



**3RD ANNUAL**

# Ralph L. Brinster Symposium

*Presentation of the Elaine Redding  
Brinster Prize in Science or Medicine*

**March 13, 2024**

Arthur H. Rubenstein Auditorium & Commons  
Smilow Center for Translational Research

# AGENDA

## Ralph L. Brinster Symposium

### 9:00 AM Welcome & Opening Remarks

Ken Zaret, PhD, *IRM Director*

Andrew Hoffman, DVM, *Gilbert S. Kahn Dean of Veterinary Medicine*

### 9:15 AM Film tribute to Dr. Brinster's career

## AM Session

Chair: Guo-li Ming, MD, PhD, *IRM Associate Director*

### 9:30 AM Dissecting the Biological Complexity of Animal Regeneration

Alejandro Sánchez Alvarado, PhD, *President and Chief Scientific Officer  
Stowers Institute for Medical Research*

### 10:15 AM Break

### 10:45 AM Mending broken hearts with neural crest cells

Marianne Bronner, PhD, *Edward B. Lewis Professor of Biology  
California Institute of Technology*

### 11:30 AM A second end-replication problem solved by CST-Pola/primase, not telomerase

Titia de Lange, PhD, *Professor and Head of Laboratory of Cell Biology and Genetics,  
Director, Anderson Center for Cancer Research  
Rockefeller University*

### 12:15 PM Lunch

## PM Session

Chair: Ken Zaret, PhD, *IRM Director*

### 1:15 PM Saving the Synapse: developmental critical periods and Alzheimer's disease

Carla J. Shatz, PhD, *Sapp Family Provostial Professor of Biology and Neurobiology and  
Catherine Holman Johnson Director of Stanford Bio-X,  
Stanford University*

### 2:00 PM Break

## Elaine Redding Brinster Prize Ceremony

### 2:30 PM Introduction to the Elaine Redding Brinster Prize in Science or Medicine & Presentation of the Prize Medallion and Certificate

Ken Zaret, PhD, *IRM Director*

Jon Epstein, MD, PhD, *Interim Executive Vice President, University of Pennsylvania for  
the Health System & Dean, Perelman School of Medicine*

Video on Ralph L. Brinster, VMD, PhD, *Richard King Mellon Professor of Reproductive  
Physiology*

### 2:50 PM Turning back the clock on hemoglobin: genetics, mechanism, editing therapy, and the future

Stuart H. Orkin, MD, *David G. Nathan Distinguished Professor of Pediatrics (Harvard  
University), Investigator (Howard Hughes Medical Institute)*

### 3:35 PM A conversation with the Prizewinner, Dr. Orkin, Dr. Zaret, and Ridley High School Students

### 4:00 PM Event concludes – Refreshments available in the Smilow Commons

# Stuart H. Orkin, MD

*David G. Nathan Distinguished Professor of Pediatrics, Harvard Medical School  
Investigator, Howard Hughes Medical*



Stuart Orkin, MD, is the David G. Nathan Distinguished Professor of Pediatrics at Harvard Medical School and an Investigator of the Howard Hughes Medical Institute. Dr. Orkin graduated from the Massachusetts Institute of Technology and received his medical degree from Harvard Medical School.

When Dr. Orkin initiated his research over 40 years ago, little was understood about how different kinds of blood cells are programmed from blood stem cells in embryonic development. His work laid the foundation for the molecular study of functional blood cell formation. His focus has been on the red cell as a model, given how defects in red cell formation and function lead to thalassemias, a deadly spectrum of blood disorders. The genetics of thalassemia illustrated how different mutations cause the disease, but failed to answer how genes, such as for hemoglobin, are specifically productive in red cells. Coincident with another investigator (G. Felsenfeld, NIH), Orkin and colleagues discovered GATA1, the first master blood stem cell regulator and which has served as a paradigm for understanding mammalian gene regulation. Orkin's laboratory identified other related factors, including GATA2, the first blood stem cell regulator to function in the blood lineage. Members of the GATA family have provided critical insights into development of the heart, brain, nervous system, and gut, and cancer.

A major clinically relevant question remained: How is the switch from fetal hemoglobin to adult hemoglobin controlled? Based on family studies, reactivation of fetal hemoglobin gene expression in adults with thalassemia or sickle cell disease was proposed as a potential therapy. Orkin and his colleagues elucidated the mechanism of the fetal-to-adult globin switch by discovering that the protein BCL11A in adults normally silences fetal hemoglobin by acting directly on the fetal globin gene. The Orkin laboratory showed that diminishing BCL11A in adult erythroid cells leads to high level fetal globin expression that can suppresses sickle cell disease. Orkin and associates discovered that common genetic variation within a gene regulatory sequence for the BCL11A gene controls BCL11A gene expression. They identified a GATA1 binding site in the gene regulatory sequence whose disruption impairs BCL11A activation in adults, thereby permitting fetal globin gene reactivation. This favorable target for CRISPR/Cas9 editing was leveraged for first-in-man gene editing therapy in a collaboration between two companies, CRISPR Therapeutics and Vertex, for both sickle-cell disease and thalassemia.

