching! It was a few conversations later before I finally figured out he was saying 'practically', and it was just a throw away word without much impact on what he was saying! George for me was one of the most open thinkers. He was interested in anything that could shed light on the mechanism by which globin gene expression is switched during development, and of course how it might be manipulated. I am very pleased that he was with us long enough to see his life time involvement in these issues start coming to fruition, in no small way due to his own efforts. He will be sadly missed.

George Stam was one of my role models. He was the real McCoy . He was a no nonsense scientist who always reached for excellence. He was all business and he wanted to get there in a hurry. I respected this approach and to this day I emulate it.There was also,however a kindness and humanity to this man which I also valued. When I was entering this field he always said hi to me and encouraged me to do what I was doing. He invited me to meetings and was interested in my work. This was an invaluable gift because it made me feel that I was on the right track. George and I both attended a small meeting two decades ago with our wives(Thalia and Nan) that I will always remember fondly. During that trip we all discovered Grappa and I learned that George also knew how to have a good time. This showed me another facet of his enormous personality. George was a founder of the field of of molecular hematology. His legacy is his numerous contributions to this discipline which serve as a foundation for the continued healthy marriage between hematology and genetics. I will always miss at meetings when he inevitably called me jokingly "a young man" ;this always made feel like I was in part his student. To me George was larger than life I will miss him and remember him.

Ron Hoffman Mount Sinai School of Medicine, N.Y.,N.Y.

Dr. George Stamatoyannopoulos was a brilliant scientist, who not only did pioneering research and made great contributions to the field of hemoglobinopathies, but a man with a great vision. He was touched by the high prevalence of hemoglobinopathies in Greece and wanted to find ways to cure these disorders. He organized this meeting that we all religiously attend, to study regulation and complexities of hemoglobin expression. From his effort and vision, he motivated so many, who joined in making outstanding contributions to the understanding of hemoglobinopathies. He also envisioned that genetic therapies as the ultimate cure for this disease. In fact, he was the founder of the American Society of Gene Therapy, now the main (and the only forum) where the latest and the greatest gene therapy science is presented. In his passing, the field has lost a great leader, visionary and scientist who was an inspiration to many.

Punam Malik

Relationship with George Stamatoyannopoulos

I first met George at an American Society of Hematology meeting which was held in San Diego in 1976 or 1977. We had a shared interest in the mechanism of hemoglobin switching because of the therapeutic potential of fetal hemoglobin for the treatment of Beta-thalassemia and sickle cell disease. It seemed clear to us that the field would benefit from a regular meeting to bring together those interested in hemoglobin switching and also to draw in scientists whose work was relevant even though their own primary focus was not on the switching mechanism. We organized the first meeting at the Batelle Institute in Seattle in 1978. The meetings have continued biannually ever since. The 21st Switching Conference is scheduled to occur within the next year. The proceedings of the conferences were often published thereby providing a permanent record of the conferences. We also edited a book entitled "Molecular Basis of Blood Diseases' which provided an additional summary of the status of the field. In addition to organizing the conferences, George and I interacted frequently. For a period of perhaps 20 years or more we talked by telephone or in person every weekday. We discussed our own plans and work by others that we judged to be relevant.

George visited often while I was in Bethesda working at the National Institutes of Health. Often we would meet and discuss our interests until the very last minute and then have to rush George to the airport for his flight to Seattle. On one occasion we did leave early and pulled into the National Airport with more than an hour and half to spare. I said to him, "Well George, we've finally got you here in time." He responded with "Well "Nienhois" (he always call me by that name), I'm leaving from Dulles not National". We left and traveled at very high rates of speed to allow him to catch his flight. Fortunately, no accident or citation for speeding occurred.

While I still at the NIH, I had the pleasure of having his son, John, work in my laboratory for a period of time. John was extremely brilliant although sometimes a little neglectful of optimal laboratory technique. I am delighted to observe his career development and appreciate his impact on the field of molecular genetics.

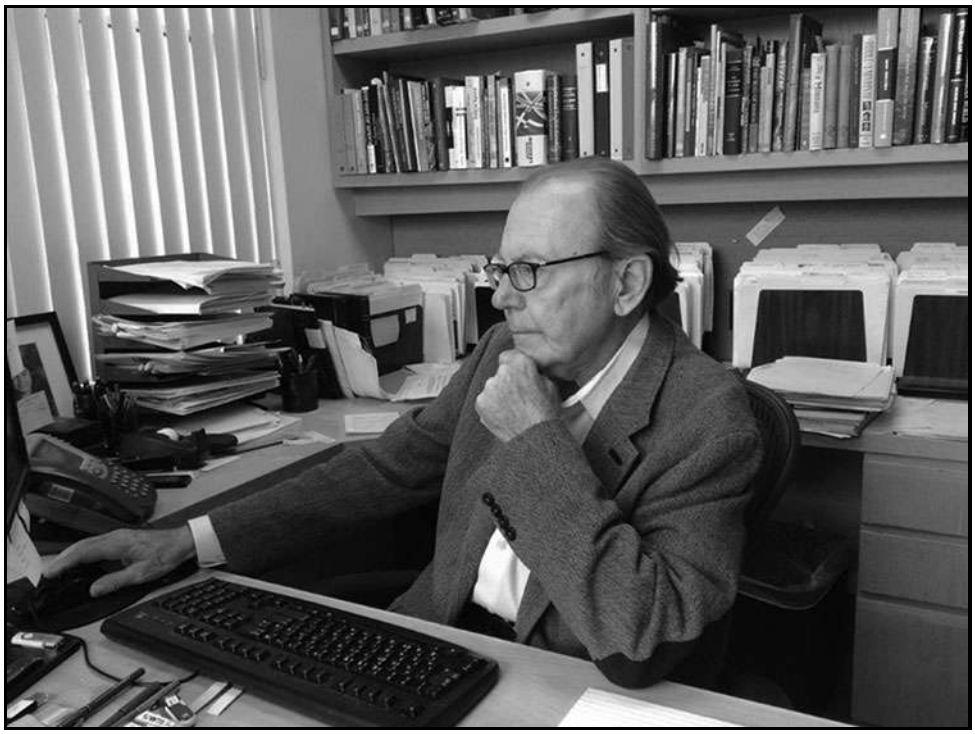
George will undoubtedly have a lasting legacy in the field of hemoglobin switching. We've learned a great deal over the years regarding the mechanism of switching. In addition, our therapeutic objectives have also been realized with the development of drugs capable of inducing fetal hemoglobin synthesis in patients with thalassemia and sickle cell disease. My efforts, along with my colleagues, including Tim Ley, focused on the development of 5-azacytidine. Many colleagues, including George, were quite concerned that it was carcinogenic and argued that we should seek to use other agents without this perceived risk. In response to this challenge, David Nathan and colleagues at Boston Children's Hospital fostered the use of hydroxyurea. Indeed this drug was developed and is now in broad use for the treatment of patients with sickle cell disease. If is much less efficacious in patients with severe Beta-thalassemia. 5-azacytidine, which turned out not to be carcinogenic but rather has been used as a cancer preventive agent, is also beginning to be put into use for treatment of hemaglobinopathies.

