2018 Association of American Physicians George M. Kober Medal Presentation

Stu Orkin is a superhero

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Dr. Stu Orkin is a model physician-scientist and a man for whom I have the utmost respect — not only for his life's work and mentoring, but also for his friendship.

Early life

Stu Orkin grew up in the Bronx and is unfortunately still a Yankees fan. His father was a urologist and practiced at Montefiore and the Beth Israel Hospitals in New York. Stu attended Riverdale Country School. Although he was very smart, his parents were repeatedly told he was not that good at citizenship. While other kids played together at camp, Stu was more comfortable by himself. But he did find friends. He had an intrinsic fascination with animals that seemed to flock to him (Figure 1).

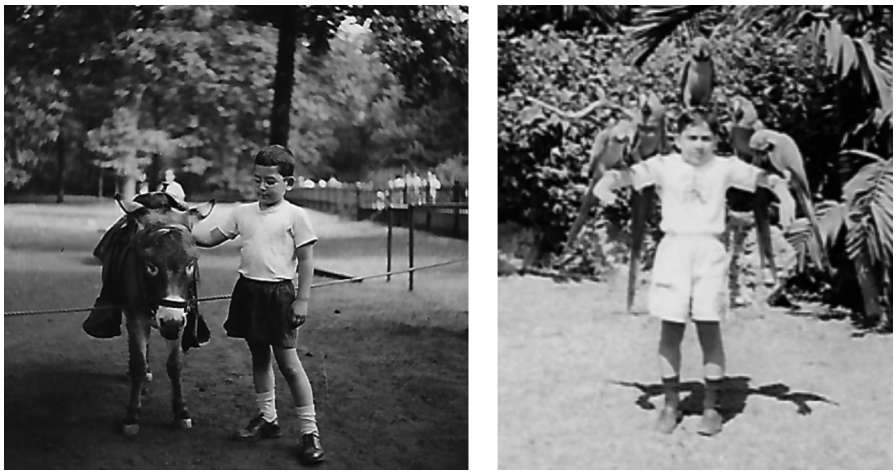

Figure 1. Pictures of Dr. Stuart Orkin and the animals that flocked to him.

Stu went off to MIT for four years (Figure 2) and then went to Harvard Medical School. Stu completed a one-year internship in pediatrics at Boston Children's Hospital. He joined the Public Health Service at the tail end of the Vietnam War era to do research training in Phil Leder's lab at the NIH. He spent two years there working on globin gene expression. Stu mapped globin RNA using restriction enzymes that he purified alongside Leder.

No one can underestimate the influence of David Nathan

Stu returned for a one-year residency at Boston Children's Hospital and then entered the pediatric hematology-oncology fellowship program. During his residency year, David Nathan and Stu had lunch. Bernie Forget was leaving for Yale, and Stu would get his technician and laboratory (Figure 3). Stu was instructed by David to write grant applications to the NIH and March of Dimes and start a laboratory with leftover equipment from Y. W. Kan and Bernie. There was great hope for Stu. Here is an early picture from Harvard about the future of hematology with other Kober medalists — David Nathan and William Castle — and Stu (Figure 4).

Figure 2. Early photo of Dr. Orkin while training.

Let's listen to David Nathan describe his early thoughts about Stu Orkin (Supplemental Video 1; available online with this article; https://doi.org/10.1172/JCI124493DS1).

Dr. Nathan would charge Stu with his lifelong project (Supplemental Video 2).

Let's listen to Sam Lux, who was chief of hematology, after David Nathan comments on Stu's approach (Supplemental Video 3).

Then there was the accident. Stu worked at a bench in his lab for about 15 years. Most people knew him as "Dr. Radioactivity." When you went home at night, it was important to monitor Stu's area, since spilling a millicurie here and there was, well, kind of routine. There was that fateful evening when no one else was in the lab, and there was a spill of massive proportions. Stu's DNA became mutated and he acquired superhero powers. Those powers would help him tackle projects.

Stu — now Dr. Radioactivity — needed a disguise to hide his identity and to fight

Figure 3. Dr. Orkin, in his initial lab, with the late Dr. Alan Michelson.

