

**FRED HUTCH®**  
**BASIC SCIENCES DIVISION**  
40th Anniversary



*Founded 1981*



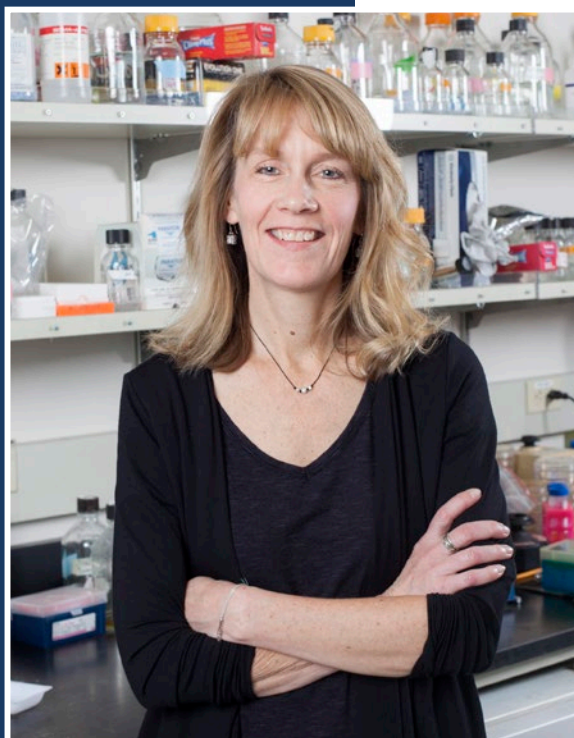
# Celebrating 40 years of Foundational Discoveries

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## FROM THE DIRECTOR OF THE BASIC SCIENCES DIVISION



**Dr. Sue Biggins**  
Director of the  
Basic Sciences Division

It is an honor to reflect on the accomplishments that the Division of Basic Sciences has achieved since its inception forty years ago. As the Center has continued to grow, the Division has maintained a steady group of 30 labs that continue to make cutting-edge discoveries. The Division was founded with the vision of creating a culture where creative scientists would be encouraged to take risks and push the boundaries of science. Equity was a driving principle in setting up the Division. All faculty have equal space and salary for their rank, creating an environment where success is not measured by how much grant money a lab is awarded. Instead, the equitable policies create an environment where scientific risks are encouraged because failures are not penalized by reduced resources.

Over the years, we have witnessed the success that a unique culture can foster. This booklet chronicles many of them, spanning the breakthroughs of identifying the atomic structures of proteins, elucidating the molecular details of gene regulation, understanding the principles of development, and translating fundamental discoveries to treating multiple sclerosis, cancer, and other diseases. Many of the most impactful discoveries were serendipitous, which is one of the reasons that fundamental science continues to be so important to our future. It is impossible to predict what the next breakthrough finding will be. The pandemic we are in is a great example of how critical basic science is because the quick vaccine development required basic

science discoveries such as solving the structure of the spike protein to years of research understanding mRNA biology.

As we think forward to the next 40 years, it is clear that the pressure to justify curiosity-driven science is increasing while federal funding to support it is decreasing. However, it is more important than ever that we maintain our curiosity and passion for asking questions that no one else has and figuring out techniques to answer them. Discoveries are more rapid than ever now with the open science movement and rapid dissemination of data. The pandemic is also a great reminder that it is difficult to predict what basic sciences discoveries will be needed to solve problems in the future.

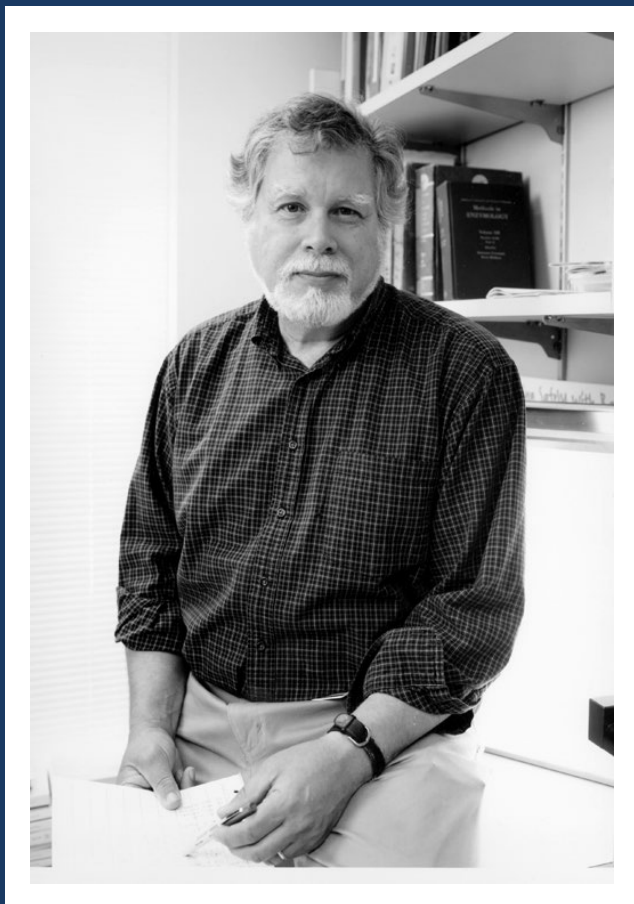
The Division of Basic Sciences has been able to maintain a phenomenal track record of discoveries over the past 40 and I hope you enjoy reading the perspectives from each of the labs that has contributed to this success. I am confident that we are well-poised to continue to tackle fundamental questions for the next 40 years and beyond.

Dr. Sue Biggins

*Dr. Sue Biggins*



# DRIVEN BY CURIOSITY. BUILDING THE FOUNDATION OF KNOWLEDGE.



Dr. Paul Neiman

“Defining the basic science program of the Hutchinson Center was sometimes frustrating to the leadership of the center, who were charged with explaining and promoting the research program to the community and the public at large.”

— **Dr. Paul Neiman**, first director of the Basic Sciences Division

The term “basic sciences” can appear enigmatic. This is not without cause, as basic science can apply to a broad spectrum of research subjects, including physics, chemistry, pure mathematics, biology, and more. At its core, the basic sciences are interested in advancing our fundamental understanding of how the universe works. When applied to biology, basic research seeks to understand topics ranging from cellular division, protein synthesis, nervous system function, viruses, genetics, and many other subjects. If it involves life, basic scientists are interested in solving its mysteries.

Importantly, to understand why things go awry in disease and how to develop treatments, it is crucial to know how they

should function normally. Basic research is at the foundation of all scientific discoveries, ultimately underlying the innovative cures and treatments developed worldwide and at Fred Hutch.

Founded in 1981, the Basic Sciences Division has continually evolved to be at the forefront of discovery, seeking to understand the fundamental underpinnings of our own biology as well as the dysregulations that cause disease. The division has yielded numerous landmark breakthroughs and scientific advances throughout its history. The division was founded on the principles that an inclusive, collaborative, egalitarian, and creative

environment is the basis for scientific innovation and world-changing discoveries.

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***“The Basic Sciences Division puts creative people together and gives them the resources and liberty to follow their instincts. I marvel at the great work they do.”***

— Dr. Jon Cooper, fourth director of the Basic Sciences Division.

When asked what the role of basic science was for society, this is what a selection of faculty past and present had to say:

***“I think the pandemic has been a great illustration of why investing in and carrying out basic science is so important. We would not have had a successful vaccine in such a short time if many aspects of basic research that were considered “curiosity driven” had not been done.”***

— Dr. Sue Biggins

***“Basic science is just the term we apply to research before we figure out how, exactly, it will transform life, health, and society. That it will do so is beyond question – centuries of history make that obvious. Everything that is translational or applied in biology today was pie-in-the-sky within living memory, and a vast array of yesterday’s meaningless, trivial details loom large in technology and society today.”***

— Dr. Ed Giniger

***“I teach a class to MCB students called “The Developmental Basis of Human Disease”. Each week we choose a different human genetic developmental disorder—disorders that cause vertebral asymmetries, or extra digits, or structural heart defects, or autism or cancer, and for each we explore the genes and molecules and even the biophysical processes that have been shown underlie these human tragedies. All of which we’ve learned in the past ~40 years. That’s what basic science has done for society.”***

— Dr. Cecilia Moens

***“Basic science provides information on the mechanisms underlying biological functions. It is only with this knowledge that we can understand the causes of disease and be able to develop appropriate preventions and cures for disease.”***

— Dr. Linda Buck

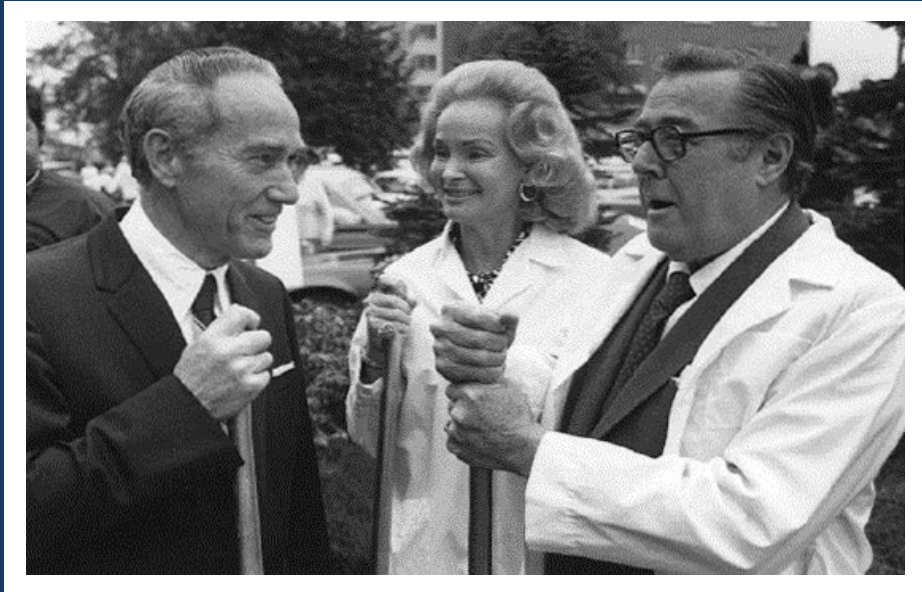
***“Since it got rolling around the 1720s, a core tenet of the Enlightenment is that the continuing exercise of human reason will lead to better understanding of the natural and human-made worlds. A corollary assertion has been that increases in human knowledge of the natural world and of human institutions will lead [perhaps by fits and starts] to increases in human felicity. I submit that these ideas have so far stood the test of time. Certainly, 300 years later, as they carry out their daily work, basic scientists continue to generate knowledge that will allow the truth of these assertions to be evaluated by future generations.”***

— Dr. Roger Brent

***“Same as it has always been – to understand life.”***

— Dr. Mark Roth

# THE HISTORY OF THE BASIC SCIENCES DIVISION AT FRED HUTCH



William B. Hutchinson (left), with Senator and Mrs. Magnuson at the center's groundbreaking ceremony in 1973.

## Groundbreaking and building blocks for the Fred Hutchinson Cancer Center

1973

- **Groundbreaking for what would become the Fred Hutchinson Cancer Research Center, founded by Dr. William B. Hutchinson and named in honor of his brother.**

*"The Fred Hutchinson Cancer Research Center developed from one surgeon's commitment and drive to help cancer patients in the Pacific Northwest into a renowned biomedical research institute, a major asset in the war against cancer and holder of a highly respected place among leading academic research institutions world-wide. This uniquely rapid record of development was not underwritten by a major philanthropic endowment, nor driven primarily by singular leadership [though effective leadership there was], but rather achieved through the combined efforts of a remarkable group of men and women: scientists, physicians, administrators, staff professionals and volunteer members of the community. The challenges faced and decisions taken by individuals and groups within the Center make a remarkable story of institution-building."*

— **From Dr. Paul Neiman and Dr. Barbara Berg's** History Project.

# The Program Era: 1973-1981

For the earliest years of the center's history, it was organized with a programmatic structure, where scientists conducted their research in a defined subject area under the leadership of a program head. Junior faculty would be recruited into distinct laboratory programs. Among the programs that would later evolve into the Basic Sciences Division included: immunology, membrane biochemistry, and chemical carcinogenesis. Additional programs at the center included epidemiology and biostatistics, gastroenterology, and medical oncology, among others.

## 1973

► **Drs. Karl-Erik Hellstrom and Ingegerd Hellstrom join the center.** The Hellstroms helped establish and lead programs in cellular and tumor immunology which would go on to constitute a significant part of the biotechnology industry that persists in the Seattle area today.



The Hellstrom's working in the lab in 1975.

► **Dr. Sen-Itiroh Hakomori joins the center.**

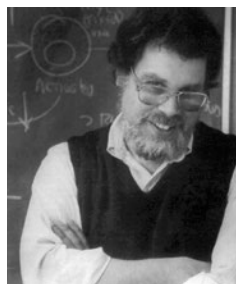
Hakomori, a cell membrane biochemist, studied proteins on the surface of cancer cells. This research would form the basis of The Biomembrane Institute, a private research institute founded by Hakomori.



Hakomori at the first center scientific retreat in 1981.

► **Dr. Paul Neiman joins the center.**

Neiman helped found the Basic Sciences Division and would serve as its first director from 1981-1995. Neiman retired from Fred Hutch in 2010 and would pass away in 2017 of complications from pancreatic cancer.



Dr. Paul Neiman

*"I think there wouldn't be a Hutch as a first-class research institute if it wasn't for Paul Neiman."*

— Maxine Linial, former postdoctoral fellow in Neiman's Lab and professor emeritus in Basic Sciences.



Members of the original bone marrow transplant team in 1989. From left: Drs. Neiman, Alex Fefer, E. Donnal Thomas, C. Dean Buckner and Rainer Storb.

Neiman, a physician-scientist, worked tirelessly on behalf of his patients and furthering cancer research. Neiman was part of E. Donnal Thomas' team of transplant physicians, who developed the first bone marrow transplant protocols for the treatment of leukemia.

As a researcher, Neiman worked to understand the molecules that drive tumor formation. Among his many findings included the discovery that the oncogene

Myc causes genetic damage and instability in cancer cells.

*"Paul was known for being as dedicated to his patients as he was to the fundamental research he championed. He recognized that having great basic science at a cancer research center was essential to future advances for patients."*

—Dr. Gary Gilliland, Fred Hutch's fifth president, and director.



Given Neiman's prominence and dedication to Fred Hutch and the Basic Sciences Division, the central atrium of the Weintraub Building was named in his honor.

*"He loved to think about connections between people and which connections will work and make things happen. If it weren't for him, the face of the Hutch would be really different now."*

— Dr. Robert Eisenman, a molecular biologist who was one of Neiman's first recruits to join the newly formed Fred Hutchinson Cancer Center.

Beyond being a physician and scientist, Neiman was a caring mentor dedicated to the training of young scientists. He was instrumental in establishing the world-renowned Molecular & Cellular Biology Graduate Program, jointly administered between the Hutch and the University of Washington. He also helped mentor



numerous prominent scientists, including Craig Thompson, president of the Memorial Sloan Kettering Cancer Center, as well as Basic Sciences' professors, Maxine Linial, Robert Eisenman, and Mark Groudine.

*"Paul was a wonderful mentor who was instrumental in shaping my career. Upon transitioning to my own lab and later to administrative positions, Paul and I remained close colleagues and friends, and he continued to provide guidance as my career followed in his footsteps."*

—Mark Groudine

## 1975



► **The Fred Hutchinson Cancer Research Center opens its doors in Seattle's First Hill neighborhood.**

► **Dr. Robert Nowinski joins the center.**

Nowinski, a national leader in the study of lymphomas caused by Murine Leukemia Viruses, would develop the center's research program in retrovirology. Among the first scientists in the Seattle region to become interested in developing a biotechnology company, he would go on to form Genetic Systems, a pioneer of monoclonal antibody technology.

► **Dr. Maxine Linial joins the center.**

Linial was recruited by Neiman into the program of viral oncology. Following the center's transition to a divisional structure, her lab would go on to make several



Linial, right, alongside Denise Galloway, center, and Hal Weintraub, left, in 1981.

breakthroughs on the multiplication of retroviruses, particularly into the class known as foamy viruses.

## 1976

► **Dr. Robert Eisenman joins the center.**

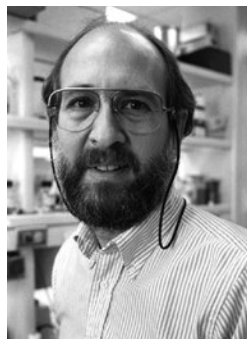
Eisenman has become internationally recognized for his work on a cancer-causing gene called the Myc oncogene. Beyond this, he also has led critical studies of a network of proteins [the Myc/Max/Mad network] that control the activity of numerous genes regulating cell behavior which, when defective, contribute to the development of cancer.



Eisenman in the lab in 1976.

► **Dr. Larry Rohrschneider joins the center.**

Rohrschneider led fundamental studies of cell-signaling proteins, including Fms, which play essential roles in regulating normal and abnormal differentiation of blood-forming cells.



Rohrschneider in the lab in 1991.

## 1978

► **Dr. Chris Henney joins the center.**

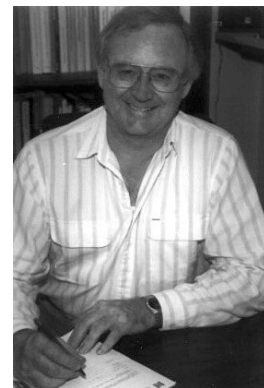
Alongside Drs. Karl-Eric Hellstrom and Ingegerd Hellstrom, Henney helped develop the center's programs in cellular and tumor immunology. He would go on to form the company Immunex with Dr. Steve Gillis.



Henney, left, talking with Dr. Karl-Eric Hellstrom in 1981.

► **Drs. Denise Galloway and James McDougall join the center.**

Galloway and MacDougall's initial work on the possible role of herpes simplex viruses in human malignancies evolved into an interest in the role of human papillomaviruses in cancer. Galloway and MacDougall migrated from Basic Sciences to the Division of Public Health Sciences, where they founded the Cancer Biology program within that division.

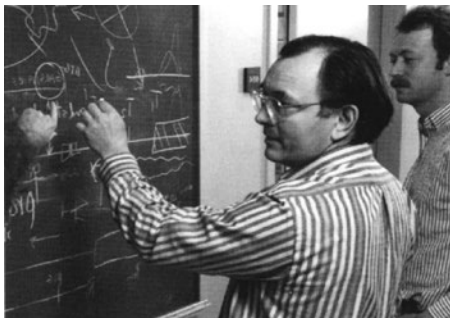


McDougall in his office, in 1990.