As this brief summary indicates, George has had a very lasting impact and I've enjoyed working with him. As indicated above, I spoke with him on the phone daily until my responsibilities as Director of St. Jude Children's Research Hospital beginning in 1993 precluded my availability for such interactions. Nonetheless, I think back with great fondness of George and pride in what we were able to accomplish together.

Art Nienhuis

A Tribute to George Stamatoyannopoulos

Arun Srivastava, Mark A. Kay, Takis Athanasopoulos, Michael Angastiniotis, Achilles Anagnostopoulos, Garyfalia Karponi, Evangelia Yannaki, Leonard I. Zon, Carsten W. Lederer, Marios S. Phylactides, and Marina Kleanthous



ODE TO GEORGE

AT THE OUTSET, I wish to express my deep sense of appreciation and gratitude to George Stamatoyannopoulos for his farsightedness in launching the American Society of Gene (and Cell) Therapy, the first annual meeting of which was held in Seattle, Washington, in 1998. I vividly recall the moving inaugural Presidential Address that George gave, emphasizing the role the young generation of scientists should play in the future success of the Society. Here, I would like to narrate two distinct reminiscences and stories about George.

My first story dates back to circa 1990, when I first reached out to George soon after we described the generation of an AAV2-parvovirus B19 hybrid virus[1] in the hopes of using it as a vector to deliver the β-globin gene. The general idea at the time was to achieve site-specific integration by AAV2 (a landmark discovery by Dr. Kenneth I. Berns and his colleagues)[2] and erythroid progenitor cell-restricted expression from the parvovirus B19 promoter.[3–5] While our studies with the AAV2-B19-β-globin vector were underway, Art Nienhuis and Jude Samulski joined forces and reported AAV2 vector-mediated γ-globin gene transfer and expression in human K562 erythroleukemia cells at the RNA level.[6] George was not only extremely gracious in sharing his β-globin expression cassette, but his laboratory also performed β-globin gene expression in human K562 cells at the RNA as well as at the protein level.

Assuming that George was a Member of the National Academy of Sciences, I asked him whether

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he could contribute our manuscript to *PNAS* as well, to which he responded wryly, "They don't let Greeks and Indians into the Academy." In any event, our coauthored article was eventually published in *Gene Therapy* in 1996,[7] of which I remain immensely proud two decades later.

In retrospect, the use of AAV2 (the only available serotype vector available at the time) was not ideal since AAV2 transduces murine hematopoietic stem/progenitor cells (HSPCs) poorly. Thus, despite our sustained efforts,[8–11] the use of a murine model to demonstrate the feasibility of AAV2 vectors for the potential gene therapy of hemoglobinopathies did not succeed. It wasn't until 2013 when we identified AAV6 as the most efficient serotype for transducing *human* HSPCs,[12,13] and it is my fervent hope that the optimized AAV6-B19-β-globin vector will prove to be a useful alternative for the potential gene therapy of human hemoglobinopathies in the not-too-distant future, based on recent success with AAV6 vectors and human HSPCs.[14–16]

My second story about George is somewhat more personal. I would occasionally run into George at the annual meetings of the ASGCT, but in 2011, when George saw me, he immediately blurted out, "You have gained 15 pounds." I was astonished as to how precisely he was able to guess the extent of my weight gain. Needless to add that George's comment motivated me to shed those extra 15 lbs [plus 5 more!] over the ensuing 2 years, for which I will remain eternally grateful to him, because that weight loss was instrumental in reversing my prediabetic diagnosis.

I saw George again at the ASGCT meeting in 2015 in New Orleans, and he told me that he just turned 81 years young. I told him that my wish was to look half as good as he does when—and if—I turn 81.

In sum, the fact that, despite overwhelming odds, I have continued to pursue AAV vector-mediated β-globin gene delivery more than a quarter of a century after I first reached out to George is a very small token of my deep sense of appreciation, as well as the utmost respect and awe in which I hold George.

Long live George!

Arun Srivastava, PhD
George H. Kitzman Professor of Genetics
Chief, Division of Cellular and Molecular Therapy
Departments of Pediatrics, Molecular Genetics & Microbiology
Powell Gene Therapy Center, Cancer and Genetics Research Complex
2033 Mowry Road, Room 492-A
University of Florida College of Medicine
Gainesville, FL 32611-3633

E-mail: aruns@peds.ufl.edu

PRAISE FOR GEORGE STAMATOYANNOPOULOS

It is an honor and privilege to participate in this Festschrift issue to acknowledge George Stamatoyannopoulos, who we commonly refer to as George Stam.