Reference information: *J Clin Invest.* 2018;128(10):4213–4217. https://doi.org/10.1172/JCI124493.
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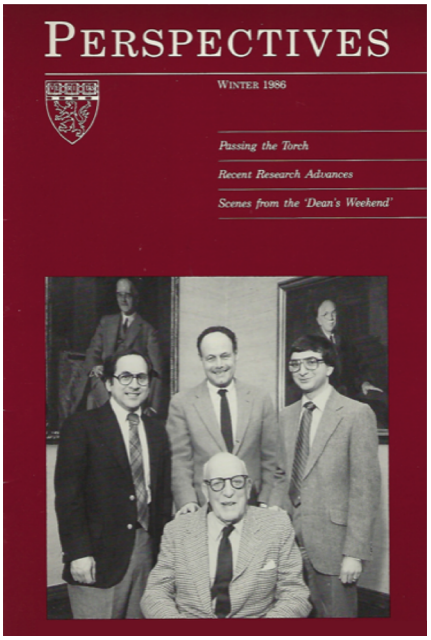

Figure 4. Harvard Medical Perspectives with three winners of the Kober Medal: Stuart Orkin (left), David Nathan (middle back), and William Castle (middle front). Also in the picture is Alan Michelson.

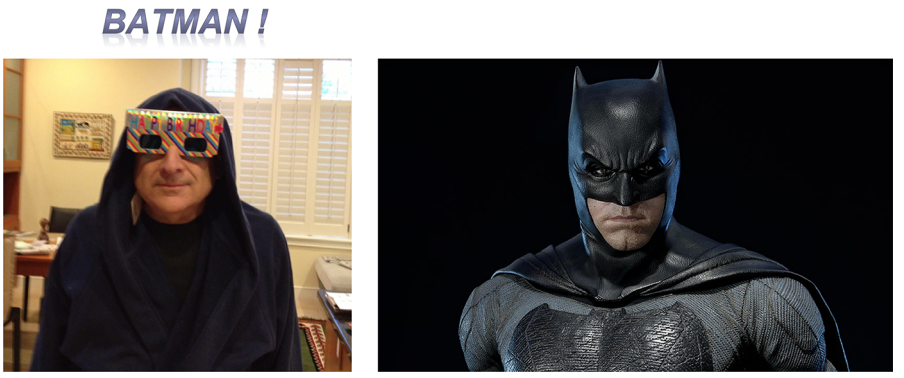

Figure 5. Stu as Dr. Radioactivity.

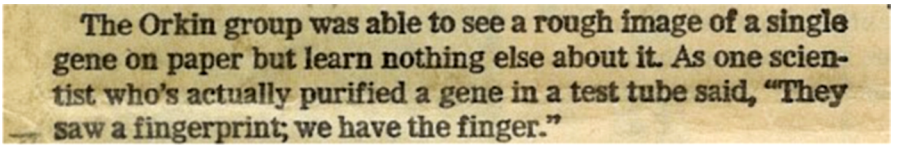
The Orkin group was able to see a rough image of a single gene on paper but learn nothing else about it. As one scientist who's actually purified a gene in a test tube said, "They saw a fingerprint; we have the finger."

Figure 6. Quote from the *Washington Post* in 1978 commenting on Stu's status in the field.

disease. He tried any number of failed styles and fashions: punk rocker (just not "Stu" enough), James Bond (he was missing the killer instinct), Einstein (not really smart enough), Elvis (no musical talent), Spider-Man (Stu can spin a web, but there'd be too many sticky situations), Blue Beetle (clever for a guy whose last name is Orkin), Iron Man (not flashy enough), The Flash (not fast enough), Captain America (too much of a Yankee), and the She Hulk (honestly, just a little hard to pull off). Finally, he adopted a costume similar to that of Batman, Stu's idol (Figure 5).

Stu now used his new superpowers to study hemoglobin switching.

In 1978, Stu had a super-ability to do Southern blots. David Nathan and Blanche Alter wanted to do prenatal diagnosis and obtained amniotic fluid cells from a patient in Turkey. The patient had a deletion, based on Stu's Southern blot, and had Δ-β thalassemia (1).

On the front page of the *New York Times*, there was an article about Stu's *New England Journal of Medicine* paper, but the big news that day was about Louise Brown, the first test-tube baby. Genetics was at the forefront, thanks to these two stories. Orkin's work was also covered in the *Washington Post* (2), but Stu was attacked in the press by others in the genetics community:

"The announcement of that application in the *New England Journal of Medicine* last month brought wide publicity for the research team and its head, Harvard's Dr. Stuart Orkin. Ironically, Orkin is considered in the scientific community as a minor researcher who happened to latch on quickly to a set of techniques and show their direct human applications. The *New England Journal*, which rushed his report into print, is being criticized privately by some scientists who say the weekly journal leapfrogged ahead of other journals carrying more important research findings but which won't be published for several more weeks or months" (2).

"The Orkin group was able to see a rough image of a single gene on paper but learn nothing else about it. As one scientist who's actually purified a gene in a test tube said, 'They saw a fingerprint; we have the finger'" (2) (Figure 6).

