



The Jane Coffin Childs

MEMORIAL FUND FOR
MEDICAL RESEARCH

Introducing the New JCC Fellows

This spring, The Jane Coffin Childs Fund awarded fellowships to 27 exceptional young biomedical scientists. Here we introduce four, chosen to represent a cross-section of interests and backgrounds.



Lindsey Macpherson

While savoring a bite to eat, most people are oblivious to the molecular basis of the taste sensations they experience. But what happens after something touches the tongue?

According to current evidence, food most likely stimulates taste-specific lines of communication to the brain. Chocolate cake, for example, activates sweet taste receptor cells within taste buds, which trigger sweet gustatory neurons, which then signal the perception of the sweet taste in the brain.

JCC fellow Lindsey Macpherson, who recently joined Charles Zuker's lab at the

University of California, San Diego, is studying how taste cells signal to the peripheral ganglion neurons that innervate the tongue. Considering that the tongue's taste cells survive only about ten days, new cells must continually connect with the correct neurons.

Just imagine the gustatory mayhem that would result if sweet receptor cells mistakenly signaled salt-sensing neurons. In fact, this is what Macpherson has envisioned. She plans to identify candidate molecules that mediate taste cell-neuron interactions and then generate mice with mutations in the genes coding for those molecules. Intentionally mis-wiring connections between taste cells and neurons could change mouse behavior and elucidate the molecular mechanisms behind the cells' interactions.

Macpherson enjoys her new research, which continues her interest in sensory biology. "I'm learning new imaging techniques that are really fun," she says. "I've done cell-based assays before, and now I'm moving toward whole-animal approaches."

As a graduate student with Ardem Patapoutian at Scripps Research Institute, she discovered that garlic activates TRPA1, an ion channel expressed in pain-sensing neurons, to produce the burning sensation of raw garlic. She is happy to remain in San Diego, where she grew up.



Luciano Marraffini

When JCC fellow Luciano Marraffini considered postdoctoral projects, he sought uncharted territory. He found it within Clustered Regularly Interspaced Short Palindromic Repeat loci, known as CRISPR. Occurring in bacteria, these repeated segments are separated by sequences of nucleotides

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that share homology with phages and plasmids and confer resistance to them.

CRISPR function has been likened to RNAi, a form of eukaryotic gene control that triggers the destruction of specific RNA fragments. Recently, RNAi research has exploded, as scientists illuminate its natural role and harness it as a research tool for gene silencing and high-throughput genetic screens. Some scientists suspect that CRISPR study could revolutionize prokaryotic genetics in a similar manner.

In addition to its relevance in genetics, CRISPR research has potential clinical applications. Phages can transfer virulence and plasmids can deliver antimicrobial resistance among bacterial pathogens. Because CRISPR interferes with phage infection and plasmid transfer, this natural system could possibly be used to prevent the spread of virulence and antibiotic resistance. Given the recent emergence of harmful bacterial strains such as MRSA, this is an area ripe for research. “We have to first learn how this works,” Marraffini explains, before any clinical application can be realized.

Marraffini joined Erik Sontheimer’s lab at Northwestern University in order to explore whether CRISPR prevents plasmid conjugation among staphylococcal strains. In particular, he is interested in *Staphylococcus epidermidis*, one of the most common causes of hospital-acquired infection.

Originally from Argentina, Marraffini came to the United States for his Ph.D. with Olaf Schneewind at the University of Chicago. Staying in Chicago for his postdoctoral fellowship allows him to maintain

connections with former microbiology colleagues. “It’s very important for me to discuss hypotheses and techniques with as many people as possible because it generates lots of ideas,” he says.



Jacob Corn

“It’s always easy to do what you know,” says JCC fellow Jacob Corn. But Corn was not looking for the path of least resistance. He wanted a challenge.

During his graduate career in James Berger’s lab at the University of California, Berkeley, Corn used X-ray crystallography and NMR to solve the three-dimensional structure of bacterial primase, a protein that cooperates with other enzymes to replicate DNA.

“At Berkeley, I gained a love for the structure of proteins. They’re beautiful, really,” Corn says, explaining that he appreciates the functional insight gained from solving protein structures. From his structural data, he determined that the interaction between two distinct primase monomers regulates its activity. He also found that the enzyme binds nonspecifically to single-stranded DNA, apparently offering flexibility until it reaches a primer initiation site.