Back in 1992, after several visits to Seattle, Dr. Stam took a chance and offered me a faculty position in his Division of Medical Genetics as part of the Markey Molecular Medicine Center at the University of Washington. This came at a time when my scientific colleagues were telling me I had enough sense to stay away from gene therapy because it was not real science. The initial contact was not easy. I had written and called several times in 1991/1992, but I literally had to pull him aside at an evening reception at the American Society of Human Genetics to get his ear. George had many redeeming qualities as a mentor. His willingness and ability to rip apart my grants (fortunately prior to submission) was invaluable. He would say, "Young man, the science is great, but presentation is key to getting a good score." I still remember the hours I spent going through his handwritten notes, as in those days word processing programs were relatively archaic. I sometimes wondered if there were a few Greek terms thrown in to see if I was paying attention. Nevertheless, these lessons were vital for me and helped me advance my own career. George liked to solicit the views of others, but he was tough. I remember discussing an important topic during my first faculty meeting. After much debate, he turned to me and said, "Young man, what do you think?" I replied, "I think we have heard both sides and I am ready to vote." George paused and chuckled, "Vote? In my many years as division head—we never vote."

George would come and discuss his frustration on how the American Society for Human Genetics failed to devote much time to gene therapy topics at the annual meeting. I still remember George walking into my office to ask my opinion and discuss his idea for starting what is now the American Society for Gene (and Cell) Therapy (see doi:10.1038/mt.2010.11 and doi:10.1038/sj.mt.6300284 for historical prospective). Of course, being a new assistant professor, I had no idea how one goes about starting a society, but it sounded like a great idea. I was fortunate to see and learn the steps and processes required for such a major undertaking. George kept with it and the rest, as we say, is history. I appreciate that he selected me to be on the Society's founding Board of Directors. Those who have more recently joined the gene therapy com-

munity may not fully appreciate what George did to get the Society on its feet and keep it going, even during the field's darker days. The payoff has been great because the Society has been so important in bringing together diverse scientific, medical, manufacturing, and regulatory communities from across the globe. I am grateful to what George taught me, and our community is indebted to his contributions to our field. Almost 25 years later, I look forward to seeing George and hearing the greeting, "Young man."

Mark A. Kay, MD, PhD
Dennis Farrey Family Professor
Departments of Pediatrics and Genetics
Stanford University

E-mail: markay@stanford.edu

THE GODFATHER OF OUR FIELD

Modern science is a multinational and collaborative endeavor. As one of the many Greek "scientific immigrants," I made the journey from the lab of Professor Aglaia Athanassiadou to doctoral studies in the George Dickson's lab, where I was also mentored by Professor Nick Anagnou. Both professors Athanassiadou and Anagnou themselves had sojourned elsewhere for many years before returning to Greece. It was during this period that I encountered the work of Professor George Stamatoyannopoulos, the eminent Greek "scientific immigrant" who has had such an impact on gene/cell therapy via his research, not least through founding the American Society of Gene & Cell Therapy (ASGCT). With more than 2,000 members in the United States and worldwide, ASGCT is the largest association of individuals involved in genetic and cellular therapeutics.

Professor Stamatoyannopoulos received his MD from the University of Athens and his doctorate of science degree from the University of Athens, before his own "scientific migration" to the United States. Professor Stam, as he is more widely known to the community (and because Stamatoyannopoulos can often be a mouthful to non-Greek speakers!), has more than 400 research publications and thousands of citations. He has been the founder of multiple biotech companies and is widely acknowledged as a leader in the field of hemoglobinopathies. For over-four decades his research has focused on the delineation of the cellular and molecular processes by which hemoglobin switches from fetal to adult form during development. His research is currently focusing on the control of human globin genes during development and differentiation, the development of treatments for sickle cell disease, the development of somatic gene therapy for β chain hemoglobinopathies (together with Dr. Lila Yannaki in Thessaloniki), the identification and delineation of regulatory elements of the human genome (together with his son, John Stamatoyannopoulos, who is also an eminent scientist), and the investigation of molecular genetics of Bronze Age populations inhabiting the Aegean basin in Greece and in the Balkans. George has been the recipient of several prestigious honors and awards, the latest being this very Festschrift.

I first met George at an ASGCT congress in Washington DC that I attended with my wife Nadia, a nonscientist. We were both impressed by two things: his vast and equally extensive and deep scientific and nonscientific knowledge (including history and philosophy), and his devotion of time and limitless encouragement and mentorship to the younger generation. When I finished my talk in 2014 at another conference held in Patras, Greece (where his earth-shattering data were preceded by a real earthquake!), I still remember George congratulating me (to his long-time friend and colleague at the University of Washington, Professor Thalia Papayianopoulou) with the line, "The kid is progressing well." I am proud to be one of many of George's "scientific kids" and delighted and honored to have met him in my "scientific migrant" life. I will always keep him in the highest esteem! For all of us "relatively speaking" younger scientists/members of the gene/cell therapy societies, I think Professor George Stamatoyannopoulos is rightfully acknowledged as the scientific godfather of the gene and cell therapy field for Greek (and other) scientists.

Dr. Takis Athanasopoulos, PhD, AHEA
Lecturer in Molecular Biotechnology
Faculty of Science and Engineering, University of Wolverhampton (UoW)
City Campus South, MA Building, Room MA206
Wulfruna St., Wolverhampton, WV1 1LY
United Kingdom

E-mail: t.athanasopoulos@wlv.ac.uk

and

Academic Visitor and Research Consultant
Royal Holloway University of London (RHUL)

E-mail: p.athanasopoulos@rhul.ac.uk

GEORGE STAMATOYANNOPOULOS AND THE PREVENTION OF THALASSEMIA: THE EXPERIENCE OF CYPRUS

The concept of the possible prevention of thalassemia was first put forward by Ida Bianco and Enzo Silvestroni in 1955 when they suggested to Italian health authorities the establishment of a center for

the study of "microcytemia," which would include free medical care for patients and the establishment of large-scale screening and preventive counseling programs. This suggestion required investigation on the social, legal, and cultural level if it was to become a practical policy for the limitation of new affected births. Prenatal diagnosis was not an option in those days, so the result of screening and counseling could only be avoidance of marriage between carriers. This would predictably meet with resistance even by at-risk couples, and the people had to be asked whether such a program would be acceptable. Such an enquiry was not undertaken until the 1960s when George Stamatoyannopoulos stepped in.