In 1980, Stu started cloning and identifying nearly all of the thalassemia mutations. Stu worked with Haig Kazazian for many of the mutations (3). People in the globin field were upset that there was a new superhero scientist who seemed to be doing better work than they were. They used to publish single *Nature* papers on one mutation, and Stu basically published all mutations in one paper.

Doug Higgs comments about Stu coming into the globin field (Supplemental Video 4).

Stu had very strong competition from Frank Grosveld. Let's hear a comment from Frank about his thoughts on Stu's excellent work (Supplemental Video 5).

Stu needed a team and developed his superhero family

Here are early pictures of his family and how they grew up together (Figure 7).

Stu insisted that the team have costumes. Stu sure was pushing the hero thing. I have been informed about who is really running the show. Roz deserves a lot of credit. Stu is a super grandfather. Here he is with the whole family (Figure 8). But like the Bat family, he insists that the family suit up (Figure 9).

As with every major superhero, Stu needed a sidekick

David Ginsburg, now the Distinguished University Professor at Michigan, took

Figure 7. Early pictures of Stu and his family. This includes Roz and Jane Orkin.

Figure 8. Picture of the entire family: Roz, Stu, Jacob, Jane, Lilah, and Dan Glazer.

Figure 9. Picture of the Bat family, and Stu with his grandkids.

on that role. Here is the eminent James V. Neel University Professor, Dr. Ginsburg, putting on his outfit (Supplemental Video 6). In 1984, Ginsburg cloned VWF using a lambda gt11 library. The disclosure was made in 1984, the patent was issued in 2013, and the product was on the market in 2016. So now Stu and Dave will become rich.

In 1986, Stu's lab member Brigitte Royer-Pokora cloned the chronic granulomatous disease (CGD) gene with the help of Lou Kunkel (4). Lou was searching for the Duchenne muscular dystrophy (DMD) gene, and there was a patient with retinitis pigmentosa (RP), DMD, and CGD. Stu used a subtractive hybridization strategy that could be envisioned as the first positional cloning of a gene. Mary Dinauer used an antibody to identify the protein (5). Alan Ezekowitz found that the gene was IFN inducible, and IFN worked in the clinic to raise levels, as reported in the *New England Journal of Medicine* (6).

Stu became involved in gene therapy

Dave Williams came from MIT to Children's — or as Stu says, he "escaped" from the Mulligan lab. Stu did the cDNA cloning of ADA and provided the clone to French Anderson, who cloned it into Mulligan's vector, and soon this went into patients. It was an exciting time, but gene therapy had a rocky beginning. In 1986, Harold Varmus, Director of the NIH at the time, asked Stu to co-chair a committee on the NIH investment in gene therapy.

The panel found that: (a) Somatic gene therapy is a logical and natural progression in the application of fundamental biomedical science to medicine. That's GOOD. (b) Clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol. That's BAD. (c) There is a clear and legitimate need for clinical studies to evaluate various aspects of gene therapy approaches. That's GOOD. (d) The results of laboratory and clinical studies have been oversold by investigators and their sponsors. That's BAD.

Several people discussed the panel's findings. Francis Collins: "He seemed to be waffling on his opinion" (Supplemental Video 7). George Stamatoyannopoulos:

Figure 10. Stu Orkin flying the Bat Plane.

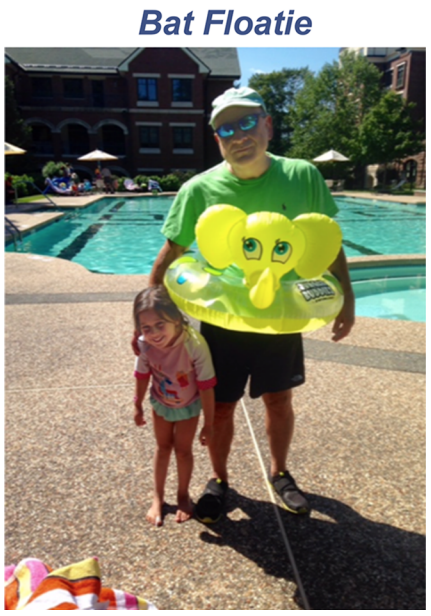

Figure 11. Stu Orkin developed the Bat Floatie.

Figure 12. Stu tackling sharks, such as those at the Dana-Farber Cancer Institute.

"No one understood why Orkin was even involved" (Supplemental Video 8).

This reminded me of the movie *Marathon Man*, in which Laurence Olivier plays the dentist and Dustin Hoffman the patient (Supplemental Video 9).

There is always an epilogue. David Williams declares: "Gene therapy works. Guess it did take a few years" (Supplemental Video 10).