Now, as a postdoctoral fellow with David Baker at the University of Washington, Corn is turning his attention to computational protein design. “If we

think we understand a protein,” he explains, “the true test of that understanding is whether or not we can design one to behave in a predictable way.”

In this field, scientists use lessons learned from nature to invent new molecules with predictable behaviors. The approach, which represents an exciting methodological challenge for Corn, contributes to the fundamental understanding of proteins and opens potential avenues for drug design. He plans to reconfigure several components of the Insulin-like Growth Factor (IGF) pathway, which controls both aging and cellular proliferation in metazoans, and test the changes in vitro and in vivo.

After six years in California, Corn is happy to return to the Pacific Northwest, where he grew up. “I want to make the most of my time here,” he says.



Elcin Unal

Creating offspring is complicated business. At the cellular level, an individual must first produce gametes through the highly ordered process of meiosis. Normally, progenitor cells transition from mitotic division to meiosis and then double, shuffle, and divide their genetic information. Things do not always run smoothly, however, and JCC fellow Elcin Unal seeks to understand why.

Meiotic problems are often linked to age. Unal’s first goal as a postdoctoral fellow with Angelika Amon at the Massachusetts Institute of Technology is to uncover the molecular mechanism behind these problems, using the budding yeast *Saccharomyces cerevisiae*. Aged cells tend to stumble at two particular places in meiosis, and Unal will investigate both. Cells could fail to transition from mitosis to meiosis, stalling gamete production. Also, chromosomes could segregate incorrectly, creating gametes with too many or too few chromosomes. In humans, this is a leading cause of miscarriage and mental retardation.

Unal’s second goal is to determine if special mechanisms exist in germ cells to reduce age-induced damage. Scientists have proposed that meiosis could rejuvenate germ cells by reversing DNA damage and removing damaged proteins, but this idea has not been tested extensively yet. Unal sees great potential for exploration, with possible implications for developmental, regenerative, and stem cell biology.

Unal is thrilled to work with Amon. “She’s one of my heroes,” Unal says. “She’s creative, highly enthusiastic, collaborative, and accessible. She has all the qualities one would expect in a great scientist.”

As a graduate student with Douglas Koshland at the Carnegie Institute, Unal studied the protein complex cohesin, which is mainly known for its role in chromosome segregation. She discovered that the cohesin complex plays a specific role in the repair of DNA double-strand breaks. Her work also uncovered how cohesin-mediated linkage between sister chromatids is established during the cell cycle. *

DIRECTOR'S CORNER

Tough Times and How to Make Them Better



As we welcome a new class of outstanding Childs fellows, the news on the biomedical research support front remains mixed. Private foundations such as the Howard Hughes Medical Institute have selected many promising young investigators for funding and have initiated a new program of early career support. Unfortunately, for the first time in over a generation, the NIH has suffered flat-line funding and a cut in inflation-adjusted budgets for several years in succession. Pay lines have tightened with particular damage to beginning investigators and innovative science. The situation is made worse by funding decisions that favor safe senior and established investigators over early career scientists. At the NIH, the average age for first-time grant recipients has increased to 42 and the success rate for first proposals has dropped from 30 to 19%. While more funding is always welcome, it cannot guarantee innovation unless money is directed to those who have bold ideas. Certain fundamental problems with the review process hinder the recognition of unproven talent and unusual ideas.

A recent study commissioned by the American Academy of Arts and Sciences (ARISE: <http://www.amacad.org/arisefolder/default.aspx>) provides evidence of dwindling support for early career biomedical scientists. Although most biomedical scientists favor a change in our national priorities, the ARISE report identifies areas where a small investment could pay big dividends.

One proposal is to enhance the interaction between staff in the funding agencies and frontline investigators in emerging disciplines. In past years, program officers from the federal agencies participated actively in small research meetings, such as Gordon Conferences, where the newest unpublished and promising results are shared. Funding restrictions and a lack of reinforcement in the program officer career path curtailed such contact. Such disinvestment is unwise. A small allocation of travel funds and encouragement in career advancement would return those responsible for funding decisions back into contact with the best beginning and innovative investigators.