He chose a village in Greece in the Arta region, known to have a high carrier rate for beta thalassemia, where he first went to screen the population and to counsel them concerning the risk of marriage between carriers. He suggested avoidance of such marriages and returned a year later to see the result. He noted that there was no marriage avoidance on the basis of genetic risk. These results were published in 1974 in *Exerpta Medica*.

His next stop was Cyprus in 1972, another high prevalence area. In the early 1970s, the treatment of thalassemia was accepted to be regular blood transfusion and iron chelation using desferrioxamine. The dose of the drug was not well defined, and the government was providing 12 (500 mg) vials per month to each patient. It was however known that many patients and doctors were using increasing doses, and that demands on hospital admissions and blood donations were increasing dramatically. The Ministry of Health requested a World Health Organization (WHO) consultancy and George Stamatoyannopoulos was selected. By this time, WHO expert groups were also suggesting screening of couples to identify carriers and prenatal diagnosis, "provided they are willing to have the affected pregnancy termination."[17] The results of his consultancy were presented and adopted by the Ministry immediately. A summary was published in the *British Medical Journal*.[18] In his discussion he states: "This small Mediterranean nation is thus burdened with one of the highest frequencies of thalassaemia genes in man. The local public health service has to face the problems of a severe disease whose management is completely inadequate, whose cure is not in sight, and whose prenatal diagnosis is unavailable."

The actions taken in Cyprus following his report are well known, have resulted in the minimization of new births, and as a result existing patients were given the best possible resources to survive. If there was no prevention, the increasing number of patients would have had little chance, even for an adequate supply of blood.

Dr. Michael Angastiniotis
TIF Medical Advisor
Thalassaemia International Federation
PO Box 28807, 2083 Strovolos
Cyprus

E-mail: thalassaemia@cytanet.com.cy

THE BRILLIANT GEORGE STAMATOYANNOPOULOS

Writing about Dr. George Stamatoyannopoulos is quite a challenge—what at first glance may appear as hyperbole is none other than an accurate reflection of an enormous personality and an equally enormous body of work.

George was already internationally known in the early 1960s when he moved from Greece to Seattle, where he pursued a brilliant academic career as professor of medicine, pathology, and genome sciences and director of the Markey Molecular Medicine Center at the University of Washington, producing more than 400 original publications. His research led to the discovery and understanding of the molecular mechanisms of red blood cell production during human ontogeny and made an essential contribution toward the elucidation of the genetic basis of thalassemia and hemoglobinopathies at large. He has been a pioneer worldwide in the ever-growing field of gene therapy; his unique vision was instrumental for the development and implementation of innovative approaches for preclinical models of gene therapy and the establishment of the American Society of Gene Therapy, where he became the first president.

George is a father figure to his team members, whom he inspires for the best. He has a strong personality and rare human qualities. He is a born leader and a true visionary with a capacity to transform his ideas to plans and actions, an original thinker, impressively effective, demanding with both himself and his colleagues, and a rationalist who is also rich in emotions, always eager to assist and offer. George is especially fond of the younger generation and has never forgotten his roots.

Dr. Stamatoyannopoulos is a legend for the members of the Hellenic Society of Gene Therapy and Regenerative Medicine (HSGTRM), the members of the Hellenic Society of Haematology, and the Greek patients with thalassemia. Many members of both societies, including three of seven board members of the HSGTRM (Drs. Anagnou,

Vasilopoulos, and Yannaki), have had the privilege to be trained by George in his department, but perhaps more importantly, received his mentorship throughout their professional life.

The Hellenic Society of Gene Therapy and Regenerative Medicine is organizing its inaugural meeting, including an International Symposium on the Advances of Gene Therapy, in Thessaloniki, Greece on September 23–24, 2016. Dr. Stamatoyannopoulos is the president of the Scientific Committee and is working enthusiastically toward preparing an outstanding program.

On a personal note, George is my mentor, especially in matters of organizing and developing new units and scientific events, a valuable advisor and friend. Among other things, he guided me through the establishment and operation of the Gene and Cell Therapy Centre at the George Papanicolaou Hospital in Thessaloniki, he trained our scientific personnel in his department, and is continuously collaborating with us in pioneering studies on gene therapy of thalassemia and beyond.

Overall, I sincerely believe that the terms charismatic and outstanding are apt for his personality and achievements. George, on behalf of the Hellenic Society of Gene Therapy and Regenerative Medicine, may you live long and share with us your many gifts!

Achilles Anagnostopoulos
President, Hellenic Society of Gene Therapy and Regenerative Medicine
Director and Head
Haematology Department, BMT Unit, Gene and Cell Therapy Centre,
Public Cord Blood Bank
George Papanicolaou Hospital
Thessaloniki 57010
Greece

E-mail: achanagh@gmail.com

AN INSPIRATION

Dr. Stamatoyannopoulos is a long-term collaborator with the Gene and Cell Therapy Center (Dr. Yannaki's lab) of the George Papanicolaou Hospital in Thessaloniki, Greece, with which I am affiliated. I've known Dr. Stamatoyannopoulos since 2005, when I started working at the Center. In 2006, I was blessed to receive a year's training in gene therapy techniques in his laboratory in Seattle and work under his direct supervision. I still remember his warm welcome and his effort to encourage every small scientific step I was taking forward. Although I was only a BSc holder at the time, he showed a remarkable trust in my research capabilities that further awakened my interest in gene therapy. Until now, he remains a close mentor and strong supporter of the research we are conducting in Dr. Yannaki's lab. Importantly, despite his outstanding scientific contributions, beyond any doubt Dr. Stamatoyannopoulos remains very humane and kind. In short, I dare to regard Dr. Stamatoyannopoulos as my continuous source of inspiration, and I am proud to be one of the many Greek researchers who were given the chance to meet and work with him.