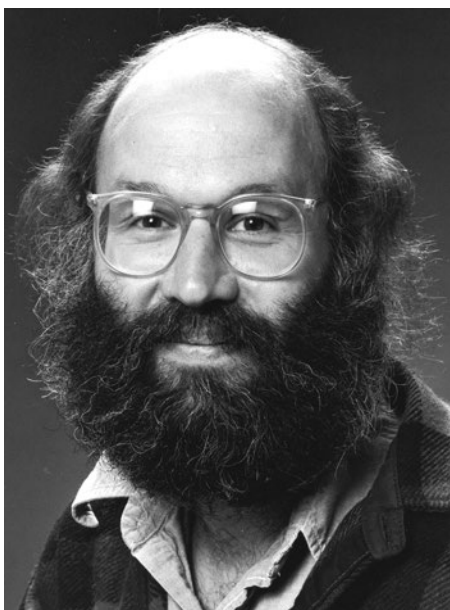
Galloway in the lab in 1978.

► **Dr. Ron Reeder joins the center.** Reeder made early advances into the biochemistry of gene expression, studying a subset of genes that served as the blueprints for the construction of the ribosome, the cellular machine that synthesizes proteins. Reeder played an important role in establishing the division's interest in gene expression and its control.



Reeder working in 1978.

► **Dr. Hal Weintraub joins the center.** Weintraub, one of the center's earliest recruits, joined Fred Hutch in 1978 following an assistant professorship at Princeton University.



Weintraub

*"When most of us left [Princeton] in the late 1970s, Hal, typically concerned more with research opportunity than with glamour, went to a young research institution where the practice of science would be paramount."*

— Dr. Marc Kirschner, cell biologist, and former Princeton colleague. From "In Memory of Harold Weintraub" *Molecular Biology of the Cell*, 6(7), 757–758.

Weintraub would remain at Fred Hutch until his death in 1995 from brain cancer. He made extensive contributions to Fred Hutch, the Basic Sciences Division, and scientific inquiry. His legacy as a caring mentor, supportive colleague, and pioneering scientist remains an inspiration.

His curiosity-driven approach to research led to a diversity of scientific discoveries. Weintraub was the first to describe using anti-sense RNA to elicit specific mutant phenotypes in vertebrate organisms, a finding that is now used broadly in research and clinical therapeutics. Weintraub also identified the transcription factor MyoD [myoblast determination protein 1], a crucial protein that regulates muscle differentiation.



Zakian presenting to colleagues in 1978.

► **Dr. Virginia Zakian joins the center.** Zakian was a pioneer of using the now ubiquitous model organism, yeast, and was instrumental in establishing its presence at the center and division. Basic Sciences now houses several labs that use yeast as a model system to understand the molecular functioning of cells. During her time in the division and beyond, she made many discoveries related to the regulation of chromosomes by telomeres [the ends of chromosomes].

► **Dr. Walter Newman joins the center.**

## 1979

► **Dr. Fayth Yoshimura joins the center.**



Fayth Yoshimura, right, alongside Mark Groudine in 1981.

► **Drs. Richard Gelinas and Robert Margolis join the center.** Much of Margolis' research centered on microtubules, proteins that help give a cell structure and are involved in cell division and cytoplasmic organization. Margolis would purify the histone CENP-A, work that has provided an understanding of the epigenetic inheritance of centromeres and kinetochore assembly.



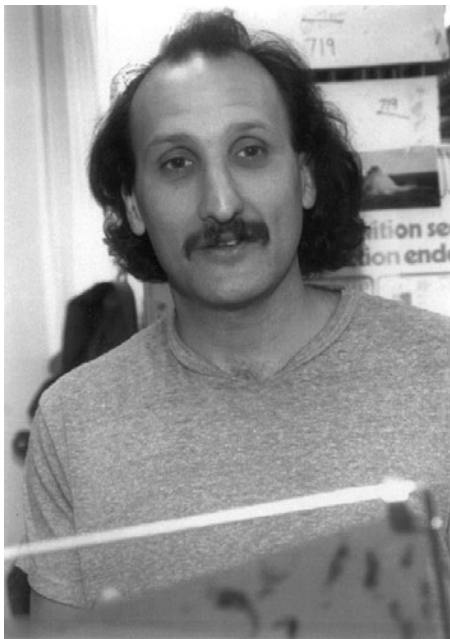
Gelinas, left, Margolis, center, and Larry Rohrschneider, right, at the center's first scientific retreat in 1981.

► **Dr. William Green joins the center.**

► **Dr. Mark Groudine joins the center.**

Groudine is renowned for his research on gene expression and the structure of chromatin. He demonstrated the role of chromatin in repressing fetal hemoglobin expression in adults; loss of this regulation can cause thalassemia, a disorder in which the body does not produce enough hemoglobin.

Groudine was a longtime friend and collaborator with Hal Weintraub. Together, they showed that cell-type-specific regional nucleosome modifications made



Groudine in the lab in 1988

genes available for expression in different cell lineages. This work set the model for epigenetic research for subsequent decades.

Groudine would serve as the director of the Basic Sciences Division from 1995 to 2004, deputy director of Fred Hutch from 1997 to 2016, executive vice president from 2005 to 2016, and acting president and director of Fred Hutch in 2010 and 2014.

### HOW HAS SCIENCE CHANGED?

**"The 1970s and '80s were an exciting and fun time in the field of chromatin structure and gene expression. Investigators readily shared unpublished results on the phone and at meetings. Speaking only about published or "in press" work was the exception, not the rule as it is today."**

— Dr. Mark Groudine

## 1979

► **Dr. Steve McKnight joins center.** Despite his appointment at Fred Hutch being McKnight's first faculty position, he was already a nationally recognized pioneer in the field of transcriptional regulation.



McKnight in the lab in 1982.

## 1980

► **Dr. James B. Lewis joins center.**

## 1981

► **Dr. Steve Henikoff joins center.** Early in his career, Henikoff introduced *Drosophila* as an experimental model system at the center. He would become world-renowned for the development of several tools [CUT&RUN and CUT&Tag] that are used in countless labs studying gene expression.



Henikoff, center, chatting with Robert Eisenman, left, and Jim Lewis, right, in 1981.

► **Dr. Steve Gillis joins the center.** Gillis would go on to found the biotech company Immunex, alongside Chris Henney.



# THE FOUNDING OF THE BASIC SCIENCES DIVISION AND ITS GUIDING PRINCIPLES



Dr. Robert Day, right, speaking with Dr. Sen-Itiroh Hakomori, left, in 1981. Day served as Fred Hutch's seconded director and would help oversee its transition to a divisional structure.

## Fred Hutch transitions from a programmatic structure to a divisional structure.

1981

► **The Basic Sciences Division is founded with Paul Neiman appointed as its first director.** 1981 marks a momentous year in the history of the Fred Hutchinson Cancer Center: the transition from its original programmatic structure to a divisional structure.

Dr. Paul Neiman, who would become the division's first director, summed up the impetus for the change:

*"As more junior faculty were recruited to the center, the program structure became increasingly controversial in some quarters. The younger faculty, especially in the basic science laboratories, desired a more egalitarian faculty organization, with each member leading an independent laboratory."*



These concerns would ultimately lead to a restructuring of the whole center in late 1981. Within the new structure, individual faculty members would run their own laboratory, associated with one [or more] distinct divisions. As of 2021, there are five research divisions at Fred Hutch: Basic Sciences, Clinical Research, Human Biology, Public Health Science, and Vaccine and Infectious Diseases.

At the founding of the Basic Sciences Division, the faculty came to a consensus regarding the principles that would direct the future of the young division.

The most significant change was that the division faculty as a whole, would select and hire new faculty members to join the division, instead of new hires being recruited by a program leader to fill a particular slot in a pre-determined research area topic. Recruitment of in-house trainees was also discouraged, although there have been several exceptions throughout the division's history. Neiman described some of the thinking behind this policy: "limiting recruitment of junior faculty from an institution's own laboratories avoided the development of empires, which was a liability, many felt, of the original program structure." In general, recruitment into the division focused on hiring and developing talented young faculty whose career and body of work would be done within the division and center. It was believed that this approach would have a more significant impact and be of greater social value than simply moving established



Scientific retreat in 1982. David Thomas, left, Virginia Zakain, center, Hal Weintraub right.

scientists from one institution to another.

The primary approach was to recruit entry-level faculty of exceptional ability and do everything possible to aid in their success. A key tenet was to have broad-based enthusiasm for individual recruitments, with as many faculty members as possible have a stake in these recruitments. Throughout a scientist's career, allocations of space, increases in salary, and distribution of other resources would be based on reviews carried out in conjunction with the promotional processes. Therefore, all faculty members understood that increases in available resources would be based solely on rigorous peer review. This approach served to cut down considerably on internal politics within the divisional scientific community and to allowed energy to focus mainly on the conduct of research.

Another principle that helped guide the division was the maintenance of modest laboratory sizes. Smaller laboratories meant

that, if desired, principle investigators could remain active bench scientists and not simply administrate over many trainees, as can often be the case with successful scientists. Moreover, the small-laboratory model encouraged collaboration between laboratories, not only for intellectual exchange and sharing of techniques but also for the purchase of major equipment and research resources that could be shared among laboratories, thereby helping to cement the community together.

As part of this community building, several traditions from the earliest days of the division have persisted to the present. These functions have remained at the core of the division's scientific culture, highlighting the interest and collegiality of its members, despite the diversity of their research interests. Dating back to when the center was in the original building at First Hill, there was a small conference room where faculty would hold a weekly lunch, during which each faculty member would take a turn presenting the current research focus of their laboratory. In addition to the faculty lunch, the whole division would get together once a week to hear talks from trainees, helping inform everyone about the latest research occurring in the division and allowing trainees to practice their scientific presentation skills. Finally, the division holds an annual scientific retreat during which each of the faculty members would present a summary of their research to the division and potential graduate recruits.

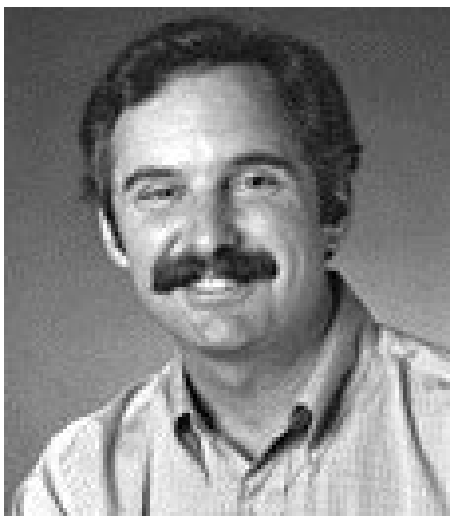


Basic Sciences retreat in 2019.

## 1982

### ► Dr. Jerry Nepom joins Basic Sciences.

Nepom was responsible for some of the earliest discoveries into the human leukocyte antigen system, a complex of genes responsible for the regulation of the immune system. Mutations to these genes have been linked to autoimmune disorders such as type 1 diabetes, juvenile and adult forms of rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease. Nepom worked closely with John Hansen, part of Fred Hutch's Clinical Division, who pioneered investigations of human leukocyte antigen disparities in bone marrow transplantation.



Dr. Jerry Nepom

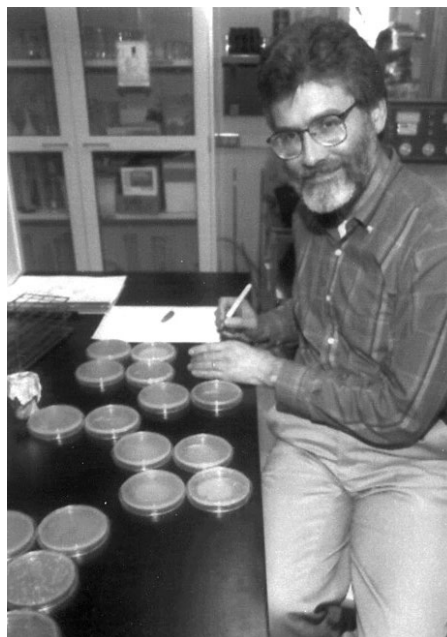
### HOW HAS SCIENCE CHANGED?

**"Translational opportunities are now routinely sought and appreciated, with a widespread recognition that basic science discoveries can be amplified and even improved through considering medical applications. That is a welcome development, breaking down artificial barriers between basic and clinical science. My own career has followed this trajectory, as I left the FHCRC in 1985 to start a translational immunology institution, now known as the Benaroya Research Institute, which has become a high-impact center of immunological science."**

— Dr. Jerry Nepom

### ► Dr. Gerry Smith joins Basic Sciences.

Smith, a well-established scientist when he joined the division, has made several ground-breaking discoveries throughout his career into the mechanisms of DNA recombination, first in *E. coli* and later in yeast. He showed that the RecBCD enzyme has fast and slow helicase activities with opposite DNA strand polarity, which explained how looped recombination intermediates are generated.



Smith in the lab in 1988.

### ► Dr. Bill Carter joins Basic Sciences.

Carter began his career at the center as a Postdoc with Sen-Itiroh Hakomori. His own lab studied the extracellular matrix, a complex mixture of molecules that surrounds and supports cells. He made crucial discoveries into the adhesive interactions between cells and the extracellular matrix, helping understand cell movement, cell division, and wound healing.

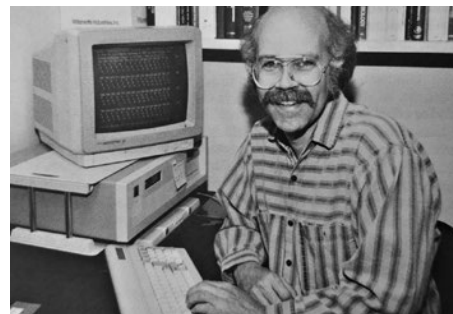


Dr. Bill Carter

## 1984

### ► Dr. Arthur "Dusty" Miller joins Basic Sciences.

Miller contributed significantly to the development of gene therapy techniques which could serve as effective treatments for many disorders, including hemophilia and cystic fibrosis.



Miller at his computer in 1988.

## 1985

### ► Dr. Phil Meneely joins Basic Sciences.

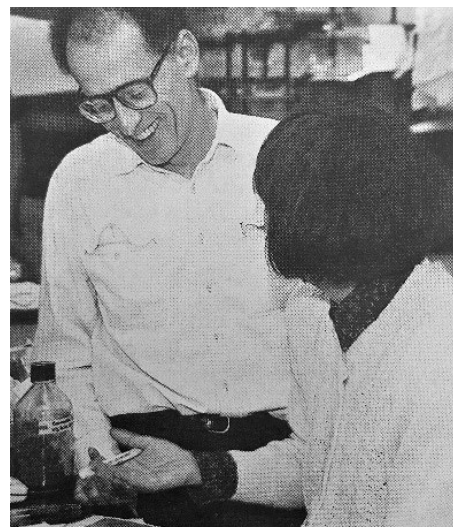
Using the nematode worm, *C. elegans*, Meneely investigated the role of sex chromosomes in morphological differentiation and sex determination.



Meneely in the lab in 1993.

### ► Dr. Harvey Eisen joins Basic Sciences.

Eisen worked to understand host-parasite interactions, advancing the understanding of how an organism differentiates 'itself' from a parasitic invader.



Eisen, left, with Paola Minoprio in the lab in 1988.



► **Dr. Jon Cooper joins Basic Sciences.**

Cooper's research has helped elucidate the networks of proteins that cells use to communicate with each other. His discoveries have provided a mechanistic link between two human oncogenes [Ras and Raf] that helped help illuminate this kinase signaling pathway.

Cooper would direct the Basic Sciences Division from 2009 to 2018.

### HOW HAS SCIENCE CHANGED?

"Science has become more of a business since I started in BSD in 1985. I was lucky to start when there was more grant funding and ideas than there were scientists. Over the past decades, experiments have become more costly, and we have become more specialized."

— Dr. Jon Cooper



Cooper in the lab in 1985.

► **Dr. Tom St. John joins Basic Sciences.**

St. John investigated gene expression during Hematopoiesis, the differentiation of stem cells to form the cellular components of blood.



St. John in the lab in 1985.

► **Dr. Michael Gallatin joins Basic Sciences.**

Among Gallatin's many research subjects included work identifying the adhesive mechanisms that control the migration of lymphocytes, a type of white blood cell in the immune system, through sites of inflammation.

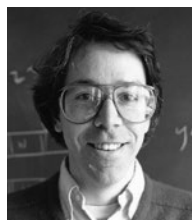


Gallatin in the lab in 1988.

## 1986

► **Dr. Robert Levis joins Basic Sciences.**

Levis' research sought to understand the structure and function of telomeres, the structure at the end of chromosomes. His research helped further the understanding of their contribution to gene expression and the consequences of telomeric mutation.



Dr. Robert Levis

► **Dr. Meng Chao Yao joins Basic Sciences.**

Yao brought a new model system to the center, a single-celled organism called Tetrahymena, which allowed for analysis of complex changes in DNA structure, rearrangement, and a process known as amplification. Using this system, he worked to understand the processes that affect genome stability, the dysregulation of which is a key cause of cancer.

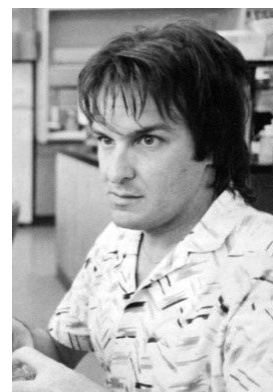


Dr. Meng Chao Yao

► **Dr. Hal Weintraub elected to the National Academy of Sciences.**

► **Dr. Keith Fournier joins Basic Sciences.**

Fournier was an innovator in the development of novel genetics techniques, including the creation of methods



Fournier in the lab in 1987.

that allowed for the transfer of a single chromosome from one mammalian cell to another. In collaboration with Mark Groudine, Fournier devised a chromosome shuttle system that allowed for the modification of human chromosomal genes by homologous recombination and the assessment of how those modifications affected gene expression and chromatin structure.

**A memory from Dr. Keith Fournier:** I was a graduate student at Princeton when Hal Weintraub was a newly minted assistant professor in the department, and I always admired his approach to science. I had the opportunity to join Hal and the fledgling Basic Sciences group at the FHCRC at the end of my postdoc at Yale in 1978 but elected to start my independent career at the Norris Cancer Center at USC. Nine years later, I joined the faculty in Basic Sciences at the FHCRC. Our quirky, cramped facility on First Hill fostered the kind of informal collegiality that I had enjoyed in the nascent Molecular Biology Department at Princeton; it was a special time.

### HOW HAS SCIENCE CHANGED?

"Where to begin! No terabyte data downloads, no high-throughput platforms, no interminable cataloging! Cleverly designed experiments that answered important questions used to get names- Luria-Delbrück, Meselson-Stahl, PaJaMo. Can you think of a recent experiment with that kind of gravitas?"

— Dr. Keith Fournier

# 1987

## ► Dr. Robert Hinrichsen Joins Basic

**Sciences.** Hinrichsen's research was interested in the mechanisms of cellular behavior in the protozoan *Paramecium tetraurelia*. His discoveries furthered the fundamental knowledge of how cells transmit sensory information and regulate behavior, even at the single-cellular level.

## ► Dr. James Roberts joins Basic

**Sciences.** Roberts, an early exception to the policy of not recruiting individuals from within the center, began his career as a postdoctoral fellow with Hal Weintraub. His lab would make several significant findings, including the discovery of the Cyclin E protein, which was crucial for understanding cell cycle regulation and provided key markers for classifying and treating breast cancers.