In 1987, I joined the lab. Stu wanted to find the major erythroid transcription factor that bound to GATA. David Martin and Peter Tsai had invested in purifying and sequencing the protein. I decided to take an expression-cloning scheme by transfecting pools of cDNAs into COS cells and looking for an activity that caused a gel mobility shift (7). Stu took a picture of me while I was cloning GATA1. That technique worked well, and this cloning opened up the field of transcription for blood-specific genes.

Stu, as Dr. Radioactivity, was summoned throughout the world and needed to travel to meetings in style

When he traveled to Washington, he would use the Bat Plane (Figure 10). In 1988, people wanted to sequence the human genome. Bruce Alberts, James Watson, and Wally Gilbert were on the committee. Stu and Shirley Tilghman were the young folks. This committee formed the blueprint for the genome project. Stu had to tread difficult waters and developed a new form of transportation: the Bat Floatie (Figure 11).

At a hemoglobin switching meeting in the early 1990s, the major globin regulatory element was being referred to as the dominant control region (DCR) by Mark Groudine, or as the locus activation region (LAR) by Frank Grosveld. GF1, NFE1, and eryf1 were names for the same protein that bound GATA. A meeting of the minds happened. The locus control region, or "LCR," became the compromise name for the region — this really was the first super-enhancer. Stu was vocal and GATA1 was named after the binding site.

In the 1990s, Stu's lab was one of the first to do gene knockouts. GATA1 was one of the first to be done, as it was on the X chromosome. He then knocked out every blood-related factor under the sun, and thus began the age of molecular hematology.

Stu became interested in stem cells

Here is George Daley, discussing Stu's work (Supplemental Video 11).

"We should say a few words about his extensive contributions to the stem cell field. Let me tell you a little about it." (The screen goes blank for 3 seconds.) It appears that George didn't have much to say.

In 2003, Stu started working on embryonic stem and induced pluripotent stem cell pluripotency and differentiation. Stu realized that Nanog could be used as a hook, and he purified the pluripotency protein complex (8). During his Howard Hughes Medical Institute (HHMI) review that year, the reviewers said that the project could not be done, but Stu loves a challenge. He only partially succeeded, but Shinya Yamanaka demonstrated that cells could be readily reprogrammed to pluripotency.

Stu decided to tackle the sharks at the Dana-Farber Cancer Institute (Figure 12). In 2000, Stu became the chairman of pediatric oncology at the Dana-Farber Cancer Institute. I asked him why he was doing this. He said that it is always good to know you have a good boss. The faculty Stu recruited were a who's who of pediatric medicine that included Loren Walensky, Charlie Roberts, and many women scientists including Kim Stegmaier, Cigall Kadoch, Roni George, and Birgit Knochel.

Stu particularly enjoyed working with Ed Benz (Supplemental Video 12).

Stu did such a good job that it made it tough for anyone who followed. Scott Armstrong adds, "Stu really screwed it up for me!" (Supplemental Video 13).

Over the past 10 years, Stu has gone back to globin

There was linkage analysis showing that an F-enhancing locus was on the short arm of the X chromosome. Vijay Sankaran from Stu's lab found that *Bcl11a* was the responsible gene. By the end of Vijay's thesis, hemoglobin F was induced with an shRNA to *Bcl11a* (9).

Jian Xu from Stu's lab showed that the knockout of *Bcl11a* would rescue the mouse model of sickle cell anemia (10). Dan Bauer characterized the *Bcl11a* erythroid enhancer (11). David Williams created an shRNA gene therapy vector that is being tested clinically. Sangamo has an investigational new drug (IND) to target the *Bcl11a* enhancer with zinc fingers, Vertex and CRISPR Therapeutics have an IND, and Novartis and Intellia Therapeutics are applying to target the enhancer with CRISPR for thalassemia and later for SCD.

Stu is a major trainer of superhero talent

One thing about Stu is that he is very proud of his trainees and colleagues, so he decided to form the Justice League with new superhero scientists. Stu had many trainees who rose to fame and fortune, six of whom became HHMI investigators.

The future of treating globin diseases – the final battle

Stu believes that the future of treating globin diseases is to make small molecules and that this will help the greatest number people. He is on the brink of conquering red blood cell sickling. I don't think it is too far-fetched for Stu to be a comic book character, as he truly is a superhero. Here he is in one of his toughest battles with his arch nemesis, the sickle cell (Supplemental Video 14). And there — he has reversed sickle cell disease!

Stu's fellow researchers, colleagues, and patients thank him for all that he has done. It would be a different field without him. Stu has had a brilliant career. It is my pleasure to congratulate Dr. Radioactivity himself, Stu Orkin, for being awarded the George M. Kober Medal.

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