Garyfalia Karponi, PhD
Molecular Biologist-Geneticist
Gene and Cell Therapy Center
Hematology-BMT Unit
George Papanicolaou Hospital
Thessaloniki
Greece

E-mail: aminoxy@yahoo.gr

GEORGE STAMATOYANNOPOULOS: THE MENTOR, THE FATHER, AND THE PROUD GREEK

The mentor. I have been blessed to have George Stamatoyannopoulos as a mentor for the past 18 years. My encounter with Dr. Stam had an outsized impact on the path my career and my life took after I met him in 1998, early after obtaining my Greek board certification in hematology. I have had the considerable privilege of being supervised by him during my first steps in gene therapy and closely interacting with his personal authenticity, passionate commitment to research, and selfless work ethic. At that time, I had also the privilege to witness some of his legendary verbal fights over scientific matters with Thalia, his loveliest and toughest competitor ever, that were generating a unique learning atmosphere in the lab. Upon my return to Greece, George has been instrumental in helping me to set up a gene and cell therapy program at the G. Papanicolaou Hospital in Thessaloniki, and since then, a long-standing collaboration between the two institutions has been established, translated in two clinical trials and studies on the optimization of mobilization and graft sources for thalassemia gene therapy. Our mentor–mentee interaction continues up to now, and I often seek his advice on critical scientific questions or dilemmas. I am and I will be eternally grateful for his mentorship!

Among diseases, thalassemia syndromes have always been his scientific passion and life-long challenge. He likes to narrate how enthusiastically and with true devotion in the late 1950s, he, a young doctor during his military service, used to fill a small wooden chest (*kaselaki* in Greek) and visit by bus or on foot, in some instances, remote

mountainous and difficult-to-access villages in the Greek mainland and islands in order to take blood samples and study families with hereditary traits. At those times, he managed, with as little as a *kaselaki* but with extreme motivation and deep thinking, to pioneer the population genetics of red cell enzymopathies and hemoglobinopathies.

What is not a very well-known aspect of his personality is his inexhaustible love of history and collection of invaluable rare editions of ancient historical books. In order to combine his childhood dream of becoming a historian with his passionate curiosity, he is currently investigating the genetics of the Bronze Age population of Minoans and Myceneans and the genetics of the populations of Greece and the Balkan peninsula. To pursue this goal, in his 80s and more than 50 years after his first campaigns in the Greek countryside, he, himself, visited rural Greece once more from one side to the other.

The father. George has been a father figure in my life, offering guidance the times I felt lost and overwhelmed and teaching me lessons that impacted my life. In times of tragedy, his wise words and paradigms retrieved from Greek legends and history have softened the soul pain and created meaning.

The proud Greek. George, although being a world citizen for more than 50 years, never forgot his Greek origin and the unique history and legacy of his staggeringly beautiful mother country. He is emotionally suffering for the proud, but powerless, Greece these last years that Greece has been hurting under austerity.

Now in his eighties, George keeps scientifically active and motivated like when I first met him. I can see that he is still carrying his *kaselaki* of his first youth with the research passion and the endeavor to pursue it to the best of his ability and above all obstacles. He is an inspired and inspiring academic leader and a real intellectual whose scientific productivity and intellectual vigor advances with his aging, as a natural consequence. In his words, "The career of the real intellectuals never reaches a sunset. It simply ends abruptly with their death."

Evangelia Yannaki, MD
Affiliate Associate Professor
University of Washington

and

Director
Gene and Cell Therapy Center
Hematology Dpt-BMT Unit
G. Papanicolaou Hospital
Thessaloniki 57010
Greece

E-mail: eyannaki@u.washington.edu

A TRIBUTE TO GEORGE

I sat outside a conference room at the American Society of Hematology meeting and was greeted by George. In a Greek accent, "Zon, how are those fish doing?" I told him that the mutants we had were great, but it will be very difficult to clone the genes. "Zon, the only way you will ever get this done is if Harold Varmus (the NIH director) wants a zebrafish genome project." I knew this was a brilliant idea, and the next day, I called Harold and asked for his advice. He thought it was a great idea, and that started the Trans-NIH Zebrafish Genome Initiative. Without George, there would be no zebrafish genome project.

When I started the International Society for Stem Cell Research (ISSCR), I called one person, George. Given what he did for the Gene Therapy Society, he would have the right advice. I was so excited when he showed up at the ISSCR meetings. He has always been so supportive.

These stories illustrate how far-reaching George's contributions to society have been. Thanks, George, for being you!!

Leonard I. Zon
Division of Hematology/Oncology, Boston Children's Hospital and Dana-Farber Cancer Institute, Howard Hughes Medical Institute, Harvard Stem Cell Institute, Harvard Medical School
Boston, MA 02115
Chemical Biology Program
Harvard University
Cambridge, MA 02138

Mailing address:
Karp Research Building
7th Floor 300 Longwood Ave
Boston, MA 02115

E-mail: zon@enders.tch.harvard.edu

PROFESSOR STAMATOYANNOPOULOS AND CYPRUS

When George Stamatoyannopoulos first cast his scientific eye over the island of Cyprus, most authors of this short praise had not even been conceived. The resulting study, published in 1973, truly put "thalassemia in Cyprus," both alpha and beta, on the map, establishing our small country as exceptionally afflicted by the disease and, at the same time, as a potential role model for its control and management.

Much has changed since, facilitated by fundamental insights into the hemoglobin switching gained, animal models developed, and scientific attention focused on thalassemia by the now eminent Professor Stam. Cyprus has the most effective

thalassemia control program worldwide, keeping annual births of thalassemics below 5% of the expected birth rate. Mandatory premarital testing, prenatal molecular diagnosis, preimplantation genetic diagnosis, and, soon, noninvasive prenatal diagnosis contribute to giving at-risk couples a choice of whether or not to carry an affected pregnancy to term. Disease management, helped by the dedicated national Thalassemia Centre and by improvements in iron chelation and blood supply and safety, has enabled patients to live ever longer, ever fuller lives, with birth rates from thalassemic women even surpassing those in the population at large. The high carrier rate is still there, but the stigma, as thalassemia is still called in local everyday language, has lost its sting. In answer to a quizzical note posed by George and his coauthors, some 40 years later we can confidently say that "prospective genetic counseling applied at the level of populations has beneficial effects" indeed.