Roberts would direct the Basic Sciences Division from 2005 to 2009.



Roberts, right, with Hal Weintraub.

## ► Dr. Linda Breeden joins Basic Sciences.

Throughout Breeden's career, her lab has investigated many aspects of the cell cycle process. Breeden identified the Yox1 and Yhp1 repressors and showed they restrict ECB-mediated transcription to M/G1, work that was critical to understanding how cells ensure accurate cell cycle transitions. She was also an early pioneer into the mechanisms of quiescence, a state in which cells go dormant and stop dividing.



Dr. Linda Breeden

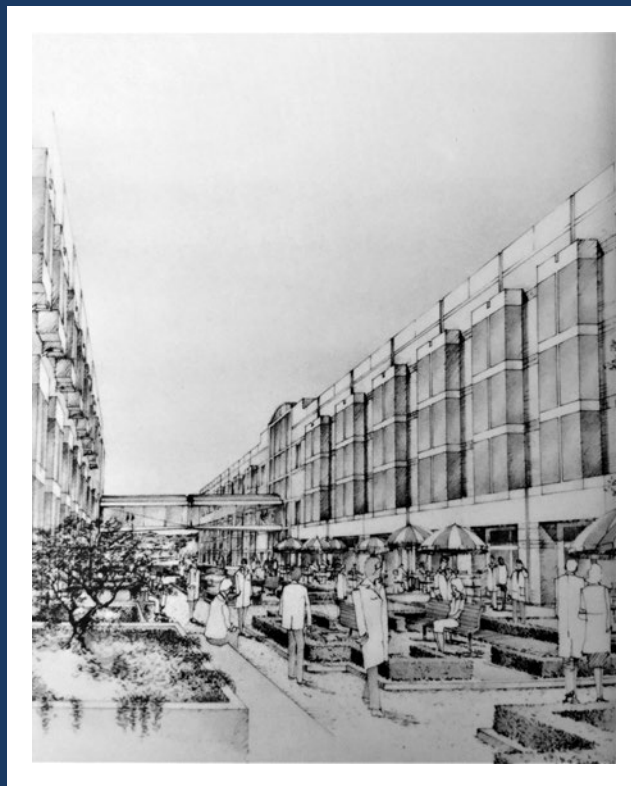
## ► Dr. James Priess joins Basic Sciences.

Priess has made numerous advances in our understanding of cell fate specification, the process by which cells go from non-specialized to having distinct functions. These advances include the identification of PIE-1, a protein localized exclusively to cells destined to become germ cells and involved in keeping them totipotent.



Priess in the lab in 1987.

# FRED HUTCH PLANS ITS BIG MOVE



Architectural render of what would become the first two research buildings of Fred Hutch's South Lake Union Campus.

## 1988

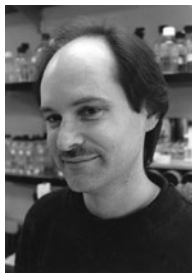
► **Seven acres of land purchased for Fred Hutch's new South Lake Union campus.** Fred Hutch's leadership decided that the development of new laboratory space was essential for the development and growth of the center, leading to the purchase of land in Seattle's South Lake Union neighborhood, then the second-largest land acquisition in Seattle history behind the Seattle Center.

*"By the end of the 1980s, the laboratory component of the center, principally the Basic Sciences Division, had overrun the laboratory space available in the original First Hill facility."* – Dr. Paul Neiman

## 1988

### ► Dr. Steve Hahn joins Basic Sciences.

Hahn has worked to understand the machinery that produces and regulates messenger RNA, the genetic material that is translated into proteins. Hahn, in collaboration with Ron Reeder, discovered that the TATA-binding protein is used by all three eukaryotic RNA Pols and found mutations that revealed an underlying specificity for subsets of promoters.



Dr. Steve Hahn

### ► Dr. Mark Roth joins Basic Sciences.

Roth's research has focused on understanding "metabolic flexibility," how organisms induce a state of reversible suspended animation, with the purpose of improving the treatment of disease. Roth developed the first significant screening breakthrough for Lupus by realizing SR proteins are biomarkers for the disease, which led to an FDA-approved diagnostic test. He also founded the company Faraday Pharmaceuticals, which is developing treatments for heart attacks.



Dr. Mark Roth

## 1989

### ► The division's computers are networked together.

In 1989, the division completed the process of networking its computers together. The network consisted of approximately 70 personal computers and two Unix-based file servers, including a NeXT computer with an external 600 MB disc, that contained the most up-to-date versions of all available DNA and protein sequence databases. As of 2021, the division manages about 450 computers.



Lynn Adams, manager of microcomputer shared resources, showing off new equipment in 1989.

## 1991

### ► Dr. Karen Blöchlinger joins Basic Sciences.

Blöchlinger was interested in understanding how the nervous system develops. Her research took advantage of the genetics tools available using the *Drosophila* model system to investigate the genes that regulated how a cell becomes a neuron.



Dr. Karen Blöchlinger

## 1992

### ► Dr. Susan Parkhurst joins Basic Sciences.

Parkhurst has made numerous discoveries in a variety of research areas throughout her career, including wound healing and nuclear architecture. Parkhurst was the first to identify a loss-of-function mutation in any Rho family small GTPase, which allowed the characterization of its regulatory roles.



Dr. Susan Parkhurst

### HOW HAS SCIENCE CHANGED?

"When I started, PCR required three water baths at different temperatures and manually moving tubes between them. Now we are doing RNA seq on single cells, 3D genomics, and super-resolution imaging!"

— Dr. Susan Parkhurst

## 1989

### ► Dr. Michael Emerman joins Basic Sciences.

The primary focus of Emerman's scientific career has been dedicated to ending the AIDS epidemic by studying the evolution and interactions of the human immunodeficiency virus (HIV) and related retroviruses. Emerman discovered the mechanism by which HIV infects non-dividing cells, work that also led to the development of related gene therapy vectors.



Emerman in the lab in 1989.

## 1992

### ► Memory from the Weintraub Lab:

Hal loved to play pick-up basketball, and he frequently would drive to the local community courts at lunchtime to play. Basketball was not the first thing that came to one's mind when first meeting Hal. However, he was fiercely competitive and unexpectedly skilled, quickly darting



around or between surprised defenders, launching the ball from an awkward angle or unorthodox jump shot. And it almost always went through the net. Similar to his science.



Hal Weintraub, left, Virginia Zakian, center, and Mark Groudine, right, in 1992, looking over experimental results while playing basketball.

## 1993

### ► Dr. Philippe Soriano joins Basic Sciences.

Soriano in the lab, c. 1993. Soriano's research was centered on understanding the genes involved in growth and differentiation using a mouse model system. Using transgenic techniques, including gene trapping, Soriano developed mutants that helped identify genes in signal transduction pathways that played critical roles in embryonic development.



Soriano in the lab in 1993.

► **Phase 1 of the new South Lake Union campus opens.** The Basic Sciences Division moves into its new home. Dr. Barry Stoddard would be the first faculty member to set up a lab in the new facilities.

The momentous opening of the new campus was celebrated in the best way scientists know how: with a scientific symposium.



## 1993

### ► Dr. Barry Stoddard joins Basic Sciences.

Stoddard, an expert in protein structure and engineering, has used a variety of techniques over his career to determine the three-dimensional shape of proteins, all with the goal of using this information to modify natural proteins to treat or cure disease. He has solved several structures of 'Factor VIII,' a blood-clotting protein that is involved in the most common form of hemophilia; work may help treat hemophilia, as well as inform studies on stroke and heart attacks.



Dr. Barry Stoddard

The figure below shows the growth in the number of structures solved over the years and made available to the public to see what has happened in my field since I joined the Hutch at the very beginning of 1993. When I started graduate school in 1985, I was able to find and photocopy almost all the available papers describing structures of biological molecules in one long afternoon in the University Library. In January of 1993, there were still only a few hundred structures that had been solved and made public for examination by interested scientists. As of my writing this email, there are almost 180,000 structures in the database, and the pace at which they are being solved continues to accelerate. As well, the complexity and size of the structures that are being solved these days have increased dramatically due to the sudden emergence of CryoEM as a powerful new tool for such studies. I am excited that I'll be finishing my career by visualizing and studying molecular assemblages and machines that I would never have been able to visualize using older methods. In summary, the past 28 years of my career, all spent at the Hutch, have been an extraordinarily exciting time to work in my field...I feel blessed to have been a small part of what the structural biology community has achieved since the early 1990s.

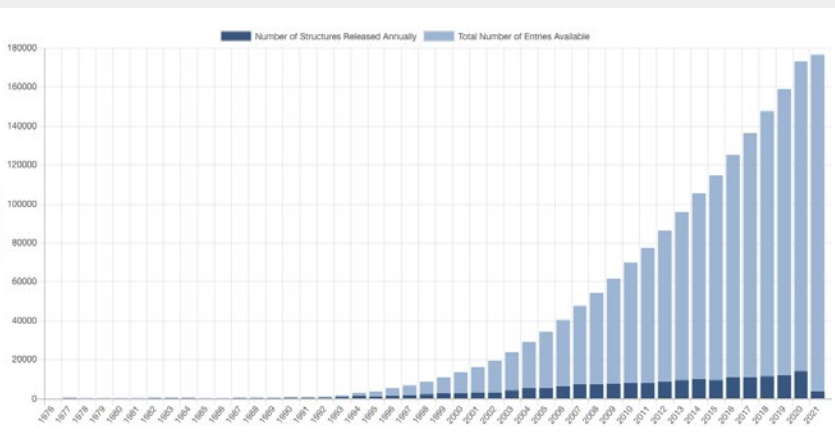


Figure showing the growth in the number of solved and deposited biological structures in the protein database from the 1970s to now.

### HOW HAS SCIENCE CHANGED?

"My career started as a graduate student in 1985, followed by my joining the Fred Hutch in 1993 to today. Being active in this field and witnessing the growth of structural information about biological systems as shown has been an extraordinary experience."

— Dr. Barry Stoddard



Mark Groudinen, left, Marc Kirschner, center, and Phil Soriano, right, at the first scientific symposium held for the opening of the new facilities in 1993.

► **Dr. Bruce Edgar joins Basic Sciences.**

Edgar was interested in uncovering the mechanisms by which a single-celled egg develops into a multicellular organism. Edgar discovered the mechanism that underlies endocycling, the replication of the genome in the absence of mitosis, finding that E2F and CLR4 form a molecular oscillator that regulates this process, critical for the morphogenesis of plants, animals, and some human organs.



Dr. Bruce Edgar

► **Dr. Ed Giniger joins Basic Sciences.**

Giniger worked to understand how connections are established between neurons as the brain develops and how those connections degrade over aging or because of neurodegenerative diseases. He showed that the *Drosophila* cell surface protein, Notch, played a vital role in the development of the intersegmental nerve, helping define its growth path.



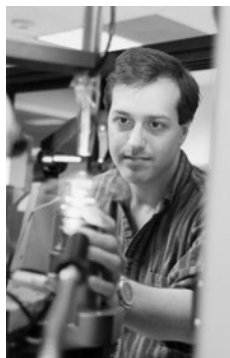
Giniger in the lab in 1993.

► **The establishment of the Molecular and Cellular Biology graduate training program; jointly administered between the Fred Hutch and the University of Washington.**

## 1994

► **Dr. Roland Strong joins Basic Sciences.**

Strong's focus has been on using protein engineering and structural biology to understand the immune system. He discovered that the immune system protein siderocalin protects against intestinal bacterial infection by scavenging iron, work that could help develop novel antibiotics. Additionally, Strong led the development of Daedalus, a rapid protein-production system.



Roland Strong in the lab in 1994.

## 1995

► **Dr. Kam Zhang joins Basic Sciences.**

Zhang studied the structure-function relationship of the proteins involved in apoptosis, a crucial process that ensures that unhealthy cells are eliminated from an organism. Defects in this process can cause a wide variety of disorders, including cancer.

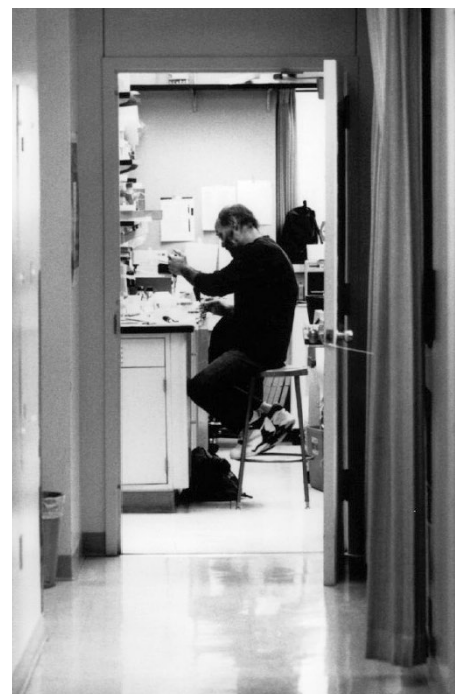


Dr. Kam Zhang

► **Dr. Hal Weintraub, deeply respected as a caring mentor, supportive colleague, and pioneering scientist passes away at 49 from brain cancer.**



Weintraub building dedication. Mark Groudine, center, sitting with the Weintraub family.



Weintraub in the lab.

*"He [Weintraub] was the source of a great deal of our sense of quality and commitment to excellence, and he kept our feet to the fire with respect to maintaining the highest possible standards for the recruitment and development of other scientists at the Hutchinson Center. He was an enormous help to me as the acting scientific director and director of the Basic Science Division. I always felt Hal's point of view was something to be very carefully considered. Although we did not always agree on everything, there was a very strong sense of partnership between us in the development and progress of the Division. Hal's premature death at the age of 49 was a tremendous blow to all of us, and me in particular. There was always a strong bond of both friendship and mutual respect, and I miss him to this day."*

—Dr. Paul Neiman

The Fred Hutch Weintraub and Groudine Fund was established to honor Weintraub's scientific legacy and his long-standing scientific partnership and close personal friendship with Mark Groudine. The fund aims to foster intellectual exchange by promoting programs for graduate students, fellows, and visiting scholars, including the Harold M. Weintraub Graduate Student Award, established in 2000.





Given Weintraub's significant contributions to the division as a person and scientist, the building that housed many of the Basic Sciences' laboratories was renamed the Weintraub Building.

*"I think he had a tremendous influence in keeping the department egalitarian and directed towards doing good science."*

—Gerry Smith

*"A lot of [scientists], especially now, are very cautious, and Hal never did that, and he never wanted anyone around here to do that either. The duty of being a basic scientist is to figure out hard things."*

—Dan Gottschling

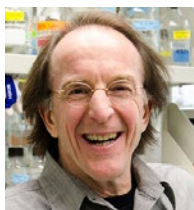
*"Hal and I were the closest friends for 25 years," Groudine said quietly, remembering their twice-weekly dinners and nearly daily basketball games. And remembering, too, his friend's legacy, he's worked over the past 20 years to honor Weintraub's vision for basic sciences research and for the Hutch. – excerpt from Remembering Fred Hutch's Dr. Harold Weintraub 20 years later.*

► **Mark Groudine succeeds Paul Neiman as Director of Basic Sciences.**

## 1996

► **Dr. Daniel Gottschling joins Basic Sciences.**

Gottschling originally trained at the center as a postdoctoral fellow with Virginia Zakian before starting his own lab, where he discovered the DOT1 methyltransferase, a critical regulator of the cell cycle among many other functions.

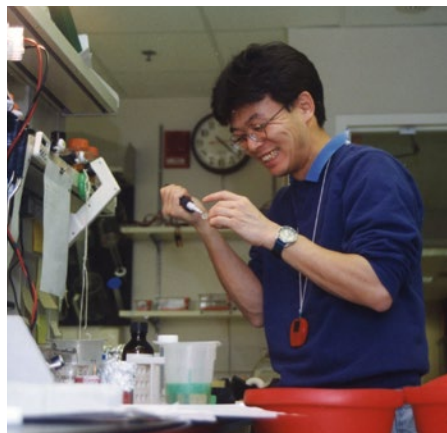


Dr. Daniel Gottschling

## 1997

► **Dr. Toshio "Toshi" Tsukiyama joins Basic Sciences.**

Tsukiyama has worked to understand how cells regulate chromatin, the packaging proteins responsible for compacting a cell's DNA and regulating gene expression. Tsukiyama was the first to determine the genome-wide functions of a chromatin regulator using a genomics method, which helped elucidate how chromatin regulators control transcription and replication.



Tsukiyama in the lab in 1997.

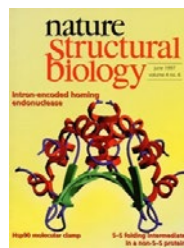
### HOW HAS SCIENCE CHANGED?

*"It's hard to believe, but the word 'genomics' did not exist when I started my lab at the end of 1997. This is the main approach our lab uses now."*

— Dr. Toshio Tsukiyama

► **A Memory from Dr. Barry Stoddard:**

The first structure solved solely in my lab, using data collected solely with our own instrumentation at the Hutch, was a profound highlight both for my own research and for the structural biology program. The structure was of a gene-targeting protein called I-Crel and was solved by Pat Heath [then a postdoc in my lab, now a member of



Cover of Nature Structural Biology (May 1997) illustrating the first structure solved in the Stoddard Lab of the I-Crel homing endonuclease [Heath et al.]

the Administrative Division]. The structure was published in 1997, featured on the cover of Nature Structural Biology and was the starting point for a 25 year-long project that formed the foundation and core of much of our work over the following years.

## 1998

► **Dr. Cecilia Moens Joins Basic Sciences.**

Moens's research has been dedicated to studying how genes control the brain's early development. Moens was the first to discover how the Planar Cell Polarity pathway regulates neuronal migration in the hindbrain, work that is critical to understanding how the brain forms functional circuits.



Moens in the Lab alongside her lab's model organism, the zebra fish in 1998.

### HOW HAS SCIENCE CHANGED?

*"Changes in mutagenesis, sequencing, and imaging technologies have completely changed the landscape of developmental biology and neuroscience. When I started my post-doc in 1993, we used chemicals as random mutagens and looked at unlabeled, albeit transparent, embryos for mutant phenotypes under a stereomicroscope. Today we CRISPR any gene at will and screen live mutant embryos for the position of a single fluorescently labeled neuron or axon, or even a single [large] synapse. We can assess mutant phenotypes by reading out the transcriptome and the watching lineage of every cell in the animal."*

— Dr. Cecilia Moens

► **Dr. Robert N. Eisenman elected to the National Academy of Sciences.**

**A memory from Dr. Jon Cooper:** In 1998, postdoc Brian Howell phoned me at home one weekend evening to say he had looked at slides of the brain of a mouse mutant he had made, gone to the library, and found a similar looking defect in the Reeler mouse mutant that had been identified in the 1950s in Scotland. This led to an exciting few years in which we and a handful of other labs worked out how neurons move from one part of the brain to another during fetal development.