Private funding agencies can help. Selective private sources of research support tend to favor the most highly acclaimed young scholars, some of whom may have adequate resources. Support tends to focus on individuals in a select few elite institutions. The ARISE report encourages agencies to favor other scholars who may not yet have secured extramural funding.

Universities also have a role to play. Research buildings are erected as in a “field of dreams” with the expectation that investigators will take responsibility for core facilities. The ARISE report recommends that institutions fundraise for building endowments to support the creation and staffing of core facilities, rather than relying exclusively on expensive recharges to individual investigators. And even more importantly, universities and research institutes should assume greater responsibility for faculty salaries, particularly where faculty serve teaching and administrative functions that support the institution as well as the research enterprise. Such cost-sharing measures by federal grant recipients would stretch the research dollar to permit more support for beginning investigators.

On behalf of my colleagues on the Board of Scientific Advisors, I wish to thank Liz Blackburn and Pam Silver who will leave the Board after eight years of dedicated service. In their place, I am pleased to welcome our newest Board members Carol Greider and Rich Losick. *

— Randy Schekman, Director of the Board of Scientific Advisors

Fellows Awarded Spring 2008

- **Andrea J. Berman**
Holding on for dear life: Primer binding and processivity in *Tetrahymena thermophila* telomerase, with Thomas Cech, Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado
- **Elizabeth S. Harris**
Role of the APC multi-protein complex in regulating microtubule function at the membrane, with W. James Nelson, Department of Biology, Stanford University, Stanford, California
- **Lindsey J. Macpherson**
HHMI Fellow
Molecular characterization of gustatory labeled lines, with Charles Zuker, Department of Biological Sciences, University of California San Diego, La Jolla, California
- **June L. Round**
Merck Fellow
The contribution of the intestinal microbiota to development of colon cancer, with Sarkis Mazmanian, Division of Biology, California Institute of Technology, Pasadena, California
- **Liang Cai**
Actin cytoskeleton reorganization during tubulogenesis, with Keith Mostov, Department of Anatomy, University of California, San Francisco, California
- **John R. James**
HHMI Fellow
Defining the role of the actin cytoskeleton in plasma membrane organization during T-cell activation, with Ronald D. Vale, Department of Cellular and Molecular Pharmacology, University of California, San Francisco, California
- **Luciano Marraffini**
Mechanisms of sequence-based resistance to bacteriophages and plasmids in *Eubacteria*, with Erik J. Sontheimer, Department of Biochemistry, Molecular Biology and Cell Biology, Northwestern University, Evanston, Illinois
- **Rahul Roy**
Role of nuclear organization in gene regulation, with Sunney X. Xie, Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts
- **Damon A. Clark**
Visual feedback modulation in behaving *Drosophila*, with Thomas Clandinin, Department of Neurobiology, Stanford University, Stanford, California
- **Hyun-Eui Kim**
Study of relationship between metabolism and protein homeostasis in neurodegenerative diseases, with Andrew Dillin, Molecular and Cellular Biology Laboratory, The Salk Institute for Biological Studies, La Jolla, California
- **Florian T. Merkle**
Generation of hypocretin neurons from narcoleptic patients, with Alexander Schier, Department of Molecular and Cellular Biology, Harvard University, Cambridge, Massachusetts
- **Anne-Lore Schlaitz**
The role of organelle-microtubule linker proteins in the spatial organization of the cell, with Rebecca Heald, Department of Molecular and Cell Biology, University of California, Berkeley, California
- **Robert E. Collins**
RabGDI displacement factors: mechanism and function in membrane traffic, with David Lambright, Program In Molecular Medicine University of Massachusetts Medical School, Worcester, Massachusetts
- **Alexandre A. Neves**
Modeling Myc-induced tumorigenesis in *Drosophila*, with Robert N. Eisenman, Basic Science Division, Fred Hutchinson Cancer Research Center, Seattle, Washington
- **Elcin Unal**
HHMI Fellow
Deciphering the age effects on meiosis and vice versa, with Angelika Amon, David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, Massachusetts
- **Jacob E. Corn**
HHMI Fellow
Computational design of eukaryotic signal transduction, with David Baker, Department of Biochemistry, University of Washington, Seattle, Washington
- **Brant K. Peterson**
Exploring and exploiting phenotypic complexity to unearth the genetic architecture of adaptation and disease, with Hopi Hoekstra, Department of OEB, Museum of Comparative Zoology, Harvard University, Cambridge, Massachusetts
- **Alina M. Vrabioiu**
Planar cell polarity protein activity and function in developing *Drosophila* epithelia, with Gary Struhl, Department of Genetics and Development, Columbia University, New York
- **Robert Driscoll**
Molecular dissection of the replication checkpoint, with Karlene Cimprich, Department of Chemical and Systems Biology, Stanford University School of Medicine, Stanford, California
- **Soo-Hee Lee**
Mechanism for translational regulation of HMG CoA reductase, with Russell DeBose-Boyd, Department of Molecular Genetics, The University of Texas Southwestern Medical Center at Dallas, Texas
- **Assaf S. Zemach**
Comparative genomic analysis of DNA methylation in animals, with Daniel Zilberman, Department of Plant and Microbial Biology, University of California, Berkeley, California
- **Ellen J. Ezratty**
Stem cell migration during wound-induced reepithelialization, with Elaine Fuchs, Laboratory of Mammalian Cell Biology and Development, The Rockefeller University, New York
- **Xin Liu**
Structural, biochemical and genetic studies of the role of the trigger loop in substrate specificity and catalysis in RNA polymerase II transcription, with Roger Kornberg, Department of Structural Biology, Stanford University School of Medicine, Stanford, California
- **Zachary S. Pincus**
Quantitative longitudinal analysis of aging *C. elegans* populations, with Frank Slack, Department of Molecular, Cellular and Developmental Biology, Yale University, New Haven, Connecticut
- **Dragana Rogulja**
A search for the molecular mechanisms and physiological basis of sleep, with Michael Young, Laboratory of Genetics, The Rockefeller University, New York