George and his immediate associates (or, should we say, disciples) continue to be productive collaborators and coauthors in local and international projects, be it in the chemical induction of γ-globin as a drug therapy for β-globinopathies, in the application of lentiviral gene therapy for β-thalassemia, or by the inclusion of Cypriots in George's effort to map the distribution of Hellenic DNA around the globe. George continues to look forward, and we keep looking forward to his next visit to Cyprus!

Carsten W. Lederer
Marios S. Phylactides
Marina Kleanthous
Molecular Genetics Thalassaemia Department
The Cyprus Institute of Neurology and Genetics
6 International Airport Avenue
1683 Nicosia
Cyprus

E-mail: Lederer@cing.ac.cy

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HEADLINES FROM Washington

Congress Begins Work on FY 2019 Appropriations Process

Following the Trump Administration's submission of its proposed fiscal year (FY) 2019 budget earlier this year, Congress has begun the process of crafting the 12 appropriations bills that fund different government agencies including the National Institutes of Health (NIH). As this issue of *The Hematologist* went to press, congressional appropriators had set an ambitious schedule, pledging to finish drafting of the spending bills by the end of June. This timeline could theoretically give Congress the ability to vote on and finalize all bills before the start of the next FY on October 1, 2018; however, Congress has not passed all 12 bills on time since 1996.

The appropriations process is critical to hematology. Congress allocates funding for medical research through the NIH and supports numerous public health agencies, such as the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA). These agencies will not be able to continue or expand vital health programs without additional funding.

Thanks to the hard work of hematology advocates from ASH and the larger biomedical research community, the NIH has seen several consecutive years of significant increases in funding including a $3 billion increase in funding in the current FY, bringing the agency's total funding level to slightly more than $37 billion. The CDC also received an increase of $1.1 billion in FY 2018, for a total funding level of approximately $8.3 billion.

Despite these gains, threats to public health program funding remain. In May, President Trump officially submitted to lawmakers a $15.4 billion package of proposed rescissions — reductions of funding previously provided in law. Nearly half of the proposed cuts, $7 billion, would come from unspent Children's Health Insurance Program (CHIP) funds, and almost $5 billion would be cut from dormant Energy Department loan programs. The President has the authority under the Congressional Budget and Impoundment Control Act of 1974 to amend and reduce funding levels previously provided by law. Since the administration cannot rescind funding without congressional approval, Congress must pass legislation for the cuts to take effect. As this issue went to press, the Senate chose not to act on the President's rescission request before special procedural powers expired and a 60-vote threshold set in, severely lowering the chance of passage.

ASH continues to advocate for robust funding for the NIH, seeking $39.3 billion for the agency in FY 2019. In an effort to temper expectations, Chairman of the House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies, Representative Tom Cole (R-OK), has warned members of the research community not to expect such large increases for FY 2019 – making advocacy by the research community all the more vital to ensuring NIH receives sustained funding.

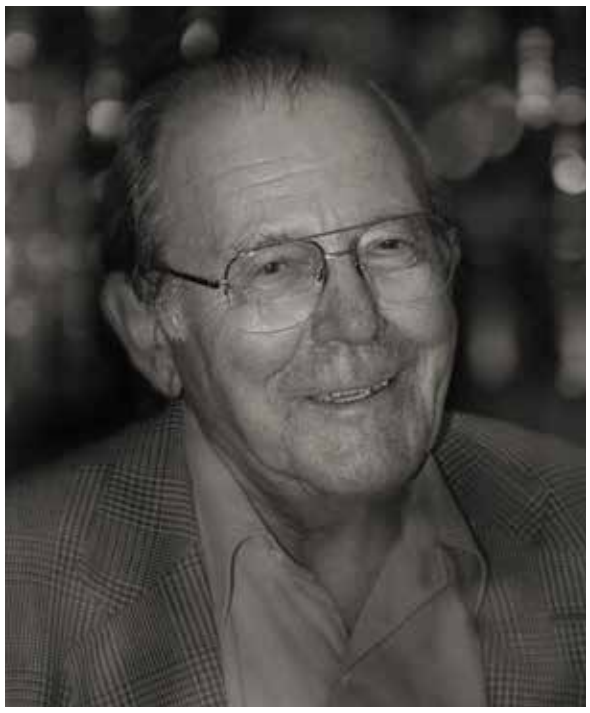
ASH members have been advocating with members of Congress, and the Society continues to work with its members to schedule meetings with legislators both in Washington, DC, and back home. These face-to-face meetings are an essential component of ASH's advocacy efforts, providing an opportunity for members of Congress and their staff to gain insight into issues of concern to hematologists and their patients. However, the Society needs the help of all its members to focus attention on the importance of federal research funding and the need for predictable and sustained funding for NIH and federal public health programs. Visit *www.hematology.org/Advocacy* for updates on the FY 2019 budget process and information about how you can contact your elected officials in support of NIH funding for FY 2019.

ASH Action on CAR T

ASH is actively working to ensure adequate reimbursement for chimeric antigen receptor T cell (CAR-T) therapy. This innovative treatment, currently approved for certain patients with leukemia and lymphoma, is used to treat individuals who have exhausted all other treatment options, including chemotherapy, radiation, or stem cell transplantation. Because current reimbursement systems and payment rates fall short of covering the costs associated with CAR-T therapy, institutions are forced to make difficult choices on whether to provide the treatment, resulting in long waiting lists for patients to receive the therapy. ASH continues to stay engaged on this topic as the Centers for Medicare and Medicaid Services (CMS) work to create new codes and coverage policies for these therapies. The Society submitted comments on CMS's proposed National Coverage Analysis for CAR T as well as on CAR-T–specific proposals in the Inpatient Prospective Payment System proposed rule. Additionally, ASH staff and members have participated in meetings related to coding for CAR T including a public meeting for the Healthcare Common Procedure Coding System (HCPCS) and meetings for Current Procedural Terminology (CPT) codes. It is imperative that the coding and associated billing procedures for these new and innovative treatments are appropriately defined. With more CAR-T therapies for other conditions expected to receive FDA approval in the near future, the precedent set here will influence patient access to this entire class of treatment.