## 1999

► **Adrian Ferre-D'Amare joins Basic Sciences.**

Ferre-D'Amare worked to decipher the three-dimensional structure of ribozymes, RNA molecules that function as enzymes, using X-ray crystallography. His analysis of the hairpin ribozyme would represent the first structure determination of a fully assembled ribozyme active site that catalyzes a phosphodiester cleavage without requiring metal ions.



Ferre-D'Amare in the lab.

► **Dr. Suzannah Rutherford joins Basic Sciences.**

Rutherford sought to understand how organisms stabilized their development and physiology against genetic variation. She would use, what was at the time, emerging genome-wide approaches to study latent genetic variation in Heat shock protein 90, a molecular chaperone critical to many cellular pathways, including proteostasis.



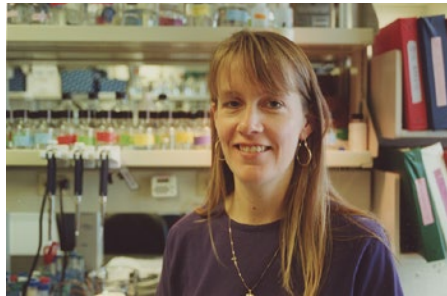
Dr. Suzannah Rutherford

## 2000

► **Dr. Sue Biggins joins Basic Sciences.**

Biggins led the team that originally isolated the kinetochore, the large molecular machine that coordinates chromosome sorting, from yeast cells. This accomplishment paved the way for critical new findings, including the role that tension plays in chromosome sorting.

Biggins currently serves as director of Basic Sciences from 2019 to the present.



Biggins in the lab 2000.

► **The establishment of the Harold M. Weintraub Graduate Student Award, created to recognize the outstanding achievements of graduate students in the biological sciences and honor “the bold, creative, pioneering spirit” embodied by Hal Weintraub.**



The 2019 recipients of the Harold M. Weintraub Graduate Student Award.

*“I think Hal would be really impressed. He loved to hear good stories and good science, and these students give fantastic talks.”*

— Dr. Susan Parkhurst, who oversees the award.

## 2001

► **Mark Groudine elected to the National Academy of Sciences.**

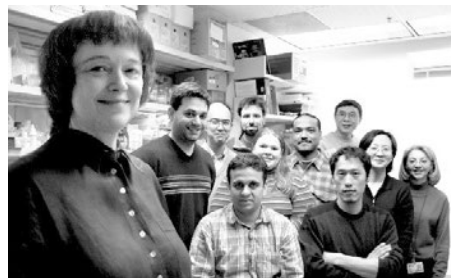


Groudine and colleagues celebrate his induction into the National Academy of Sciences.

## 2002

► **Dr. Linda Buck joins Basic Sciences.**

Buck would be awarded the Nobel Prize in 2004 in physiology or medicine, shared by Dr. Richard Axel, for discovering hundreds of receptors for odors in the nose and uncovering how information from those receptors is organized in the nose and brain. Her lab continues to make groundbreaking discoveries into the networks of neurons responsible for the sense of smell as well as the role of olfaction in stress and appetite.



Buck with her lab in 2002.

### HOW HAS SCIENCE CHANGED?

*“I have witnessed tremendous progress in the understanding of mechanisms underlying numerous biological functions and diseases. Much of this has resulted from new technologies that permitted the definition of genomes of humans and other species and allowed the investigation of biology with new tools.”*

— Dr. Linda Buck



## 2003

### ► Dr. Harmit Malik joins Basic sciences.

Malik began his career at the center as a postdoc in the Henikoff Lab. He would go on to form his own lab interested in understanding genetic conflict, the competition between genes and proteins with opposing functions that drive evolutionary change. Malik discovered an essential gene, *gfzf*, that causes hybrid incompatibility, work that contributes to uncovering mechanisms that drive speciation.



Malik in the lab in 2003.

### ► Dr. Linda Buck elected to the National Academy of Sciences

### ► Dr. Katie Peichel joins Fred Hutch.

Peichel first joined the center with a primary appointment in the Human Biology Division before switching to Basic Sciences in 2013. Peichel worked to uncover the mechanisms that underlie evolutionary adaptation to divergent habitats and the formation of new species using a fish called the threespine stickleback. Peichel developed innovative genetic and genomic tools to identify the genetic changes that underlie adaptation and speciation, behavioral evolution, and sex chromosome evolution in sticklebacks.



Peichel in the lab's threespine stickleback facility in 2003.



LEFT: Buck receiving the Nobel prize. RIGHT: Drs. Don Thomas, left, Lee Hartwell, center, seated, Linda Buck, center, standing, and Mark Groudine, right, at the Nobel news conference.

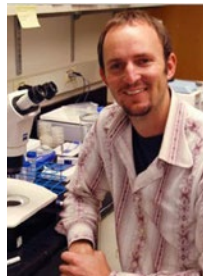
## 2004

### ► Dr. Linda Buck receives Nobel Prize for shedding new light on olfaction.

## 2005

### ► Jim Roberts succeeds Mark Groudine as Director of Basic Sciences.

► Dr. Marc Van Gilst joins Basic Sciences. Van Gilst worked to identify mechanisms that could prevent or even reverse aging by studying how changes in metabolic activity affected tissue regeneration in the nematode worm, *C. elegans*.



Van Gilst in lab in 2005.

### ► Dr. Steve Henikoff elected to the National Academy of Sciences.

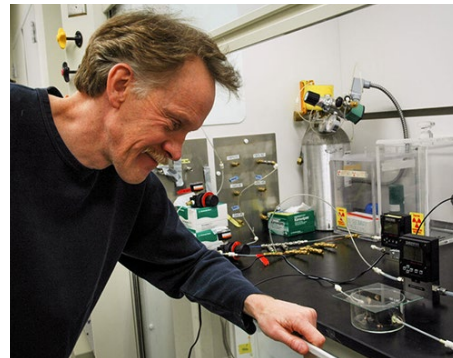
### ► Fred Hutch continues to expand its campus.



Aerial photograph of the Fred Hutch campus in 2005, highlighted against downtown Seattle.

## 2007

### ► Dr. Mark Roth wins MacArthur Fellowship "genius" award for his research in suspended animation.



Dr. Mark Roth

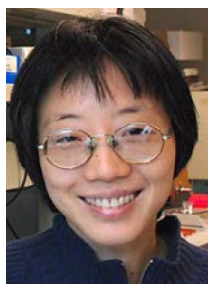
► Dr. Meng-Chao Yao retires. Yao retired from the center after 20 years of service and moved to Taipei, his birthplace, to be the director of the Institute of Molecular Biology of Academia Sinica.



Dr. Meng-Chao Yao, right, speaking with Dr. Linda Buck

► **Dr. Wenying Shou joins Basic Sciences.**

Shou worked on modeling the mechanisms and evolution of symbiosis, positive and mutually beneficial interactions between different species.



Dr. Wenying Shou

## 2008

► **Basic Sciences Administrators and IT support at a team-building exercise at the Kaspars restaurant.**

Research administrators are an essential part of the success of the division, helping support the innovative and exciting research happening in Basic Sciences.



In the foreground from left to right: Christy Majorowicz, Michele Karantsavelos, Jeremy Mseitif, Luna Yu, and Karen Brighton. Partially obscured in the background: Sue Madill, Lori Blake, Marci Burden, and Keith Lowe.

## 2009

► **Dr. Roger Brent joins Basic Sciences.**

Brent has worked to understand cell to cell variability to answer questions into why cells can have different responses to the same external signals and environmental conditions. Additionally, he has developed tools using artificial intelligence and augmented reality that helps train researchers and technicians in laboratory techniques to accelerate the pace of biological discovery.



Dr. Roger Brent

### HOW HAS SCIENCE CHANGED?

**"The continuing decline and eventual fall of the un-mourned white Patriarchy has opened up science to more people. At the same time, a number of developments have helped make research, and researchers, more conformist, operating in narrower tracks, and with an overall greatly reduced tolerance for intellectual risk taking. However, experience shows that trends usually reverse, pendulums swing back. And it's easy to imagine how the pressures of the 21st century might require the apparatus to better tolerate nonconformists and mavericks."**

— Dr. Roger Brent

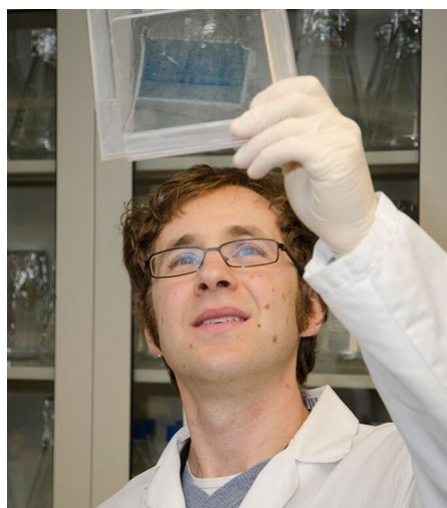
► **Jon Cooper succeeds Jim Roberts as Director of Basic Sciences.**

## 2011

► **Dr. Daniel Gottschling elected to the National Academy of Sciences**

► **Dr. Jesse Bloom joins Basic Sciences.**

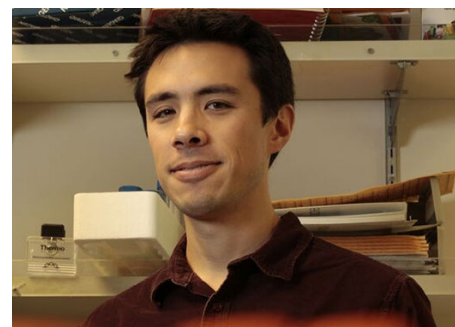
Bloom, a computational biologist, has made numerous advances in our understanding of how viral mutation shapes a pathogen's ability to infect and spread. In response to the COVID-19 pandemic, Bloom and his lab expanded their research to include SARS-CoV-2, making crucial discoveries into the origins of the virus and its evolution.



Bloom in the lab in 2011.

► **Dr. Robert Bradley joins Basic sciences.**

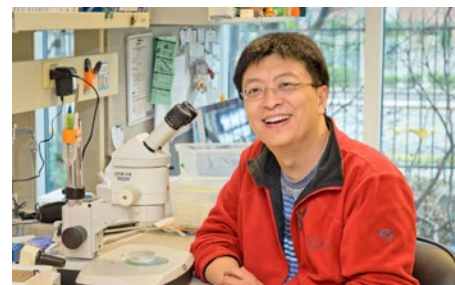
Bradley's work has spanned several different disciplines, all with the broad goal of understanding the molecular mechanisms that govern RNA splicing and how dysregulation contributes to disease. His research has led to a greater understanding of the underlying causes of facioscapulohumeral muscular dystrophy, showing that DUX4 suppresses nonsense-mediated mRNA decay.



Bradley in the lab in 2011.

► **Dr. Jihong Bai joins Basic Sciences.**

Bai's research is interested in uncovering the fundamental mechanisms of how brain circuits work. He discovered that spatial pattern discrimination requires dopamine signaling, work that informs studies on diseases with altered locomotion such as Parkinson's Disease.



Bai in the lab in 2011.

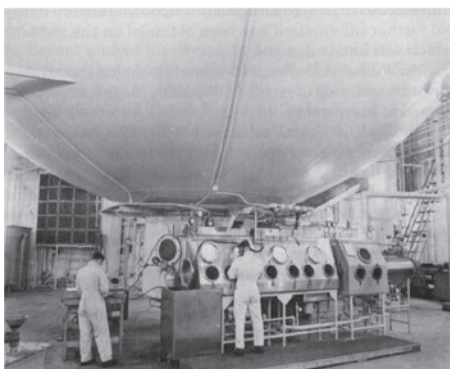
**A memory from Dr. Roger Brent:** One fun moment was in 2011, giving a talk called "Social Scientists In Our Midst", about a lab effort called the Center for Biological Futures, and being able to show a picture from 1968, from the Cold-War-era US biological warfare program. Making the points that our work as biologists is embedded in the institutions that enable it, that the lineaments of those institutions are the products of human choices, by scientists, political leaders, and others, and that those choices can have profound consequences for the human future.





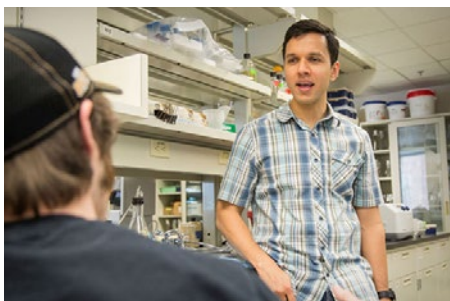
**A memory from Dr. Cecilia Moens:** In 2015, the Human Biology division needed more room for mice in the vivarium for their growing solid tumor program. Specifically, they needed to convert our 1000-square-foot fish facility into space for mice. I was distraught! How do you move all those fish? Where are they going to go? Without hesitation or complaint, the Center built a beautiful new fish facility in the Eastlake building, with better water filtration, more automation, better layout, and quarantine space. I knew then, if not before that the Hutch is boundless in its support for my research. I am forever grateful.

Figure from a talk in 2011. Photograph show technicians at base of spherical US biological warfare aerosol test chamber, aka the “8-ball”. Fort Detrick, Maryland, circa 1968. This Cold-War relic is now listed in the National Register of Historic Places.



## 2015

► **Dr. Rasi Subramaniam joins Basic Sciences.** Subramaniam, a physicist by training, discovered that ribosome collisions induce translational quality control systems to ensure accurate protein synthesis.



Subramaniam talking with a student in his lab in 2015.

► **Dr. Sue Biggins elected to the National Academy of Sciences**

## 2016

► **Dr. Emily Hatch joins Basic Sciences.**

Hatch is investigating the causes and consequences of nuclear membrane damage and repair. A ruptured nucleus can catastrophically expose a cell's DNA to damage, possibly leading to cancer. Hatch showed that chromosome length and gene density contributes to membrane stability of micronuclei that house missegregated chromosomes during cell division.



Dr. Emily Hatch

**A memory from Dr. Emily Hatch:** My favorite memory that really defines the division for me occurred during my job talk. I had gotten into a tangle about halfway through and said something vague about “we have some ideas about this, but overall it’s unclear.” Even though I had only known this faculty for about half an hour, I knew I wasn’t going to get away with that. Immediately one of my [future] colleague’s hands shot up, and they asked, “Are you going to tell us about your ideas?” The fact that this faculty member wasn’t in my field, or even in cell biology, yet had a burning curiosity that couldn’t wait until the end of the talk tells you all you need to know about how interested this division is in science in general and in their colleagues in particular. I couldn’t imagine a better place to start a lab.

► **Dr. Akhila Rajan joins Basic Sciences.**

Rajan is studying the signaling pathways that sense how much energy an organism has available and how this drives its behavior. Rajan discovered that leptin and insulin self-regulate a neural circuit to sense energy stores, work that helps to uncover the molecular basis for body-weight set points and obesity.



Dr. Akhila Rajan

## 2018

► **Dr. Meghan Koch joins Basic Sciences.**

Koch is working to understand how maternal-offspring interactions regulate neonatal health and physiology. Within the last decades, there has been a growing appreciation for the importance of understanding the role that the microbiota, the collection of microorganisms that exist on or within a host, plays in health. Koch has identified several antibodies, transmitted from mother to offspring via breastfeeding, that are crucial regulators of host-microbiota interactions in neonates.



Dr. Meghan Koch



► **Dr. Aakanksha Singhvi joins Basic Sciences.**

Singhvi researches the interactions between neurons and glia cells in the nervous system. Disruptions in glia activity underlie numerous neurological disorders, including Alzheimer's. Singhvi showed that glia actively prune neuron fragments to control their shape and alter behavior.



Dr. Aakanksha Singhvi

► **Dr. Jim Priess elected to the National Academy of Sciences.**



Susan Parkhurst, Steve Henikoff, Jon Cooper, and Jim Priess celebrating Priess' election to the National Academy of Sciences.

## 2019

► **Sue Biggins succeeds Jon Cooper as director of Basic Sciences.**



Biggins speaking during the reception in recognition of Jon Cooper's leadership of the Basic Sciences Division.

► **Dr. Meghan Koch selected as Rita Allen scholar.** Koch would be the fifth member of Basic Sciences selected as a Rita Allen scholar, the first being Harold Weintraub, selected in the foundation's inaugural year, 1976. Other Rita Allen Scholars in Basic Sciences included Bruce Edgar, Adrian R. Ferre-D'Amare, and Emily Hatch.

► **Karen Brighton, research administrator, retires after 30 years of working at Fred Hutch.**



Members of the Basic Sciences administration team celebrating Brighton's, center-left, retirement.

► **Dr. Harmit Malik elected to the National Academy of Sciences.**



Koch at a celebration in honor of being named a Rita Allen Scholar.

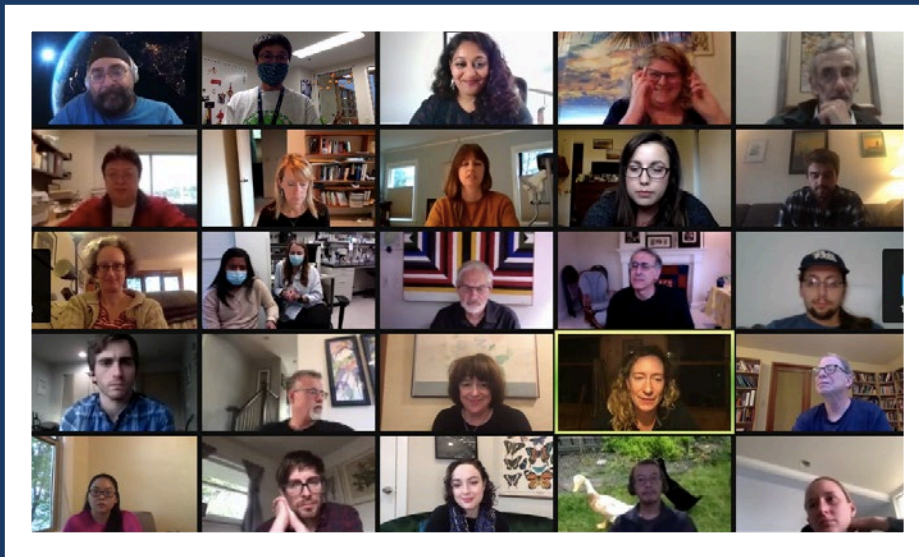
## 2019

► **Luna Yu, one of the center's IT specialists, celebrates her 25th anniversary.**



LEFT: The Human Biology and Basic Sciences Divisions come together to celebrate Luna Yu's 25th anniversary. ABOVE: Luna opening her 25th-anniversary gift.