A Conversation with Elizabeth Ford

Elizabeth Ford worked for the JCC for 55 years, from the time she graduated from college until she retired as Administrative Director in 2001. Over the years, she demonstrated great commitment to the Fund's mission. Here she recalls some of her experiences with the JCC.



How did you become involved with the JCC?

I joined the Fund in the late Forties. I was fresh out of college and looking for a job, so I went to the Yale employment office and they sent me to the Foundation, which was directed at the time by Dr. Stanhope Bayne-Jones, a former Dean of the Yale University School of Medicine. He had been a brigadier general during the Second World War and had just resumed his faculty position. When I went for the interview, he hired me as a secretarial assistant.

The Foundation had been in operation for 10 years and most of the Fund's resources were devoted entirely to the support of established investigators. In the 1940s, the fellowship program was initiated, and it provided support for applicants who had just received their doctorate. As more and more funds became available from other sources to support established research projects, the fellowship program of the Fund was expanded and eventually consumed all of the available income of the Fund.

How did your role change over the years?

Although I began my tenure with the Fund as secretarial assistant, my role and titles changed over the years. I became executive secretary, administrative secretary and, when the office of the assistant director was eliminated in 1970, I became the administrative director, the position I held upon retirement. With each succeeding director, my duties increased. I was administrator, coordinator, historian, accountant, and confidant of every participating member of the boards of the Fund, as well as the Fellows.

The office operated rather modestly, with just one full-time assistant. The volume of paperwork done manually—before the availability of computers—was tremendous. Some years more than 1,000 applications were processed. We operated a mini printing press, duplicating volumes of materials necessary for review.

People ask, "How could you possibly stay in the same position all these years?" But it wasn't the same job. Over the years, the Foundation changed, science changed, people changed. The administration of the Fund was different with each director, which created a most stimulating and challenging atmosphere. The enthusiasm and leadership of each one provided consistency and excellence to the funded research.

Interestingly, when Dr. Bayne-Jones hired me, I was

planning to obtain some experience and move on. During the interview, he was specific in asking if I planned to commit for a long period. I replied "oh yes" although my long-range plans were quite different.

And you did stay.