Trump Administration Releases Blueprint to Lower Drug Prices

On May 11, 2018, the Trump Administration released "American Patients First: The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs." The document identified challenges in the American prescription drug market such as high list prices for drugs, and high and rising out-of-pocket costs for consumers, as well as a blueprint for addressing these challenges. The administration identified four key strategies for reform: improved competition, better negotiation, incentives for lower list prices, and lowering out-of-pocket costs. The document also included ample opportunity for feedback. To view the comments submitted by ASH on July 16, visit *www.hematology.org/advocacy/testimony.aspx*.



George Stamatoyannopoulos, MD, DrSci (1934-2018)

The Passing of a True Believer

Our friend and mentor, Dr. George Stamatoyannopoulos, passed away on Saturday, June 16, 2018, at the age of 84. In addition to his nuclear family, George leaves behind many friends and colleagues in the field of biomedical research into blood and its disorders. He is owed an enormous debt of gratitude that can never be fully quantified or repaid – with hundreds, perhaps thousands of scientists and clinicians who were influenced by his considerable charm, humanity, and scientific leadership. George's passion for promoting knowledge and science never wavered, despite bravely battling through many years of ill health.

George was born in Athens, Greece, on March 11, 1934. His childhood was shaped by the cataclysmic events that engulfed Greece between 1939 and 1949, where the Nazi occupation, famine, and ensuing civil war scattered his family. Following the war, he completed a classical education, studying science during the evenings. He entered medical school in Athens at age 17, graduating at the top of his class. George's professional career began in 1958 when he was awarded an MD with highest honors at the University of Athens. While serving briefly on the faculty there, his early work, based on population studies, first suggested that carriers of thalassemia were protected from *falciparum* malaria. He also proposed the beneficial effect of fetal hemoglobin on the clinical status of patients with β-thalassemia. This work drew the attention of Dr. Arno Motulsky, a pioneer in medical genetics, who recruited him as an instructor in the department of medicine at the University of Washington in Seattle, where George remained for his entire professional career.

George was promoted through the ranks to become a professor in 1975, and founding director and division head of the medical genetics program from 1985 to 2009. He was later appointed to concurrent professorships in the departments of pathology, genetics, and genome sciences. Throughout his career he made many key advances in our understanding of the process by which hemopoietic stem cells undergo lineage specification and differentiation to form red blood cells; how the globin genes are regulated; and how this is perturbed in common forms of anemia, particularly thalassemia and sickle cell disease (SCD). Among his many honors and awards, he was the recipient of the William Dameshek Prize (1990) and the Henry M. Stratton Medal (2002), and served as president of ASH in 1992. He authored and coauthored more than a dozen transformational textbooks and more than 400 high-impact peer-reviewed scientific articles.

The academic signposts of an eminent scientists' life do not fully convey the impact that George had on generations of young scientists and their scientific progeny. Most of the current senior scientists in this field (including we, the authors of this In Memoriam), were given the very first opportunity to present our work at what was probably George's most important long-term legacy to hematology – the Biennial Hemoglobin Switching Conference. These meetings were the brainchild of George and Dr. Art Nienhuis (then at the National Institutes of Health [NIH]) and were established to convene scientists and clinicians to discuss the most recent findings in the burgeoning field studying the molecular genetics of the hemoglobinopathies, including

(Cont. on page 13)

Are Transfusions a Barrier to High-Quality End-of-Life Care in Hematology?

THOMAS W. LEBLANC, MD, MA, MHS, FAAHPM,[1] AND MARK R LITZOW, MD[2]

1. Associate Professor of Medicine, Duke Cancer Institute, Durham, NC
2. Consultant, Division of Hematology; Professor of Medicine, The Mayo Clinic, Rochester, MN


In 2017, more than 55,000 Americans died of a hematologic malignancy. That's more than the number of deaths from breast cancer, a more common malignancy. Today, over half of Americans who die of cancer receive end-of-life care services via hospice. While hospice is sometimes misconstrued as a place or a building, it is more fundamentally a philosophy of care as well as an insurance benefit. Hospice was first offered in the United States in 1982 through Medicare and has since expanded to private insurers and younger patients. Indeed, growing evidence demonstrates that hospice provides very high-quality care at the end of life. Most people receiving hospice care die in their homes, in peace and comfort, surrounded by loved ones. They spend less time in hospitals and receive less aggressive treatment in their last days when these treatments are unlikely to yield meaningful benefits. As such, hospice care has emerged as the gold standard for high-quality care of the dying in the U.S.

Unfortunately, evidence suggests that patients with hematologic malignancies are significantly less likely to use hospice care services than patients with solid tumors,[1] instead receiving aggressive care at the end of life, including chemotherapy in the last 14 days, or spending time in a hospital, intensive care unit, or emergency department in their last month, sometimes even dying in the hospital.[2-4] Furthermore, when hematologic malignancy patients do use hospice, they are more likely to do so for a very short period of time, thus missing out on many of its benefits.[5]

While the origins of this problem are likely multifactorial, it is often said that hematologic malignancies themselves pose unique barriers, such as the frequent need for transfusion support.[4,6] This is because transfusions are often not able to be provided to patients receiving hospice care, since they may be homebound, making the logistics of transfusion more difficult. Additionally, the cost of regular transfusions generally exceeds the "per diem" payment that hospice agencies receive to pay for the costs of caring for a patient, thus precluding transfusion support entirely at many smaller agencies. While there is no legal provision preventing the use of transfusions in hospice, the practical implications of doing so have made this service unavailable at most hospice agencies.[7] A national survey study of 349 practicing hematologic oncologists confirms this observation with 62 percent stating that lack of transfusion support from hospices is a barrier to hospice referral, and that they would refer more patients if red cell or platelet transfusions were allowed.[8] Clearly, many of us believe that transfusion support provides real benefits to our patients.