# RECENT EVENTS AND CHANGES SINCE THE COVID -19 PANDEMIC



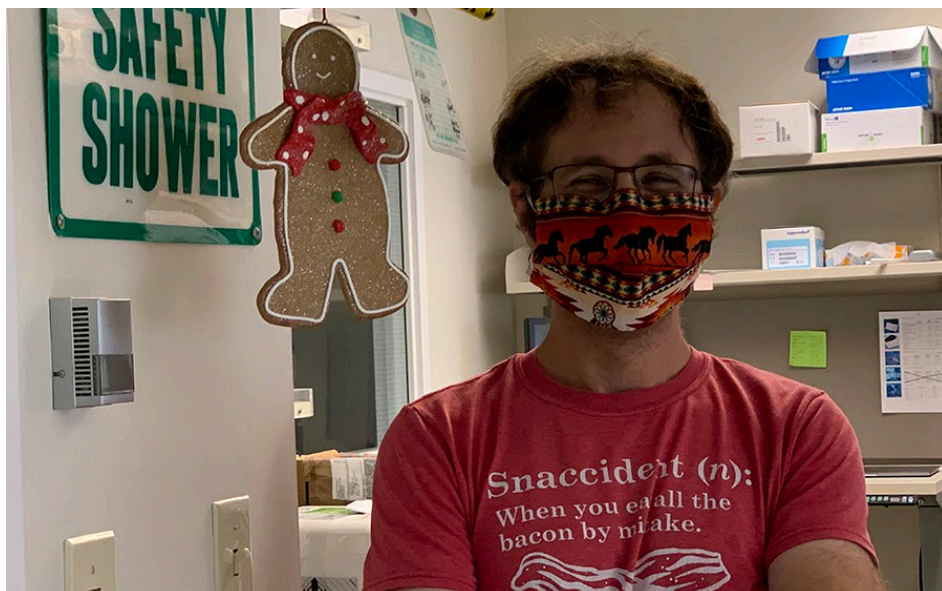
Discussion with filmmaker Sharon Shattuck, director of 'Picture a Scientist' at the 2020 Basic Sciences retreat.

## 2020

► **SARS-CoV-2 pandemic shutters the world.** First identified in late 2019, the novel coronavirus SARS-COV-2 would quickly spread, being declared a global pandemic by the World Health Organization on March 11th, 2020.

The unprecedented and ever-changing nature of the pandemic necessitated that the center adapt to help slow the spread of the virus and protect members of Fred Hutch and the broader community. This resulted in carefully controlling access to labs, mask-wearing, and many researchers and staff working from home. Meetings, seminars, conferences, and celebrations all went virtual, including the 2020 Basic Sciences retreat.





Dr. Jesse Bloom in the lab in 2020

Given the immediate need to make discoveries critical to ending the pandemic, the scientific community responded with unprecedented speed and cooperation. The importance of quickly disseminating knowledge about the virus furthered the push for researchers to publish their work on free-to-access preprint servers, such as bioRxiv. Many Fred Hutch scientists pivoted to studying SARS-CoV-2 and would quickly distinguish themselves as leaders of scientific discovery related to the virus, including Basic Sciences' Dr. Jesse Bloom. Bloom and his lab capitalized on their expertise in studying influenza viruses to better understand the origins and evolution of SARS-CoV-2. Over the pandemic, their research has been featured in everything from the New York Times to the NIH Director's blog.

Into 2021, the pandemic has continued to be ever-present as new variants emerge. The division has faced and continues to face numerous challenges related to the pandemic but remains determined to adapt and continue its mission of making foundational discoveries about biology and disease. The pandemic shows how critical basic science research is to prevent and understand disease as the rapid development of the COVID-19 vaccine required a wealth of earlier basic science discoveries, including structural research on coronaviruses and years of findings into fundamental mRNA biology.

► **Dr. Melody Campbell joins Basic Sciences.**

Campbell was recruited to Fred Hutch for her expertise in cryogenic electron microscopy, or cryo-EM, a microscopy technique that allows scientists to study the structure of proteins in a more physiologic environment. She oversaw the creation of the Hutch's cryo-EM core facility and serves as its scientific director.

Using cryo-EM, Campbell has dramatically improved our understanding of integrins, proteins that help cells communicate and interact with their environments.



Dr. Melody Campbell

## 2021

► **Dr. Manu Setty joins Basic Sciences.**

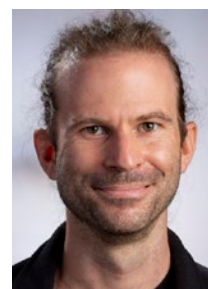
Setty was jointly recruited to Basic Sciences, Fred Hutch's Translational Data Science Integrated Research Center, and the Herbold Computational Biology Program for his multi-disciplinary expertise in using computational techniques to aid in the analysis of large-scale datasets. Setty has used these techniques to identify gene networks that govern how non-specialized cells become specialized with distinct functions.



Dr. Manu Setty

► **Dr. Nic Lehrbach joins Basic Sciences.**

Lehrbach works to understand how cells remove damaged or unwanted proteins, high levels of which are a feature of aging, cancer, neurodegenerative diseases, and many genetic disorders. By revealing the mechanisms of protein degradation, Lehrbach's work may lead to new ways to treat these diseases.



Dr. Nic Lehrbach

### HOW HAS SCIENCE CHANGED?

"Although I've only been doing cryo-EM for a decade, in that time, the power and efficiency of the hardware and software have improved dramatically. In 2011 when I started to determine most structures, scientists collected micrographs one at a time on physical film, which had to be developed in a dark room, scanned, and finally processed computationally—a procedure that took months (or years). With the equipment and software we've just finished installing in the new Cryo-EM Shared Resource downstairs, we have solved highly detailed structures in just a couple of hours (resolved enough to visualize individual water molecules). These advances in both speed and resolution have enabled us to answer questions that before would have been impossible. When I started, the family of integrin proteins that the lab works on were considered too small and too flexible to study using Cryo-EM. Now, we are seeing these proteins in such detail that we can identify the key amino acids and metal cations that mediate binding interactions."

— Dr. Melody Campbell



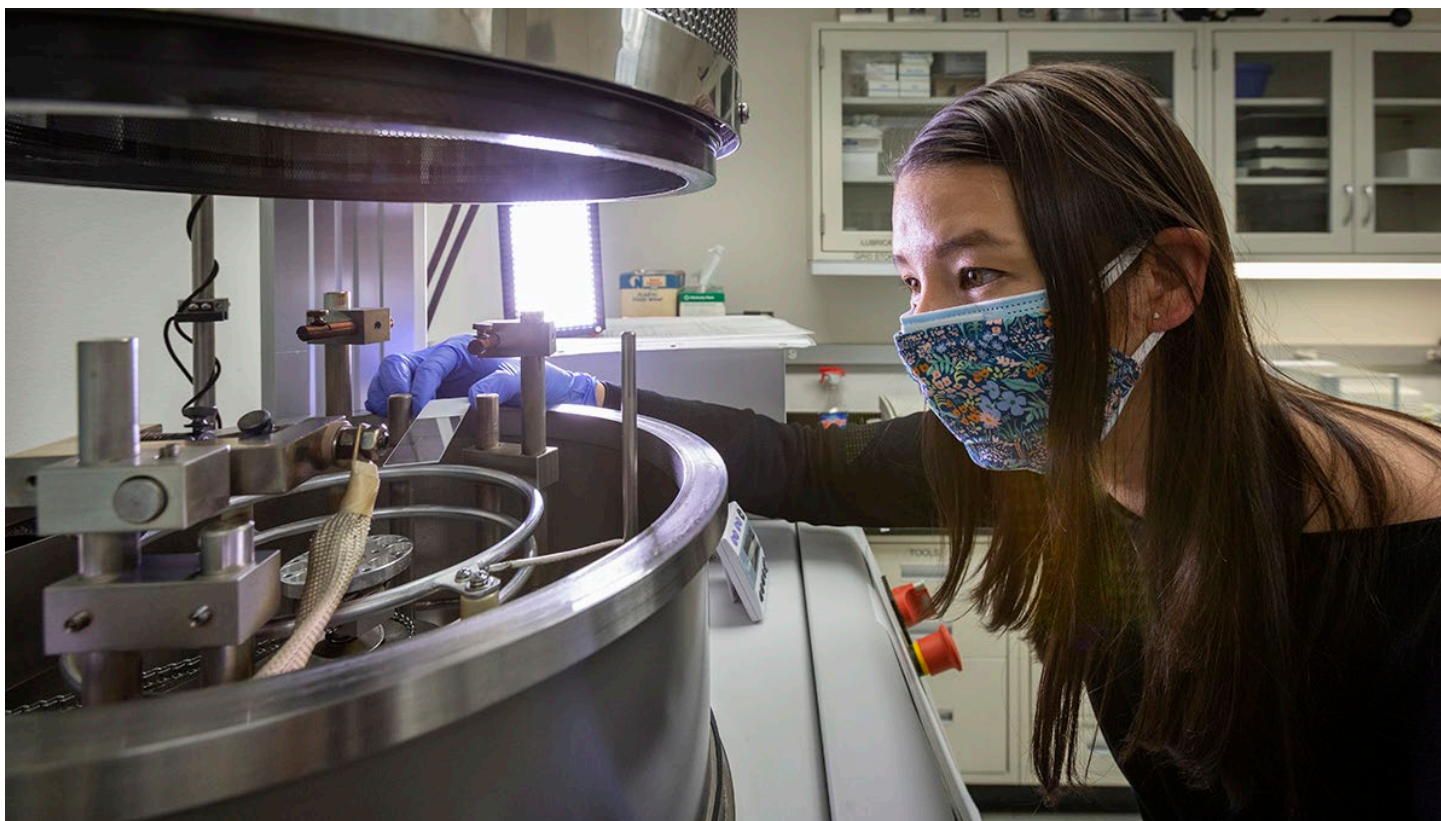
# NEW FRONTIERS IN CRYO-EM AND STRUCTURAL BIOLOGY



Facility director Melody Campbell, left, and facility manager Caleigh Azumaya in November 2020 as over twenty boxes associated with the two new electron microscopes, weighing cumulatively over 13,800 lbs, were delivered to Fred Hutch.

## 2021

► **Fred Hutch's cryo-EM core facility opens its doors with Dr. Melody Campbell serving as its director.** Cryogenic electron microscopy, or cryo-EM, is a microscopy technique that allows scientists to study the detailed structure of proteins at near-atomic resolutions in a more 'natural' environment. The structural insights gained from cryo-EM can inform applications ranging from structure-based drug design to mutational analysis. Cryo-EM also captures dynamic movements of large protein complexes and molecular machines that cannot be visualized using other structural biology techniques.



Campbell prepares a sample for cryo-EM in February 2021.

Cryogenic electron microscopy, or cryo-EM, is a microscopy technique that allows scientists to study the detailed structure of proteins at near-atomic resolutions in a more 'natural' environment. The structural insights gained from cryo-EM can inform applications ranging from structure-based drug design to mutational analysis. Cryo-EM also captures dynamic movements of large protein complexes and molecular machines that cannot be visualized using other structural biology techniques.

*"Cryo-EM is allowing structural biologists of all backgrounds, even an old crystallographer such as myself, to finally see the biological machines that we've longed dreamed of visualizing."*

— Dr. Barry Stoddard

#### A memory from Dr. Melody Campbell:

"Starting a lab and leading the set-up of the Cryo-EM Shared Resource during the SARS-CoV-2 global pandemic has been an adventure. However, with the backing and support of dozens and dozens of other scientists and staff at the Hutch, despite the constantly changing rearrangements, moving timelines, and new accommodations that had to be made in

response to COVID-19, the two microscopes have been running smoothly [largely] since we signed off last March. Recently our lab determined its first high-resolution integrin structure, and we know there are more great structures in the pipeline from the Stoddard Lab down the hall."

#### ► Dr. Jhimmy Talbot joins Basic Sciences.

Talbot's research studies how interactions between neurons and immune cells in the gut can help the body balance its immune and metabolic trade-offs. His work has revealed how changes in diet or in the intestinal microbiota may lead to metabolic dysfunction and how neuroimmune interactions could be hijacked by microbes to enable infection.



Talbot, middle left, with Drs. Nic Lehrbach, Manu Setty, and Melody Campbell.

#### ► Dr. Richard Adeyemi Joins Basic Sciences.

Adeyemi studies how our cells maintain the integrity of their DNA, both during replication and in response to events like viral infection and chemotherapy. His work provides a deeper understanding of DNA repair mechanisms and the development of novel therapies for cancer, infections, aging, and genetic disease.



Dr. Richard Adeyemi

# Q&A WITH FRED HUTCH BASIC SCIENCES LABS PAST AND PRESENT



Group photo of Basic Sciences faculty at the 2019 scientific retreat.

To help mark the 40th anniversary of the division, we asked labs past and present to tell us about their research, what made their lab stand out, and the future of science.



JOINED CENTER IN 1975

*Dr. Maxine Linial*

## Linial Lab

### Briefly tell us about your lab group's research.

Over the span of 40 years, my lab worked on retroviruses. We started by mapping the packaging sequences in avian retroviruses. We then worked on the cancer gene MYC in birds. The last area of focus was foamy viruses which are non-pathogenic retroviruses that affect all non-human primates. We showed that humans can be infected by these viruses. Our work on packaging signals and foamy viruses has implications for human gene therapy.

### What was a distinguishing feature of your lab? What made your lab stand out?

My lab concentrated on molecular virology, and we usually worked on subjects ignored by other labs. This led to some extremely interesting findings. We went where no man went before!

### If you could have taken your lab back or forward to any point in time, when would it be and why?

I guess not, but things would have been quicker if we had started our work when DNA sequencing was available.

### What excites you the most for the future of science and why?

Current science encourages most scientists to form large groups, but in my mind, it is the special, creative individual who really makes the leaps forward.

### Upon reflection of her time as the only female faculty member, Dr. Linial recalled a story that reminded her of the progress that has been made since that time.

I remember one day [in the mid-1980s] all the full members gathered in a room to discuss some divisional issues, and I was the only female. I said, "I know we are here to discuss issue X, but I have some concerns about issue Y." One of my colleagues then said, "oh Maxine, don't you remember that all of us full members met in the 3rd floor men's room and discussed this already?"

Throughout my tenure at the Hutch, I fought for women in science. The Hutch is doing much better now but the Hutch still needs to make progress on under-represented minorities in science.



*Linial speaking with Drs. Beti Thompson and Katie Peichel in 2011.*



*Linial working in the lab in the early 1990s*

JOINED CENTER IN 1976

*Dr. Robert Eisenman*

## Eisenman Lab

### Briefly tell us about your lab group's research.

When I first started my lab at Fred Hutch in 1976, our research was almost entirely focused on the assembly of retrovirus capsid proteins and their role in viral biology. Later, I became interested in the nature of ancient silent endogenous retroviral genes associated with cellular DNA. Our serendipitous discovery, in the early 1980s, that a putative retroviral encoded oncogenic protein, known as MYC, localizes to the host cell nucleus, changed the direction of our research from virology to understanding the etiology and progression of cancer. By the 1990s it was clear that the cellular form of MYC is profoundly involved in a very broad spectrum of human cancers. We discovered that MYC forms a heterodimer with the MAX protein and directly binds genomic DNA to alter gene expression. At that point we began to explore how other factors might influence MYC-MAX function. To that end, we employed MAX as a dimerization probe to identify a novel family of interacting proteins. This eventually led to the realization that MYC is only one part of a transcription factor network that integrates environmental signals to broadly regulate gene expression programs involved in cellular growth. Our most recent work has demonstrated that members of this "MYC network" can act directly to promote or to suppress oncogenesis through control of cellular gene expression.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

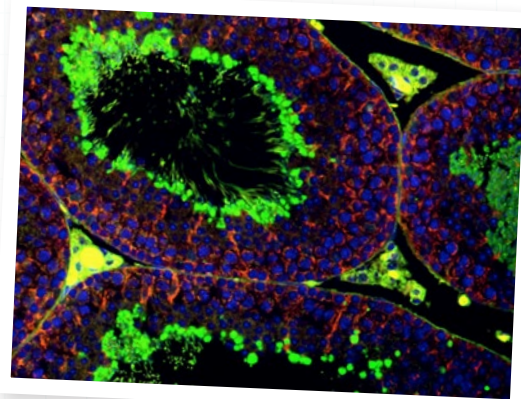
In what might be considered our rather insane pursuit of understanding a single oncogene we have employed a wide range biological systems [mammalian tissues and tumors, *Drosophila*, yeast, mice] and approaches [developmental genetics, genomics, structural biology, biochemistry]. We have also benefitted enormously from the highly collaborative atmosphere in the DBS as well as throughout Fred Hutch.

### How has science and research changed over your career?

As a postdoc in the 1970s, in order to determine the size of the proteins we were studying, we electrophoresed them in long tube gels which were then cut into hundreds of slices with razor blades and individually counted for radioactivity. We had serious conversations in which we predicted we would never in our lifetimes know the amino acid sequences, much less the complete structures, of the proteins or complexes we worked with. Head spinning advances in biochemical separation methods, recombinant DNA, genomic analysis, and structural biology have completely changed our expectations of what we can learn from experiments. It's been an amazing ride and I'm excited to see where future advances will take us.

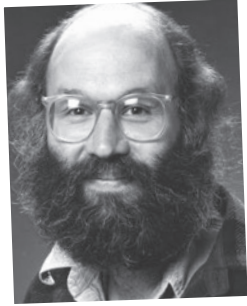


2013 Methow Valley Reunion: Eisenman lab and friends



Mouse seminiferous tubules (Green = mature spermatids, Red = mitochondria, Blue = DNA); Photo by Patrick Carroll.

JOINED CENTER IN 1978



Dr. Harold "Hal" Weintraub

# Weintraub Lab

*Response written by Stephen Tapscott together with input from Hal's trainees, including Brenda Bass, Robert Benezra, David Bentley, Keith Blackwell, Robert Davis, Billy Forrester, Richard Harland, Rafi Kopan, Mike Krause, Jackie Lee, and Dave Turner.*

## Briefly tell us about the lab group's research.

Hal died in 1995 from brain cancer, glioblastoma. Thus, the task of characterizing his research is left to his former trainees who were fortunate enough to have known and worked with him. Hal and his lab studied how cellular diversity is achieved during development, and how DNA is differentially accessed and expressed to generate cellular diversity. Stated simply: How from a fertilized egg do you build an entire organism?

His graduate work predicted that a single gene might regulate the generation of an entire cellular program, which he and his graduate advisor, Howard Holtzer, termed the Master Switch Hypothesis. Subsequently, Hal's lab identified MyoD and NeuroD as the first Master Switch genes, or Master Regulators as this class of transcription factors is now named. These discoveries were the first demonstration of cellular reprogramming by a transcription factor. Although mentioned here first because of the connection with his graduate work, this was only one of his many field-changing contributions.

Early in his career, Hal and his close friend/collaborator Mark Groudine used the emerging tools of molecular biology to show that cell-type-specific regional nucleosome modifications made genes available for expression in different cell lineages. This work set the model for epigenetic research for subsequent decades. Hal and his lab were also the first to describe anti-sense inhibition of gene expression, a discovery that is now used broadly in research and clinical therapeutics, and that led to the subsequent discoveries of endogenous small regulatory RNAs. His lab's work on double-stranded RNAs identified the cellular RNA editing machinery that protects against pathogens and regulates immune responses.