Orkin's contributions have transformed an understanding of blood cell development and the basis for diseases and led directly to the successful application of gene editing of human disorders for clinical benefit.

## SPEAKERS



### **Carla Shatz, PhD**

*Sapp Family Provostial Professor of Biology and Neurobiology, and Catherine Holman Johnson Director of Stanford Bio-X, Stanford University*

Carla J. Shatz, PhD, is Sapp Family Provostial Professor of Biology and Neurobiology and the Catherine Holman Johnson Director of Bio-X, Stanford University's pioneering interdisciplinary biosciences program. She received her B.A. in Chemistry from Radcliffe College in 1969, an M.Phil. (Physiology; 1971) from University College London as a Marshall Scholar, and a Ph.D. (Neurobiology; 1976) from Harvard Medical School. Shatz joined the faculty at Stanford in 1978, then moved to University of California at Berkeley in 1992, and to Harvard Medical School in 2000 as the first woman Chair of the Department of Neurobiology. She returned to Stanford in 2007 to direct Bio-X.

Dr. Shatz is a neuroscientist who has devoted her career to understanding the dynamic interplay between genes and environment that shapes brain circuits - the very essence of our being. Shatz has earned many honors and awards, including election to the National Academy of Sciences, the American Philosophical Society, and the Royal Society of London. She received the Gruber Neuroscience Prize in 2015. In 2016, she was the recipient of the Champalimaud Vision Prize and the Kavli Prize in Neuroscience for the discovery of mechanisms that allow experience and neural activity to remodel brain circuits. In 2018, she received the Harvey Prize in Science and Technology from the Technion Israel Institute of Technology.



### **Titia de Lange, PhD**

*Professor and Head of Laboratory of Cell Biology and Genetics, Director, Anderson Center for Cancer Research, Rockefeller University*

Titia de Lange, PhD Professor and Head of Laboratory of Cell Biology and Genetics, Director, Anderson Center for Cancer Research, Rockefeller University Dr. Titia de Lange received training in molecular biology and biochemistry at the University of Amsterdam. As an undergraduate, she did research in Richard Flavell's lab at the MRC in Mill Hill, UK. She was a graduate student in Piet Borst's lab in the Department of Biochemistry at the University of Amsterdam and moved with Borst to the Dutch Cancer Center where she first developed an interest in telomeres. After receiving her PhD in 1985, de Lange joined Harold Varmus at UCSF for postdoctoral studies. With Varmus, she isolated human telomeric DNA and was the first to show that human telomeres shorten during tumorigenesis. In 1990, she moved to the Rockefeller to take a position as a University Fellow and was appointed as Assistant Professor in 1991. She was promoted to Associate Professor in 1994 and to Professor in 1997. She currently is the Leon Hess Professor and the Director of the Anderson Center for Cancer Research at the Rockefeller University.

Dr. de Lange is a member of EMBO, the US National Academy of Science, both Dutch Royal Academies, the American Academy of Arts and Sciences, the US National Academy of Medicine. She is a foreign member of the Royal Society of London and received honorary degrees from the University of Utrecht, the University of Chicago, and the University of Groningen. De Lange's awards include the inaugural Paul Marks Prize for Cancer Research in 2001 (with Bill Kaelin, Steven Elledge, and Xiaodong Wang), the Massachusetts General Hospital Cancer Center Prize, the Judd award from MSKCC, the AACR's Charlotte Friend and G.H.A. Clowes Awards, the 2011 Vilcek Prize, the 2012 Vanderbilt Prize, the 2012 Dr. Heineken Prize for Biochemistry and Biophysics, the inaugural Breakthrough Prize in Life Sciences in 2013, the 2014 Canada Gairdner International Award, and the 2018 Lewis S. Rosenstiel Award.



## Alejandro Sánchez Alvarado, PhD

*President and Chief Scientific Officer  
Stowers Institute for Medical Research*

Alejandro Sánchez Alvarado holds the Priscilla Neaves Chair in the Biomedical Sciences at the Stowers Institute for Medical Research, where he also serves as its President and Chief Scientific Officer and as an Investigator of the Howard Hughes Medical Institute. His laboratory explores the genetic and cellular control of regeneration and tissue maintenance and has identified dozens of genes and genetic programs involved in these processes.

Sánchez Alvarado's work has the potential to lead to a better understanding of how the adult organisms, including humans, carry out their biological functions. His research also has led to insights on the molecular and genetic drivers of both regenerative and degenerative cellular processes that contribute to disease.