This raises important questions: What do data show about the role of transfusions near the end of life? Do transfusions truly have palliative benefits? There is unfortunately very little evidence to guide our thinking on this topic. To date, there have been just a few small and mostly noncontrolled, non-blinded studies assessing the palliative benefits of transfusion support in patients with cancer. These studies often include patients with solid tumors and sometimes even other noncancerous diseases, and their most common focus has been in assessing the role of red cell transfusions in alleviating symptoms like fatigue or dyspnea. Data regarding the impact of platelet transfusions are even more lacking. What little data do exist generally suggest at least some benefit without clear evidence of harm. For example, in one of the largest studies to date (101 patients), 78 percent of patients receiving red cell transfusions had improvement in one of their target symptoms (fatigue, breathlessness, weakness or dizziness).[9]

The data are a bit clearer regarding the impact of transfusion dependence on the quality of end-of-life care. In a large SEER Medicare analysis, transfusion dependence was associated with markedly less hospice use in patients with myelodysplastic syndromes.[10] Similarly, in a small, retrospective, single-institution analysis, we found that transfusion dependence was associated with more in-hospital deaths and less use of hospice.[11] Furthermore, in an analysis presented at the 2017 ASH Annual Meeting, using SEER Medicare data from over 21,000 patients with acute and chronic leukemias, we noted a markedly shorter time in hospice among transfusion-dependent (TD) patients (6 days vs. 11 days for non-TD patients, $p < .001$), suggesting that the need for transfusion support may significantly delay hospice enrollment.[12]

Absent more conclusive data on the palliative benefits of transfusions, what should practicing hematologists do? Many of us have cared for patients who we feel have derived tangible and meaningful benefits from palliative transfusion support. Some patients have experienced marked amelioration of profound fatigue or dyspnea. Others seem to have lived longer or stayed home a bit longer and had better quality of life during their last days, weeks, or months. Yet without large, robust, randomized studies, we cannot prove this. However, many of us feel strongly enough about our observations that it feels unfair and inappropriate to withhold these potentially beneficial therapies so as to enable a hospice referral. As such, many of us refer our patients to hospice care late, or not at all, even when we know the myriad benefits of hospice care (both of us are, in fact, board certified palliative care specialists).

In order to resolve this dilemma, it is clear that more research is needed. However, we also think there's enough preliminary evidence and precedent around current transfusion practices to warrant pragmatic research, such as the testing of care models that allow transfusion support concurrently with hospice care, perhaps even in patient's homes. We hypothesize that this would enable many of our end-stage hematologic malignancy patients to elect hospice care sooner, and thus derive its many benefits. Earlier hospice care should translate into more time at home with family near the end of life, with better quality of life. Patients with hematologic malignancies should not have to choose between transfusions that provide them with palliative benefits, and high-quality end-of-life care through hospice.

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Dr. LeBlanc and Dr. Litzow indicated no relevant conflicts of interest.

In Memoriam

(Cont. from page 7)

thalassemia and SCD. The name of these conferences reflect George's conviction that if we understood how the globin genes "switch" from the fetal to the adult program, and found out how to control this switch, this would provide the key to curing thalassaemia and SCD. Everyone studying the mechanisms that regulate erythropoiesis and globin gene expression from around the world was invited to these conferences, and George kept the field focused on the central question. Like all of us, George was all too human – he argued vociferously; he was not always right, but he was eternally passionate about using his prodigious knowledge and intellect to crack this scientific puzzle.

George always made a special effort to promote the careers of the young researchers who were actually making these discoveries by inviting them to present their data to their peers, allowing them to defend the experiments and their implications. In this way, he maintained international interest in globin gene regulation for the past 40 years. These conferences had, and still have, lectures and poster presentations that extend all day and into the night, most often followed by spirited discussions into the early morning hours. To say that these discussions during the meetings were lively is an understatement. George's passion for understanding globin gene regulation and developing new ways to treat the hundreds of thousands of patients with hemoglobin disorders was infectious and continued to drive the field through many fruitful stages. George witnessed and contributed to the vastly improved diagnosis and treatment of the hemoglobinopathies, and progress toward cure via stem cell transplantation, gene therapy, and the realistic prospect of genome editing in the near future.

Everyone in our field would agree that such progress would not have developed as it has without George's considerable national and international influence promoting our field in journals, societies, via pharma and biotech, and at NIH. Our gratitude for his spirit and for his passionate pursuit exploring the molecular genetics of hematology for the good of mankind cannot be overestimated. Our community will miss him enormously while we endeavour to pursue the scientific goals George established with the zeal his legacy should expect and demand.

As with many great scientists, George had wide-ranging intellectual interests, with an enduring love of history and philosophy. He assembled one of the largest private collections in the world of early printed books including Renaissance and post-Renaissance editions of classical Greek and Byzantine authors. He also spent his spare time using genetics to trace the origins of diverse European and particularly Greek populations: a topic on which, during his later years, he became an internationally recognized expert.

George is survived by his wife, Dr. Thalia Papayannopoulou, his two sons John and Alexi, and three grandchildren. Thalia and John shared George's life and his passion for biomedical research, and both continue to serve on the faculty at the University of Washington.

George requested to be buried in his beloved ancestral village near the Homeric town of Kyparissia in Greece.

–Doug Engel, PhD, Professor, Department of Cell & Developmental Biology, University of Michigan

–Doug Higgs, FRS, Director, MRC Molecular Haematology Unit, MRC Weatherall Institute of Molecular Medicine, University of Oxford