Yes. Although other opportunities did arise, I was fascinated by and committed to the way the Fund was expanding and the caliber of applicants. I enjoyed the excitement that existed and what I was learning. I eventually became like a "mother superior" to the Fellows, about 75 at a time who were located all over the world. I felt they were my responsibility. They had been in a protected environment since the time they were in school, and suddenly the world appeared rather frightening. We had many panicked calls when unexpected issues came up. One time, there was a postal strike in London, and Fellows there were frantic about receiving their stipends. A Board member who was traveling in Europe agreed to hand-deliver the checks. When you are in contact with people on a day to day basis, you become associated in a special way and try to address their concerns.

You worked with the JCC for many decades. Is any era particularly memorable?

In the turbulent sixties education took on new attitudes, people were challenging traditions and the establishment, and women were just starting to make their way in the sciences.

Sometimes the Fellows seemed arrogant—there was an arrogance in general. For example, some did not adhere to any specific dress code, and one female became quite irate with me about being called "Miss" when she wanted to be addressed as "Ms." I had to be a great diplomat.

I believe we had the first female JCC Fellow in the late 1960s. At that time, women were sparse in the sciences, but with each decade they became more prevalent. In the 1970s Marian Koshland was the first to join the Board of Scientific Advisers, and subsequently in 1991, Joan Steitz, who had been a JCC Fellow and Board member, was appointed as the first female Director. Women now have representation on both the Board of Scientific Advisers and the Board of Managers, and as applicants and Fellows.

What did you enjoy most about working with the JCC?

There were so many wonderful experiences over the years. I so enjoyed the camaraderie with family members and the distinguished board members. Following the careers of so many outstanding scientists that had been supported by the Fund was wonderful.

How are you spending your retirement?

It has been wonderful to be able to pursue new challenges—volunteering, learning and traveling. *

JCC Announces BSA Changes

The JCC Fund welcomes two renowned scientists, Harvard University microbiologist Richard Losick and Johns Hopkins University molecular biologist Carol Greider, to its Board of Scientific Advisors this year. They will replace retiring members Elizabeth Blackburn, of University of California, San Francisco, and Pamela Silver, of Harvard University. The JCC thanks them for their eight years of service with the BSA.

New BSA Members

Richard Losick, Maria Moors Cabot Professor of Biology at Harvard University, has dedicated his career to studying development in spore-forming bacteria. The focus of his research is *Bacillus subtilis*, a harmless relative of the anthrax bacterium that creates spores under specific circumstances by dividing into two cells of differing sizes. Despite possessing identical DNA, only one of the two cells becomes a spore, fostered by the other. Losick has elucidated many aspects of this process since joining the Harvard faculty in 1971. He discovered sigma factor-based gene regulation in bacteria, described crisscross regulation between the mother cell and prespore, observed the movement of proteins during sporulation, and found that spore formation occurs in localized regions within complex communities of cells.

Losick's contributions and accomplishments extend well beyond his research. His commitment to teaching was recognized when he was named a Harvard College Professor in 2000. Two years later, he was awarded a one million dollar HHMI Professor grant for undergraduate education in the life sciences. With the funds, Losick created a program known as FEEDS (Freshman from Economically or Educationally Disadvantaged Backgrounds in Science) that places



economically-disadvantaged Harvard students in campus labs, promotes active participation in meaningful research, and provides funding to relieve students of financial pressures.

His successes have earned him numerous accolades, including the 2007 Selman A. Waksman Award in Microbiology from the National Academy of Sciences. He is a member of the National Academy of Sciences and a fellow of the American Academy of Arts and Sciences, the American Philosophical Society, the American Association for the Advancement of Science, and the American Academy of Microbiology. He has also served on the editorial boards of *Cell*, since 1991, and *Science*, since 2001.

Losick's first term on the BSA continues his long-standing involvement in science education and training. He is pleased to serve with esteemed colleagues and contribute to the JCC's mission. "I care about science and the community," he says.

Carol Greider, Daniel Nathans Professor and Director of the Department of Molecular Biology and Genetics at Johns Hopkins University, studies telomeres, the protective caps on chromosomes, and telomerase, the enzyme that restores them. Her work focuses on their role in chromosome stability, stem cell failure, and cancer.

As a graduate student in 1984, Greider discovered the enzyme telomerase with outgoing BSA member Elizabeth Blackburn and later expanded her interests beyond its biochemistry to include cell and organismal biology, cancer, and aging. Over her career, she cloned and characterized the RNA component of telomerase, found that telomere length is related to cellular aging, established the secondary structure of human telomerase RNA, demonstrated that the shortest telomere in a cell triggers a DNA damage response, and developed a mouse model lacking a functional telomerase gene.