Sánchez Alvarado is the recipient of numerous honors and awards, including the Vilcek Prize in Biomedical Sciences and is an elected member of the National Academy of Sciences, the American Academy of Arts and Sciences, and is a fellow of the American Association for the Advancement of Science.



## Marianne Bronner, PhD

*Edward B. Lewis Professor of Biology  
California Institute of Technology*

Marianne Bronner, PhD is a developmental biologist and Edward B. Lewis Professor at Caltech. She is known for her studies of the neural crest, an important stem cell population that generates the peripheral nervous system, craniofacial skeleton and components of the cardiovascular system of all vertebrates. The Bronner lab formulated and is functionally testing the gene regulatory network underlying neural crest formation, migration and differentiation. Her laboratory showed that neural crest formation initiates early in development, culminating in different neural crest subpopulations along the body axis. She has used novel lineage tracing tools including indelibly labeling neural crest cells with replication incompetent retroviruses to map neural crest pathways in vivo and define the interactions that control their movement. Her recent work has revealed an important and surprising role for neural crest cells in adult heart regeneration, suggesting that persistence of neural crest stem cells in adults may someday be exploited for therapeutic purposes.

Bronner was President of the Society for Developmental Biology in 2009 and is currently President of the International Society for Developmental Biology. She serves on numerous non-profit boards. She was elected to the National Academy of Sciences in 2015 and to the American Academy of Arts and Sciences in 2009. She received the Shirley M. Malcom Mentoring Award in 2023, the Harrison Medal from the International Society for Developmental Biology in 2022, the Conklin Medal from The Society for Developmental Biology in 2013, the Women in Cell Biology Senior Award from the American Society for Cell Biology in 2012, and a Javits award from the NINDS in 2002, as well as several teaching awards from her institution.

### About the Ralph L. Brinster Symposium

The Ralph L. Brinster Symposium is a celebration of breakthrough science across the entire spectrum of biomedical research. Each spring, a select group of global leaders in biomedicine is invited to the University of Pennsylvania to present their latest research and engage the University community.

The Symposium's namesake, Ralph L Brinster, VMD, PhD, is an American geneticist, National Medal of Science laureate, and the Richard King Mellon Professor of Reproductive Physiology at the University of Pennsylvania's School of Veterinary Medicine. Dr. Brinster is a founder of the field of mammalian transgenesis and is credited with developing the first reliable in vitro culture system for early mammalian embryos. His contributions to our understanding of the mammalian germline have profoundly influenced biomedicine.

The Ralph L. Brinster Symposium is generously supported by the Family of Ralph and Elaine Brinster and co-sponsored by the Deans of the School of Veterinary Medicine and the Raymond and Ruth Perelman School of Medicine.

### About the Elaine Redding Brinster Prize in Science or Medicine

The Elaine Redding Brinster Prize in Science or Medicine is awarded annually to an individual from any country to recognize their outstanding discovery for its major impact on biomedicine. Each winner receives \$100,000, a commemorative medallion, a citation, and an invitation to present a ceremonial lecture to the University of Pennsylvania community.

Endowed by the children of Elaine Redding Brinster, the Prize recognizes remarkable scientific achievements and honors their mother, whose warmth, grace, and insightful advice has guided their lives and helped them navigate obstacles throughout their academic and professional careers.

The Elaine Redding Brinster Prize is presented on behalf of the Perelman School of Medicine and administered by the Institute for Regenerative Medicine. For more information about the Symposium or Prize, please visit [irm.med.upenn.edu/Brinster](http://irm.med.upenn.edu/Brinster).

### About the Institute for Regenerative Medicine

The Institute for Regenerative Medicine (IRM) is dedicated to research on stem cells and tissues with an eye toward turning the knowledge gained into new diagnostic and therapeutic techniques and tools. A member of the International Society for Stem Cell Research's (ISSCR) Circle of Stem Cell Institute and Center Directors, the IRM features faculty from five schools across the University of Pennsylvania and includes representation from the Children's Hospital of Philadelphia and the Wistar Institute. For more information about the IRM, please visit [irm.med.upenn.edu](http://irm.med.upenn.edu).

THANK YOU

**The Institute for Regenerative Medicine would like to offer a special thank you to the following individuals and groups for their invaluable contributions to this event:**

**DR. RALPH AND ELAINE BRINSTER**

**THE FAMILY OF RALPH AND ELAINE BRINSTER**

- Kristen A. Brinster, Esq.
- Clayton J. Brinster, MD
- Lauren R. Brinster, VMD
- Derek R. Brinster, MD

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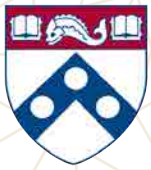
**SARAH GILMOUR**

*Director of Development for Biomedical Research*

**KELLI WALSH**

*Associate Director of Development for Biomedical Research*





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**James Read, *Associate Director for Communications & Operations***

**Jamie Shuda, EdD, *Director of Education & Outreach***