Hal's wide-ranging curiosity led to the diversity of research areas in his lab. His curiosity also brought-out the best in his colleagues and trainees, often with the simple question, "How do you know that?"

## What was a distinguishing feature of the lab? What made the lab stand out?

There were several distinguishing features that made Hal's lab a special place to do science. First and foremost was Hal himself. Hal had a Socratic approach to science. He questioned the basis of knowledge as compared to belief. He was open to any alternative hypothesis supported by available data. He challenged himself, his colleagues, and his trainees to search for the voids in knowledge that undermine our scientific structures. And then to design a simple experiment that gives a yes/no answer regarding a critical hypothesis that might bridge such a void.

Another feature of the lab was its range of biological systems: yeast, worms, newts, frogs, fish, mice, and tissue culture of mouse and human cells. This potpourri of model organisms was matched with a mix of biochemistry, molecular biology, and molecular genetic approaches that made Hal's lab an unparalleled and fun place to learn science.

## If the lab could have visited any point in time, when would it be and why?

Hal often referred to the scientists that shaped his thinking, such as Jacob's assessment that "Evolution behaves like a tinkerer, ..."; but I think he would answer this prompt with: "If I go too far forward in time, I will be dead; if too far back, not yet existing. Maybe this is the place for me. Or maybe courtside at the next NBA playoffs."

## What is most exciting for the future of science and why?

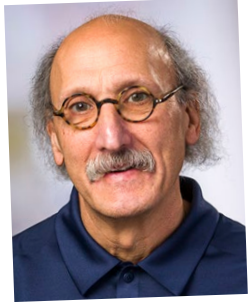
It would be great to get Hal's perspective on this. What made him a great scientist and mentor is that his answer would be different from any of ours. We often think that all the fun science has been already discovered, but Hal impressed on us that we actually know very little and that there are biological surprises waiting to be discovered for those inquisitive enough to seek the mechanistic basis of their results.



*Hal and his trusted research technician, Pei Feng Cheng. Hal never left bench work and Pei Feng was always by his side. Mat Thayer, under Hal's thumb in this photo, was a postdoc at the time and has continued Hal's quest to understand the unknown as a Professor at the Oregon Health Sciences University.*



JOINED CENTER IN 1979



Dr. Mark Groudine

## Groudine Lab

### Briefly tell us about your lab group's research.

My lab has contributed to understanding the relationships among gene expression, chromatin structure and nuclear organization. To accomplish this, we developed widely used tools, including DNase I, to distinguish different transcription and chromatin states; transcriptional run-ons to determine transcriptional activity at the levels of initiation, promoter proximal pausing and elongation; homologous and site-specific recombination to determine the contribution of specific factor binding sites to gene expression at their native genomic location rather than in transgenes; and algorithms to define chromosome adjacencies and the contribution of these adjacencies to gene expression and nuclear organization. We co-discovered locus control regions (LCRs) and were the first to perform genome wide analyses of replication timing and histone modifications in a higher eukaryote (*Drosophila*). We also discovered that enhancers antagonize transcriptional silencing by preventing localization of genes near heterochromatin, and that the organization of the eukaryotic nucleus is dynamic, with changes in sub-nuclear location of proteins and genes playing important roles in controlling developmentally regulated gene expression.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

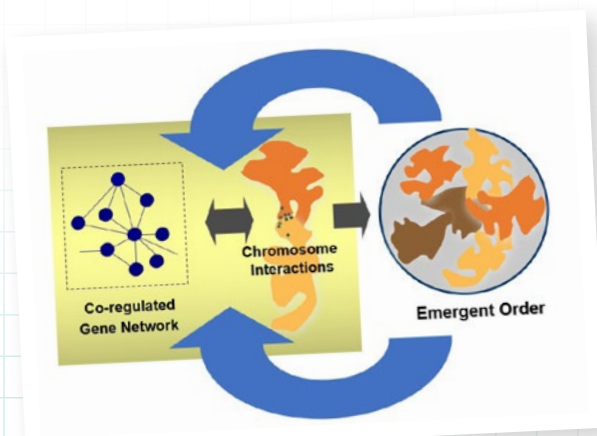
Most importantly, it has been having terrific postdocs who were more like colleagues than trainees. My greatest contribution was turning them loose to pursue the science that interested them and staying out of their way. Another aspect was developing technologies as needed to pursue scientific questions. Essentially, not letting the lack of technology get in the way.

### If you could take the lab back or forward to any point in time, when would it be and why?

I would turn the clock back to 1995 by which time we would have solved the mystery of glioblastoma resulting in a cure for that deadly disease. By doing so, Hal Weintraub who was my closest friend and colleague would still be alive, and we would not have lost one of the most important scientists of our generation. Hal's accomplishments, including discovery of myoD, development of antisense technology and various aspects of chromatin structure, are legendary and his loss has deprived us of an extraordinarily insightful mind and wonderful colleague.

### What excites you the most for the future of science or your research and why?

I am most excited by the continuing commitment of the Center to the Basic Sciences, with leadership understanding the importance of fundamental discovery. Our junior scientists are outstanding, and our recent faculty hires are among the top in the country/world.

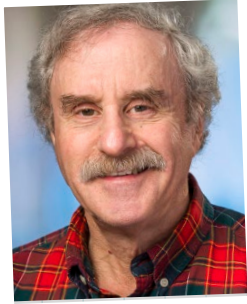


Nuclear Self-Organization



A hand drawn summary by of differential DNase I sensitivities in a region of gene activity, dating to 1970's by Hal Weintraub and Mark Groudine

JOINED CENTER IN 1981



Dr. Steve Henikoff

**Briefly tell us about your lab group's research.**

The exponential decrease in the cost of DNA sequencing has revolutionized genetics and genomics, but we still have only a sketchy understanding of how the genome is packaged, read and interpreted to program the astonishing complexity of cells and organisms. To chip away at long-standing questions in developmental biology, evolution, cellular physiology and disease research we apply genomic tools to *Drosophila*, yeast and mammalian models. We ask questions such as: How and why are centromeres so different from the rest of the genome? How can replication and

transcription machineries move along a DNA template that is tightly wound around nucleosome cores? How are genes silenced? How are gaps created in the nucleosome landscape for gene activation? What is the basis for the specificity of DNA-binding proteins? To facilitate our research on these problems we have developed several experimental and computational tools over the years.

**What is/was a distinguishing feature of your lab? What made your lab stand out?**

We have been especially interested in developing inexpensive methods that enable others to take advantage of rapidly advancing genomic technologies. For example, early in the Covid-19 pandemic, we introduced a cutting-edge chromatin profiling method that can be safely performed in a day on a counter at home. In December, our CUT&Tag@home method was highlighted by *The Scientist* magazine as among the top 5 technical advances of 2020.

**If you could take the lab back or forward to any point in time, when would it be and why?**

Next week. Our ideal experiment is one that is performed in a day, with the data generated and analyzed over the weekend, then discussed with the group, colleagues and collaborators, generating ideas for the next experiment.

**What excites you the most for the future of science or your research and why?**

I am excited most about what I'll learn next week.

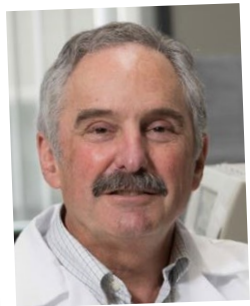


Lab farewell to Jeetu party: Jitendra Thakur leaving for Emory, November 16, 2020



CUT&amp;Tag@home





Dr. Jerry Nepom

## Nepom Lab

### Briefly tell us about your lab group's research.

When my lab was at FHCRC in the early 1980's, the HLA locus was not understood. My laboratory contributed some of the fundamental insights that moved the field from serology to a molecular and genetic framework, including the identification of a second class II locus [DS, now called DQ], identification and relationship of allelic variants within each of the then-defined HLA specificities at HLA-DR, specific associations of class II allelic variants with type 1 diabetes, juvenile and adult forms of rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease, and novel methods for replacing HLA typing with molecular techniques. We were helped immensely by close collaborations with John Hansen and colleagues in the FHCRC clinical division, who were pioneering investigations of HLA disparities in bone marrow transplantation at that time.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

Prior to joining FHCRC, I had applied molecular methods to improve understanding of the murine major histocompatibility locus, so I was already predisposed to innovate with new technologies and apply them to old problems. It was this combination of developing and using improved tools, looking at problems with fresh perspectives, and focusing on the relationship between structure and function that set us up for success.

### If you could take the lab back or forward to any point in time, when would it be and why?

It would have been interesting to have a conversation with the first investigators at the time they observed tissue incompatibilities, to have some insight into the inferences that were made at that time in the absence of any understanding of the molecular or genetic architecture behind the phenomena observed. Science doesn't develop in a vacuum, or advance linearly, and the messy origins of seminal ideas that have been subsequently lost would be fascinating to see.

### What excites you the most for the future of science or your research and why?

Over the last four decades, our original work has been rediscovered and reinvented many times over, often with newer technologies providing deeper insight. Some clinical research applications in the diagnostic and prognostic areas are now routine. Still elusive, however, is a direct translation of the key elements of this work to improvements in treatment. That day will come and will be an exciting time.



The unbiased clustering algorithm used to identify the HLA-DQ locus; at that time, before "systems biology", we called it "graph paper".

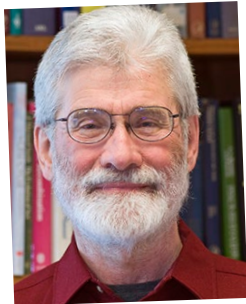
seropositive JRA the DR4 determinant itself is not the important disease marker, but merely reflects an associated serologic specificity with very broad expression. In terms of disease associations, then, it is now logical to ask whether one of these specific haplotypes or, more precisely, one of the encoded class II molecules, rather than the DR4 specificity itself, is the Ir gene product most directly associated with disease susceptibility.

Table II. HLA-DR, D Antigens in Patients with Seropositive JRA

HLA	Patients	Controls*	$\chi^2$	RR†
DR4 positive	17/22 (77%)	70/219 (32%)	17.8	7.2
DR4 homozygous	12/22 (54%)	7/219 (3%)§	72.6	36.3
Dw4 positive	16/22 (73%)	40/234 (17%)	36.2	12.9
Dw4 only	4/22 (18%) <sup>‡</sup>	2/234 (0.8%)§	17.2	25.8
LD*40" positive	8/22 (36%)	4/83 (5%)	17.1	11.3
LD*40" only	1/22 (5%) <sup>‡</sup>	0/83 (0.06%)§	3.8	47
Dw4, LD*40" positive	7/22 (32%)	0/83 (0.1%)§	27.3	116

An early cornerstone of HLA disease association studies, from Nepom, Nepom, Mickelson, Schaller, Antonelli and Hansen. *J Clin Invest.* 1984 Jul; 74(1): 287-291

JOINED DIVISION IN 1982



Dr. Gerry Smith

## Smith Lab

### Briefly tell us about your lab group's research.

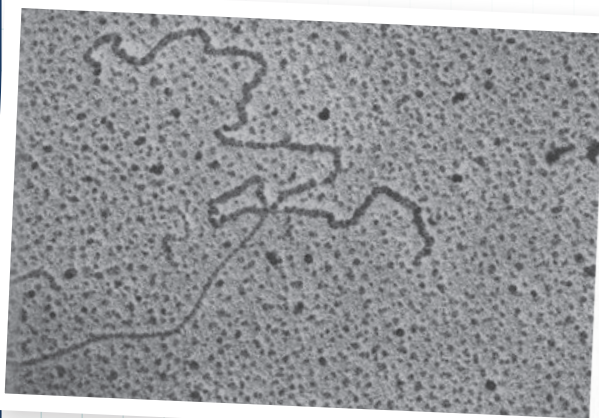
The Smith Lab studies recombination, a process cells use to increase genetic diversity by swapping, or recombining, segments of DNA from the two copies of each chromosome we inherited from our parents. When this process goes wrong, it can lead to miscarriage, developmental disorders, or cancer. We study the molecules involved in this critical process, including those that help repair the DNA breaks that occur as chromosomes trade sections. Using fission yeast as a model system, we have identified and outlined the roles of many proteins that regulate this process, most of which have human counterparts. Our lab has long studied the major mechanism by which bacteria repair breaks in their DNA that naturally occur during processes such as chromosome replication. This essential mechanism employs a complex enzyme called RecBCD that both unwinds DNA from a broken end and cuts it at special sites known as "hotspots" of recombination. We have found inhibitors of RecBCD, which could be useful novel antibiotics because bacterial DNA is often broken when bacteria infect human cells. We believe that a deeper understanding of these fundamental processes will help provide insights and compounds that can be used to improve human health.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

Scientifically, our lab is somewhat unusual in using both genetics and biochemistry to deduce the molecular mechanisms our cells use to remain healthy. Socially, our lab used to camp together once a year. We still take a hike together, but fewer people go. For me, it's hiking, backpacking, and skiing [alpine touring or skinning].

### What is most exciting for the future of science and why?

The likelihood that we'll know more and more details about how life works – going from genetics and biochemistry to molecular biology to atomic biology. This offers great opportunity to develop new drugs etc. but also the possibility that life will contain fewer mysteries. However, life is so complex that I won't be around for this last point.



Rabbit ears – 2 [what we call loop-tails] shows the initial DNA structure as RecBCD unwinds DNA. The tails anneal to form rabbit ears – 1.



The Smith Lab from about 1986.



JOINED DIVISION IN 1985



Dr. Jon Cooper

## Cooper Lab

### Briefly tell us about the lab group's research.

All multicellular organisms rely on communication between cells to function. In animals such as us, cells communicate by contact with other cells and molecules secreted by other cells. We study how such signals are relayed within the cell to regulate division, differentiation, and movement. Alterations in such signaling pathways are associated with chronic diseases such as cancer, fibrosis and degeneration. In recent years we have focused attention on the signaling pathways that regulate cell movement. Human cells start migrating when triggered by soluble and insoluble factors in the environment

– small diffusible proteins known as growth factors and the extracellular matrix – as well as cell-cell contacts. Presently we study two systems: [a] Pediatric brain cancer cells, which invade surrounding brain tissue either as single cells or as a connected stream, depending on cell-cell contacts, and [b] Normal human epithelial cells, whose migration and invasion properties are delicately tuned by growth factors and the extracellular matrix, relayed to the migration machinery by two countervailing protein modifications, phosphorylation and ubiquitination. We study these processes by use of genetically altered cells, imaging, and biochemical analysis of post-translational modifications and protein-protein interactions. This combination of techniques provides a powerful window into sub-cellular mechanisms that regulate cell movement.

### What was a distinguishing feature of the lab? What made the lab stand out?

We have always been generalists, each person in the lab taking charge of all aspects of their project. This makes science more fun and has allowed us to take advantage of the rich diversity of research done by our colleagues in BSD. Thanks to them, at various times, we have investigated signal transduction mechanisms in fruit flies, nematode worms, budding and fission yeasts, and mice!

### If the lab could have visited any point in time, when would it be and why?

I would like to go forwards to a time where the detection and quantification of proteins and protein modifications is as easy as analysis of DNA and RNA. The ability to amplify nucleic acids by PCR allows sequencing of miniscule quantities of material. In contrast, cataloging proteins on the cellular scale remains in the dark ages, despite the awesome power provided by antibody reagents and mass spectrometry. I dream of "reverse translation"!

### What is most exciting for the future of science and why?

New people bring the new ideas that move research forwards.



Lab hike 2015

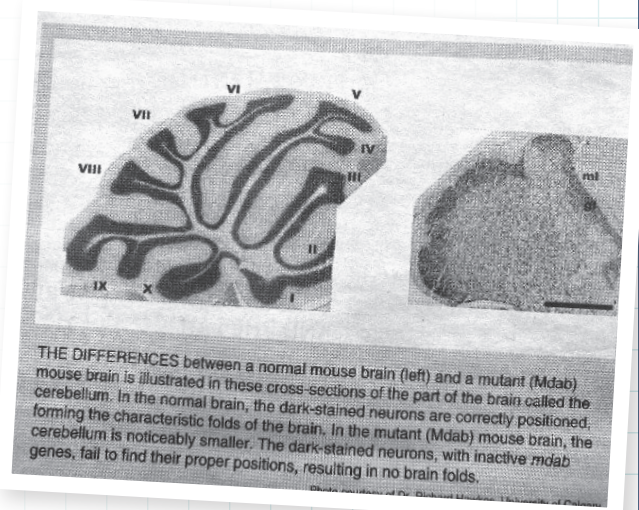


Photo from Dec 1998 Science Spotlight, then a print publication delivered to all employees, showing normal and mutant brain sections.



JOINED DIVISION IN 1987



Dr. Jim Priess

## Priess Lab

### Briefly tell us about your lab group's research.

Our lab studies several aspects of cellular and developmental biology using the genetic model organism *C. elegans*. Our early studies identified several key genes that generate cell asymmetry and distinguish cell fates; in particular, the PAR proteins turned out to have critical and conserved roles in all animals. Other projects focused on tissue morphogenesis, the Notch and Wnt signaling pathways, and genes involved in germ cell totipotency. Our most recent projects have examined a *C. elegans* retrovirus and fat deposits in cell nuclei, termed nuclear lipid droplets. Nuclear fat occurs in a organisms from humans to yeast, but little is known about why the fat forms or how it affects the cell. Our genetic and cell biology studies showed that nuclear fat appears deleterious to intestinal cells. Surprisingly, nuclear fat does not appear to affect germ cells, even in mutants where over a third of the nuclear volume is filled with fat.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

A distinctive, but not entirely unique, characteristic of our lab is that I've always worked at the bench. Also, at one point the shortest member in the lab was 6 feet tall.

### If you could take the lab back or forward to any point in time, when would it be and why?

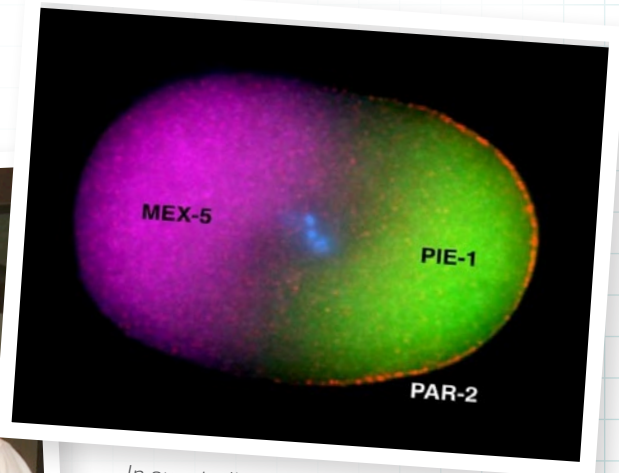
There have been far too many breakthrough moments to choose between. Besides the discovery and implications of the double helix, one time would certainly be the realization that mRNAs are assembled through splicing.

### What excites you the most for the future of science or your research and why?

Crispr-mediated gene editing and recent advances in optical microscopy have been transformative; I think we have entered a golden age for cell biology.