One current project in Greider's lab utilizes this mouse model to explore the cellular con-

sequences of telomerase dysfunction. Short telomeres initiate gamete death at the beginning of meiosis in telomerase-null mice, suggesting the existence of a DNA damage checkpoint. Greider seeks to elucidate how cells identify these short telomeres as abnormal.

Greider earned her Ph.D. in 1987 from the University of California, Berkeley and then began her independent career at Cold Spring Harbor, where she remained for nine years before moving to Johns Hopkins. Greider's accolades include the Albert Lasker Award for Basic Medical Research, the Gardiner Award, the Rosenstiel Award, the Passano Foundation Award, the Richard Lounsbery Award, the Wiley prize, the Dickson Prize, and the Louisa Gross Horwitz Prize. Greider became a member of the National Academy of Sciences and the American Academy of Arts and Sciences in 2003.

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Retiring BSA Members

Elizabeth Blackburn, Morris Herzstein Endowed Professor in Biology and Physiology in the Department of Biochemistry and Biophysics at the University of California, San Francisco, is a leader in the field of telomeres, the protective ends of eukaryotic chromosomes. In the mid-1980s, she and new BSA member Carol Greider discovered telomerase, the enzyme that replenishes telomeres, which without telomerase become shorter during cell division. Since the discovery, Blackburn has investigated the synthesis and function of telomeres and the role of telomerase in cell division.

Blackburn began her research career in Nobel-prize winner Frederick Sanger's lab at the University of Cambridge in England, where she completed her Ph.D. in 1975. She recalls her early years there fondly and recognizes the importance of access to first-rate scientists at that stage. Because she benefited from outstanding training and support as a young investigator, she enjoys giving back to the scientific community. The JCC has provided one opportunity to do so. Blackburn served for eight years on the BSA, evaluating proposals, selecting fellows, and hosting retreats. "I was happy to be part of the funding process," she says. "The Fund is terrific because it supports extraordinarily talented junior scientists, which is a fantastic use of resources."

Pamela Silver, Professor in the Department of Systems Biology at Harvard Medical School and the Director of the Harvard University-wide graduate program in Systems Biology, is completing her second term with the Board of Scientific Advisors. As an accomplished scientist in a nascent discipline, Silver brought wide-ranging expertise and experience to the Board.

Silver's research interests encompass the properties of natural biological systems and the design of artificial organisms. Among the current projects in the Silver lab are efforts to create a drug delivery cellular oscillator, a cell division counter to analyze aging, and artificial therapeutic proteins. One exciting recent development is the generation of bio-energy by controlling the flow of electrons in redox reactions.

As a JCC board member, Silver enjoyed reading proposals, interacting with colleagues on the Board and knowing that the organization helps young scientists start their careers. "I am a proponent of new directions in science and new ways of teaching and doing science," Silver says. Serving with the JCC offered a chance to fund some riskier, more forward-looking projects, while learning about young scientists' ideas and concerns for the future. "Also, the yearly symposium was a wonderful experience for mingling with other scientists at all levels and meeting the Childs family," she adds. *

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Fellowship Application Information

The Fund awards fellowships to qualified individuals for full-time postdoctoral research on cancer and related subject areas. Applicants should not have more than one year of postdoctoral experience and should hold either an M.D. or a Ph.D. in the field in which they propose to study. In some cases, evidence of equivalent training and experience will be accepted. The appointment normally lasts three years. The basic stipend for the 2009 recipients will be \$43,000 the first year, \$44,000 the second, and \$46,000 the third. Applications for 2009 must be received by Monday, February 2, 2009.

Applications must be submitted electronically.

For details, please visit the Fund's website at www.jccfund.org

The 2008 Retreat

Challenges in Biomedical Sciences: Theory and Computation in Biology

October 17–19, 2008

Interlaken Inn, Lakeville, Connecticut

HOSTED BY

Dr. Thomas D. Pollard and Dr. John Kuriyan

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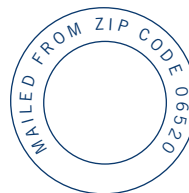
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