Priess, Bowerman, and Mello



*In our studies on how the egg produced differentiated cell types, we were excited to find that many of the genes we discovered were uniformly expressed at fertilization, but became asymmetrically localized before the first cell division.*

JOINED DIVISION IN 1987



Dr. Keith Fournier,  
The first official day of  
retirement, April 2007

## Fournier Lab

### Briefly tell us about your laboratory's research.

As a postdoc at Yale, I developed a genetic technique for transferring single chromosomes from one mammalian cell to another, a method that proved useful throughout my scientific career. This technique was also the basis of a chromosome shuttle system that we devised in collaboration with Mark Groudine's group at the FHCRC that allowed us to modify human chromosomal genes by homologous recombination, and to assess the effects of those modifications on gene expression and chromatin structure in various cell types. These studies defined long-range regulatory interactions that had not been apparent in more conventional genetic tests.

### What was a distinguishing feature of your lab? What made your lab stand out?

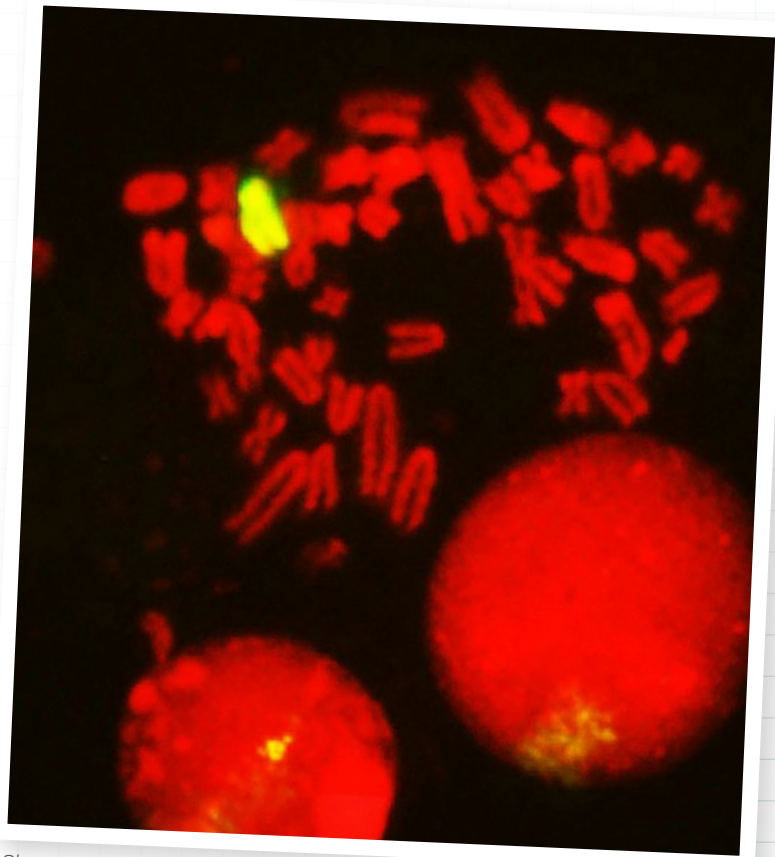
To use a currently popular phrase, my lab was never afraid to 'Follow the Science.' Whether that meant spending the time and effort to lay the groundwork for experiments that might take years to complete, or developing new and sometimes difficult experimental methods, we worked patiently towards long-term goals, and never let current trends in science (or funding) dictate our path.

### If you could go back or forward to any point in time, when would it be and why?

I should like to have a long conversation with Charles Darwin over cognac. It wouldn't be just about science.

### What excites you most for the future of science?

Anyone who thinks they can give an informed answer to this query is fooling themselves. The progress of basic science is unpredictable, and even the most insightful scientist is likely to be wrong far more often than right. It's hubris to pretend otherwise.



Chromosome complement of a genetically engineered mouse cell containing a single human chromosome.

JOINED DIVISION IN 1987



Dr. Linda Breeden

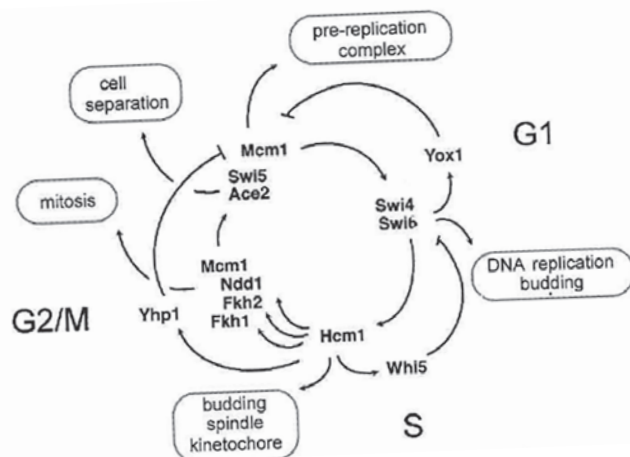
## Breeden Lab

### Briefly tell us about your laboratory's research.

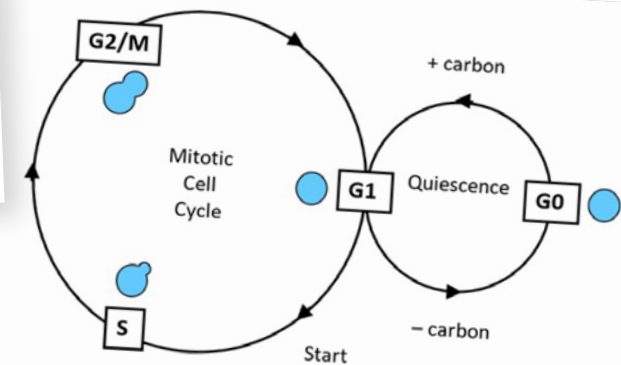
Our initial focus was on the transcriptional regulation of the cell cycle in budding yeast. I landed this job by characterizing a promoter element and two transcription factors that were responsible for activating genes that start the yeast cell cycle. For the first twenty years, we studied how these factors were regulated to perform this start-specific function and what downstream events they promoted in rapidly growing cells. Then we turned our attention to trying to understand how the cell cycle machinery is modified to enable cells to enter, maintain and exit from a quiescent state. Most cells spend most of their time in a quiescent, non-dividing state, and cancer cells can't enter or maintain this state. That's how important it is, but little was known about it because it's hard to study in multi-cellular organisms and most yeast cell cycle research was focused on the rapid growth cycle. We had to convince our peers that there was a quiescent state in yeast and that we had a new way to study it. It has been gratifying to define observe striking new biology: an asymmetrical cell division, global transcriptional changes and quiescence-specific functions for proteins that we've known about for decades, but we couldn't understand because they play no role in the rapid growth cycle.

### If you could take the lab back or forward to any point in time, when would it be and why?

Part of me would like to start all over and get the computational biology training that I see my younger colleagues using so brilliantly to crack complex problems. The other part of me doesn't want to take any more tests, but would like to start all over again, from right now, to see just how far we can take the yeast model to understand the control of quiescence.



The Breeden lab studies the transcriptional circuitry that underlies the cell cycle. Their work has contributed to understanding the roles of Swi4, Swi6, Hcm1, Mcm1, Yox1 and Yhp1 in cell cycle- specific transcription.



Virtually all cells spend most of their time in a quiescent state. The Breeden lab has re-focused their efforts on understanding the transition between mitotic growth and quiescence.



JOINED DIVISION IN 1988



Dr. Steve Hahn

## Hahn Lab

Our research focus is the regulation of eukaryotic transcription – the synthesis of RNA using a DNA template. Transcriptional regulation is a key step in controlling processes such as cell growth, differentiation, development, and cellular stress responses. Since misregulation of transcription is a major cause of human disease, deciphering these regulatory mechanisms can lead to understanding the molecular basis for defects leading to many diseases and syndromes. Our research aims to uncover fundamental mechanisms used by the cellular transcription machinery and its regulatory factors to control mRNA synthesis. We use *S. cerevisiae* [baker's yeast] as our experimental system because of the powerful mix of genomics, molecular genetics and biochemical methods that can readily be used in this model organism. Because the transcription machinery and its regulatory factors are well-conserved throughout evolution, fundamental gene regulatory mechanisms in yeast are nearly always conserved in metazoans.

Eukaryotic RNA polymerases are components of large protein machines that integrate many regulatory signals to precisely control gene expression. Key regulatory factors include gene-specific transcription factors that either activate or repress transcription in response to various signaling pathways. These factors often work via recruitment of transcription coactivators to gene regulatory regions. Coactivators are large protein complexes that interface with the basal transcription machinery and/or modify nucleosome positioning or covalent nucleosome modifications. Research in our laboratory is focused on understanding the function of the gene-specific transcription factors, how they interface with coactivator complexes and how these factors modulate early steps in the transcription pathway.

Our lab combines new and diverse approaches and technologies to investigate gene regulatory mechanisms. Examples include molecular genetics, genomics, computational biology, biochemistry, structural biology, and biophysics. This wide range of approaches has led to working with outstanding collaborators to make new and important discoveries. Most important to our success has been the exceptional lab members and trainees that have pushed scientific boundaries to make these new discoveries.

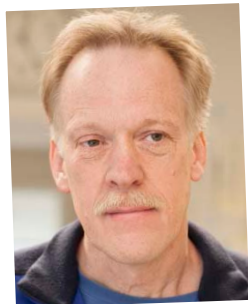


Hahn Lab 2005. Snowshoe trip to Lichtenberg Mountain [L-R] Ying Liu, Linda Warfield, Hung-Ta Chen, Gail Miller, Neeman Mohibullah, Wendy Reeves, James Fishburn, Beth Moorefield, Geetha Rani.



Hahn Lab 2021. [L-R] Jeremy Schofield, Linda Warfield, Steve Hahn, Rafal Donczew, Lakshmi Mahendrawada

JOINED DIVISION IN 1988



Dr. Mark Roth

## Roth Lab

### **Briefly tell us about your lab group's research.**

We have studied many different things over the years. Starting with cell biology of amphibian lamp brush chromosomes and pre-mRNA processing to our current interest in critical care medicine.

### **What is/was a distinguishing feature of your lab? What made your lab stand out?**

Our lab has covered a wide range of research areas.

### **If you could take the lab back or forward to any point in time, when would it be and why?**

Forward. I'd like to know whether work, originally done in our lab, changes the standard of care for people suffering a heart attack.

### **What excites you the most for the future of science or your research and why?**

The finding that ions are rapidly redistributed during severe stress provides a new way of thinking about how to improve the treatment of critically ill patients.

JOINED DIVISION IN 1989

*Dr. Michael Emerman*

## Emerman Lab

### Briefly tell us about your lab group's research.

We study host-cell interactions of the human immunodeficiency virus (HIV) and related viruses in order to understand the molecular and evolutionary basis of virus replication and pathogenesis. Our goal is to determine how HIV adapted to humans to become a pandemic virus, as well as to uncover pathways towards curing HIV infections. We do this by looking at the evolution and function of host genes that either have innate antiviral effects on virus replication or, on the other hand, are necessary for virus replication.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

The lab has studied many different aspects of HIV biology over the years. We focus on particular problems rather than particular genes or pathways. For example, we studied the unique ability of HIV to infect non-dividing cells and discovered an unexpected role of the capsid protein in nuclear entry; we discovered a role of a viral protein to affect cell cycle progression; with Harmit Malik we developed a particular way of looking at host virus interactions called "paleovirology" to study how HIV and other viruses shaped the human immune system; and we developed a new screening method to discover host genes involved in HIV replication. Projects are undertaken by the desire to uncover new biology that will have an impact on viral diseases.

### If you could take the lab back or forward to any point in time, when would it be and why?

I would take the lab back in time to Stockholm Sweden in the evening of December 12, 1975 to hear Howard Temin's Nobel Prize lecture "The DNA Provirus Hypothesis" describing the fundamental properties of retroviruses that would allow ultimately advance studies on HIV, and to listen to his speech at the banquet where he admonished the king of Sweden for smoking and then described the work of scientists "...for although the Nobel prize is awarded to individuals, we realize that science is a communal effort – what we have accomplished has rested on the achievements of others, and the future and practical significance of our work will also be determined by the achievements of others."

### What excites you the most for the future of science or your research and why?

I am very excited about the future of virology. The speed at which the SARS-CoV-2 vaccine was rolled out is a tribute to previous work on other viruses and shows the wisdom of deep knowledge of many viruses irrespective of a present pandemic. New techniques, new ways of collaborating, and new ideas will continue to enrich this field for many years to come.



*Emerman lab alumni  
at 30th Anniversary  
Symposium on  
"Innovative Research on  
HIV and Other Viruses"  
in August 2019*



JOINED DIVISION IN 1992



Dr. Susan Parkhurst

## Parkhurst Lab

### Briefly tell us about your lab group's research.

A hallmark of many diseases and cancers is a dysfunctional cytoskeleton. A properly functioning cytoskeleton is needed for a wide variety of cellular events ranging from cell shape to cell signaling and migration/metastasis. We use state-of-the-art developmental, genetic, cell, molecular, and high-resolution imaging approaches to study these dynamic structural elements in various developmental processes. Our current efforts are divided between studies of: [1] Cell wound repair, a robust process necessary for cells to navigate the unrelenting biological, physical, and chemical assaults of their daily environment or as a result of disease states, and [2] Nuclear Envelope (NE)-budding, a newly appreciated nuclear export pathway for large macromolecular machineries [including those assembled to allow co-regulation of major developmental pathways] that involves traversing the nuclear lamina/membrane independently of nuclear pores. Our goal is to understand the role of these elements in regulating normal developmental events and how this regulation goes awry in diseases/cancers, thereby providing new avenues for possible therapeutic targets.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

Our lab is small, but energetic. We have been able to take advantage of the genetic amenability and superb live imaging of the *Drosophila* model organism to pursue questions that span, and sometimes brings together, multiple research fields with a small highly interactive team.

### If you could take the lab back or forward to any point in time, when would it be and why?

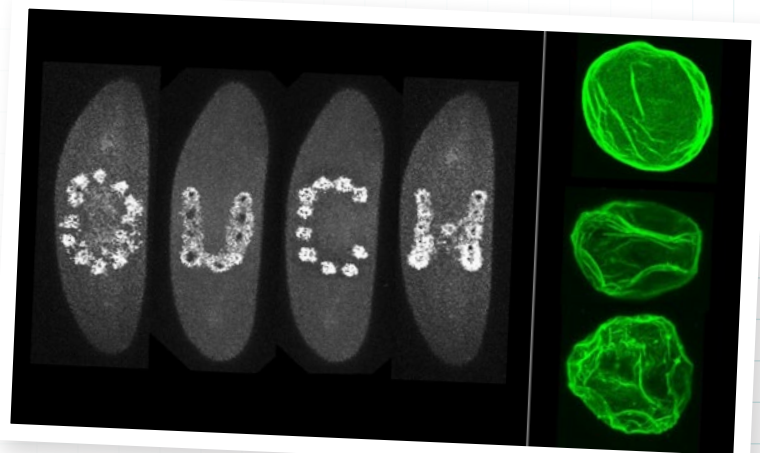
I'd want for us to go forward to the time when we have atomic resolution of all cellular events in 4D... given our lab's interest in actin dynamics we would be excited to know the van der Waals forces around every actin monomer!

### What excites you the most for the future of science or your research and why?

The speed, creativity, and innovation with which technical approaches are evolving that allow exponential advances in our understanding of fundamental cellular events.



Parkhurst Lab members heading off to the division retreat in Port Townsend, 2019.



The Parkhurst Lab studies wound repair and nuclear organization/export.

JOINED DIVISION IN 1993



Dr. Barry Stoddard

**Briefly tell us about the lab group's research.**

Our laboratory studies the structure, function, and mechanisms of a variety of proteins and protein machines. Beyond our studies of fundamental principles that govern the form and function of proteins, we also strive to understand a variety of biological processes that rely on protein factors, such as enzymatic catalysis, targeted gene modification, genetic mobility and the arms race between bacteria and the phage viruses that infect them. To do that, we primarily rely on the determination of atomic-resolution

structures (usually using X-ray crystallography, and now also using Cryogenic Electron Microscopy), protein engineering and biophysical studies of protein behavior.

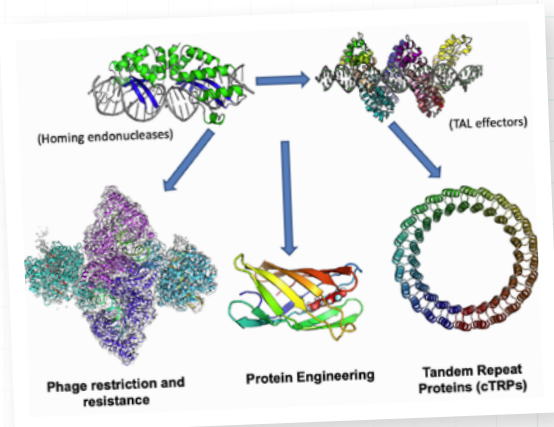
**What is/was a distinguishing feature of your lab? What made your lab stand out?**

Our lab was established in 1993 at the Hutch to initiate a new program called 'structural biology' (the determination of high-resolution three-dimensional structures of biological molecules). In the years since, we have greatly broadened our interests from the original focus of the lab (studies of enzymatic mechanism) to a broader range of biological questions, mostly focused on protein factors in bacteria that are involved in the inheritance of mobile genetic elements, in gene targeting and in anti-viral defense and resistance. Over the years we have solved almost 200 structures of various biological factors and assemblages.

It's perhaps interesting to also note that we were the first lab in Basic Sciences to move into the South Lake Union building. I started at the Hutch in December 1992 and was given keys and access to the building in January 1993, along with my first staff scientist. For about 3 months, until the first labs started moving down from First Hill, we were the only scientists in residence here, installing the first generation of X-ray diffraction instruments and instructing the construction workers and carpenters who were still finishing the building in their usage.

**If you could take the lab back or forward to any point in time, when would it be and why?**

I wouldn't take them to any other time or place. The present is more than exciting enough as it is.

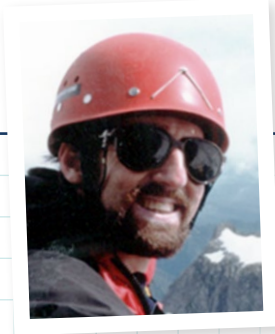


Stoddard Lab projects and scientific history: Starting in the early to mid-1990s, we turned our attention to the structure, function and mechanism of naturally evolved gene targeting proteins called homing endonucleases (upper left: structure of the I-Onu1 homing endonuclease). Found in all forms of microbial life and in the viruses that infect them, we spend the next 25 years determining the many ways in which they have evolved to carry out a wide range of biological functions, ranging from intron mobilization to RNA splicing to transcriptional regulation. That project was not only productive and successful in its own right, but served as the launching point for a series of new projects, including studies of TAL effectors (upper right), phage restriction and resistance (lower left), protein engineering (lower middle) and tandem repeat proteins (lower right).



Goodbye party for Natalia Ubilla.

JOINED DIVISION IN 1993



Dr. Ed Giniger

# Giniger Lab

Current: NIH [NINDS] Intramural Research Program

## Briefly tell us about your lab group's research.

My lab studies how connections are established between neurons as the brain develops, and why those connections are dissolved in the old brain during aging and neurodegenerative disease. As far as development is concerned, our data show that axon guidance information acts like a Maxwell's Demon, biasing the intrinsic, stochastic fluctuations of the axonal cytoskeleton to gently favor growth of an extending axon in the desired direction. Degeneration and death, in contrast, turn out to be explicitly encoded consequences of a discrete program, where aging is the developmental clock that determines the time of onset of the mortality program.

## What is/was a distinguishing feature of your lab? What made your lab stand out?

If there is one thing that I taught [and teach] my lab it is not to spend time worrying about what other people believe about how the world works. Spend your time looking at the data itself, yours and everyone else's, free from preconception, and open yourself up to what the world is trying to tell you.

## If you could take the lab back or forward to any point in time, when would it be and why?

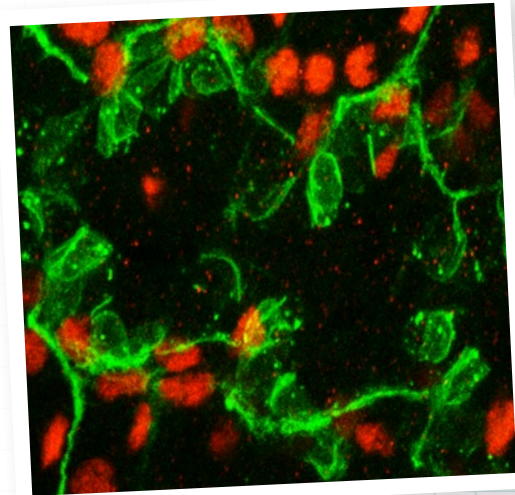
If you are asking where I would take the trainees in the lab to foster their growth, it would be back to the early days of molecular biology, in the 60s, when the limitations of the technology had to be compensated for by clarity of thought and richness of creativity. It is the perfect perspective for seeing how leaps of inspiration come about, tempered by rigorous thought and careful experimentation.

## What excites you the most for the future of science or your research and why?

For my own research, we stand at a point where the answers to our most fundamental questions are within our grasp. The power of our techniques is equal to the challenges we face, if we can only muster the insight to ask our questions the right way.



Ventral nerve cord (center) and motor nerves (left and right sides) of a dissected *Drosophila* embryo. We study the mechanisms that guide each motor nerve to innervate its target muscle.



Early "pioneer" neurons of the ventral nerve cord (green) growing axons along a track laid out by glial support cells (red) to establish the first connections between successive segments of the *Drosophila* ventral nerve cord



JOINED DIVISION IN 1994



Dr. Roland Strong

# Strong Lab

## Briefly tell us about your lab group's research.

The Strong Lab's research focus is translational biophysics, structural molecular immunology and vaccinology. We are applying biophysical approaches, like x-ray crystallography, to understand the recognition mechanisms of innate (Natural Killer cell receptors, Siderocalins) and adaptive (antibodies, T cell receptors) immunoreceptors from a molecular perspective, ultimately to further vaccine development and engineer targeted immunotheranostics. Results are exploited to engineer proteins with desirable specificities, activities and pharmacokinetic properties, but projects are always conducted with the dual propose of advancing basic science. These efforts are fostered and enabled by the highly collaborative environment at the Hutch, providing an interface to clinical investigators and global health initiatives.

## What is/was a distinguishing feature of your lab? What made your lab stand out?

My lab has been a haven for talented scientists interested in pursuing non-standard career tracks in the sciences. We also like doing experiments with plutonium.

## If you could take the lab back or forward to any point in time, when would it be and why?

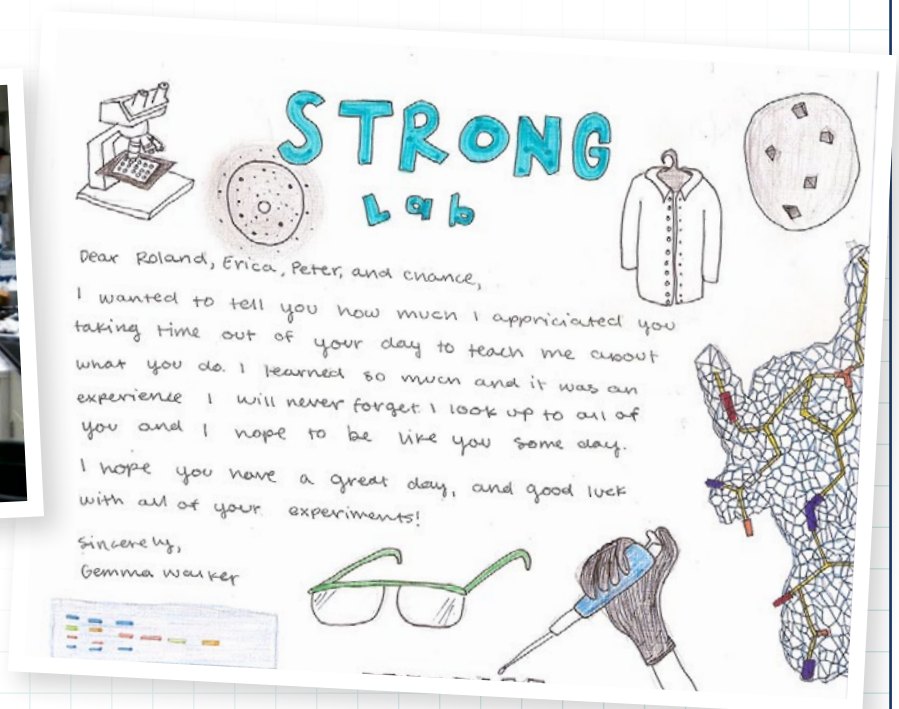
Frankly, I think I'd like to take the lab back and kick the stuffing out of Crick, Watson, and Wilkins for what they did to Rosalind Franklin.

## What excites you the most for the future of science or your research and why?

My research is based on inferring molecular function from molecular structure; the methods for rapidly and accurately determining molecular structures, both experimentally and computationally, have developed by leaps-and-bounds over the past decade.



Strong science, gothic style



JOINED DIVISION IN 1997



Dr. Toshio "Toshi" Tsukiyama

## Tsukiyama Lab

### Briefly tell us about the lab group's research.

We investigate molecular mechanisms and biological roles of chromatin regulation. Chromatin profoundly affects every DNA-dependent process, including transcription, DNA replication, recombination, DNA repair, and DNA damage response. Therefore, uncovering mechanisms of chromatin regulation is a necessary prerequisite for understanding how these essential processes are controlled. One of the major challenges the chromatin

field is to find out how chromatin is globally reprogrammed during processes like cell fate determination, development and cell-cycle control. This is a particularly important challenge, because it was recently determined that mutations in chromatin regulators represent one major class of so called cancer driver mutations, yet how these mutations drive cancer remains unknown. We study chromatin regulation in the context of cell quiescence using budding yeast as a model organism. Quiescence is a conserved and reversible dormant cell state for long-term survival. It is essential for development, homeostasis and wound repair in humans and survival of single cell organisms. In addition, some cancer cells can enter quiescence-like state to evade anti-cancer drug treatments. We have found that both entry into quiescence and exit from it are associated with enormous, global chromatin reprogramming. Our current focus is to understand molecular basis for these dramatic reprogramming events.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

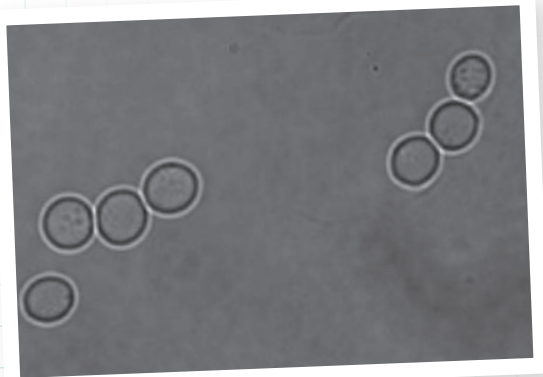
We are highly unique to focus on chromatin reprogramming in different stages of quiescence. Although cells in nature spend most of their time in quiescent state, the vast majority of studies in biology have been done using rapidly dividing cells. That means we still know very little about the state in which cells have spent most of their time during evolution.

### If you could take the lab back or forward to any point in time, when would it be and why?

I would love to go forward to the time when we can monitor chromatin changes and DNA-dependent processes at specific genomic locations in real time in single cells. That would be amazing!!

### What excites you the most for the future of science or your research and why?

I suspect more sophisticated computational analyses, like machine learning and AI, will shock us in the future by extracting currently invisible information from genomics, proteomics, microscopic and genetic interaction data.



Quiescent yeast cells.



Tsukiyama lab members pose in front of their exhibit for the pumpkin carving contest [-pumpkin]. People are holding figures of tardigrade, the champion of quiescence.

JOINED DIVISION IN 1998



Dr. Cecilia Moens

## Moens Lab

### Briefly tell us about your lab group's research.

The Moens Lab studies how genes control the brain's early development, setting up the complex structure found in adult brains. We use zebrafish as a model system to understand how genes control essential processes, such as how cells grow and change into new cell types and how they move and communicate with each other in a 3D environment over time. Specifically, we are working to understand how cranial motor neurons, which control muscles in the head and neck, move to the correct location, acquire their identity as motor neurons, and become part of a functional circuit. These processes are exquisitely regulated in developing organs — but the same genes that control development can promote cancer when awakened in adult tissue.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

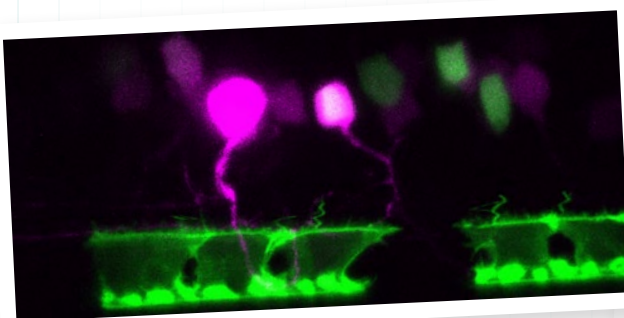
At the Hutch, we are the zebrafish lab. In the zebrafish community we are the lab that makes particularly rigorous use of cell transplantation as a way to understand how genes control nervous system development.

### If you could take the lab back or forward to any point in time, when would it be and why?

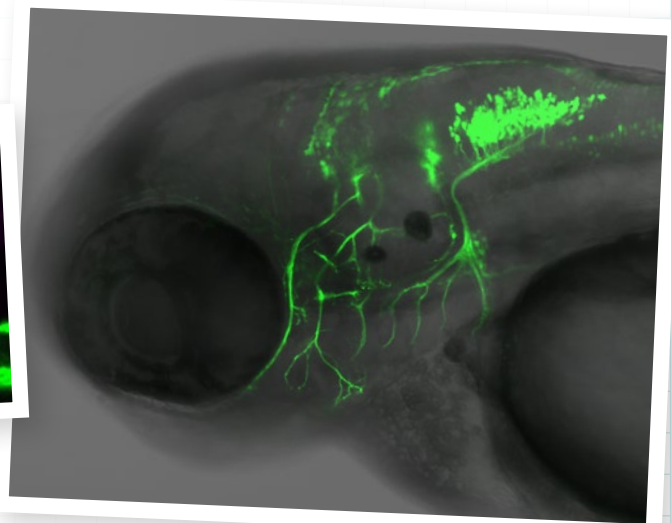
We would like to be with George Streisinger and Charline Walker when they had their first conversations about using the zebrafish as a genetic model system.

### What excites you the most for the future of science or your research and why?

The brain. We have learned so much about how it develops, the diversity of cells it is made up of and how they communicate with one another, but we are really just at the threshold of understanding even simple behaviors, let alone memory and consciousness. The tools for neuroscience research that have been developed in recent years are unparalleled—for visualizing neural activity in living, behaving animals, and for uncovering gene functions from the level of the whole genome to the level of the single cell.



Single interneurons (magenta) project axons that cross the midline of the spinal cord in the floorplate (green block-like cells). Each floorplate cell has a single wiggly cilium that projects into the central canal of the spinal cord where it detects the movement of cerebrospinal fluid. We are interested in how neurons use spatial information in the floorplate and neural tube to make axon guidance decisions.



The head of a live zebrafish embryo at 3 days of age, showing in green the cranial motor neurons that innervate the head, neck and viscera (in us too). We study how these neurons are specified and patterned, how they find their targets and how they form into neural circuits that control reflexive behaviors.



JOINED DIVISION IN 2000

*Dr. Sue Biggins*

## Biggins Lab

### Briefly tell us about the lab group's research.

The generation, survival and development of all organisms depend on the faithful execution of cell division. A key event in the cell cycle is the precise partitioning of every pair of duplicated chromosomes to daughter cells. Defects in segregation lead to aneuploidy, the state where entire chromosomes are gained or lost. Aneuploidy is a hallmark of most tumor cells and has been postulated to be a major factor in the evolution of cancer. Chromosome segregation is directed by the kinetochore, an enormous macromolecular machine that assembles onto centromeres. The kinetochore binds to the microtubules that compose the mitotic spindle and physically pulls chromosomes into daughter cells. If there are defects in kinetochore-microtubule attachments or the tension generated by microtubule pulling forces, the spindle checkpoint halts the cell cycle. Our goal is to understand the interactions between kinetochores and microtubules and the systems that monitor their interaction to provide insight into the ways the cytoskeleton dynamically self-organizes and the mechanisms that cells use to detect and transmit forces into biochemical signals. This knowledge is essential to knowing how cells maintain genomic stability, as well as to developing new therapeutic interventions that inhibit cancer cells from dividing or from evolving drug resistance.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

Our lab has taken a highly collaborative and interdisciplinary approach to understanding the assembly, functions and architecture of the kinetochore. In collaboration with Chip Asbury's lab at UW, we reconstituted kinetochore-microtubule attachments in vitro under tension for the first time and have used this assay to elucidate many of the underlying mechanisms that regulate chromosome segregation.

### If you could take the lab back or forward to any point in time, when would it be and why?

I'd take them forward to a point in time where all of the questions we have worked on for years are finally answered. It would be fun to know exactly how the catch bond that stabilizes proper kinetochore-microtubule attachments works and what a high resolution cryoEM structure of the kinetochore reveals about how they attach to microtubules. I'd love to know which of our current hypotheses are right or wrong, as well as to know what the key experiments and techniques that finally answered the long-standing questions in our field.

### What excites you the most for the future of science or your research and why?

The pace of research continues to get faster due to technological breakthroughs, so I am excited to see what the next key technologies are and how they catalyze future science.

*Lab members at the Hutch**Lab members hiking*

JOINED DIVISION IN 2002



Dr. Linda Buck

# Buck Lab

## Briefly tell us about your lab group's research.

We are interested in the mechanisms and neural circuits that underlie odor perception and instinctive odor responses. How are a multitude of diverse odorants detected in the nose and how is information about those molecules routed and organized in the brain to generate different odor perceptions and innate responses? To explore these questions, our lab employs a variety of molecular, genetic, and viral tools in experiments in mice.

We are especially interested in olfactory and other effects on fear, stress, and appetite as well as how the olfactory system might influence neurodegeneration.

## What is/was a distinguishing feature of your lab? What made your lab stand out?

In initial studies, we discovered the odorant receptor gene family, which codes for 1000 different odorant receptors in the nose. Remarkably, millions of nasal neurons each express only one receptor gene. Neurons with same receptor are scattered in the nose but all send signals to a few specific spots in the olfactory bulb, creating a stereotyped sensory map of receptor inputs. We found that the receptors are used in a combinatorial fashion to detect odorants and encode their unique identities. This explains how we can not only detect a multitude of odorants but also distinguish them as having different scents.

In other studies, we discovered additional families of olfactory receptors, two of which are candidate pheromone receptors, as well as two families of taste receptors on the tongue. More recently, we have explored how predator odors detected in the nose can stimulate fear and stress. By developing viruses that travel backwards through neural circuits, we discovered one small region of the olfactory cortex that transmits signals from the olfactory bulb to brain neurons that stimulate increases in blood stress hormones. Using single cell genomics, we are defining genes expressed in neurons that transmit signals to the stress neurons. This information lays a foundation for the development of therapeutic agents to combat fear and stress.



The Sense of Smell

## If you could take the lab back or forward to any point in time, when would it be and why?

I am excited about the future prospects for understanding how the brain controls diverse functions. I am also excited about the possibility of making discoveries that can lead to prevention or cure of devastating diseases, particularly neurodegenerative diseases.

## What excites you the most for the future of science or your research and why?

With new and powerful technologies, we are seeing the ability to answer questions that could not be investigated before.



Different receptors are expressed in different nasal neurons

JOINED DIVISION IN 2003



Dr. Harmit Malik

# Malik Lab

## Briefly tell us about your lab group's research.

I am an evolutionary geneticist by vocation. Our lab aims to forge new frontiers in the study of genetic conflicts that pervade biology. Antagonistic interactions between genetic entities vying for fitness, colloquially referred to as Red Queen interactions, spur tit-for-tat rounds of adaptation and counter-adaptation. We have pioneered the use of evolutionary innovation that emerges from these arms races to dissect the outcomes of known conflicts [e.g., host-virus interactions] and discover new conflicts that shape fundamental biological processes [e.g., chromosome segregation, speciation]. We study both genetic conflicts that occur between cells or genomes, as well as genetic conflicts that arise within cells or genomes. We study a broad range of organisms to elucidate general principles that shape both types of conflicts. Thus far, we have studied nearly a dozen different model organisms and nearly a dozen different viruses, although there remains a strong focus in *Drosophila*. While I still remain a geneticist at heart, folks in the lab have done pioneering research in virology, cell biology, meiosis, mitochondrial biology, and of course, chromosome biology.

## What is/was a distinguishing feature of your lab? What made your lab stand out?

I am most proud of our trainees. My lab is set up on the principle that all students and postdocs are in training to become independent scientists, whether they choose to stay in academia or not. All trainees work on separate projects, which no one else [except junior research technicians] works on; we stop working on these projects when postdocs leave my lab. Our philosophy is to encourage postdocs and some especially mature graduate students to develop independent research programs, which are related to the lab's core interests and skillsets, while also providing them with a smooth transition to their own future positions. I feel this allows the individual creativity of the trainees to come to the fore and allows them the maximum chance to craft their own intellectual identity. While this leads to a little more of a 'gestation period' as they refine and hone their projects, they reap the benefits of this investment when they are on the job market and in their own labs. As a result, the lab has always been a vibrant place, with a number of exciting projects. We value creativity in science and an unrelenting commitment to mentoring of peers and junior researchers.

## If you could take the lab back or forward to any point in time, when would it be and why?

It has already been 18 years since I started my lab. As grotesquely immodest as it sounds, I would love the ability to go back and stop time at any point in the past. I feel that I spent so much time focused on the science and worrying about the lab that I missed opportunities to truly appreciate the amazing people who trained with me while they were still in the lab. I would not want to change anything, just to slow things down to savour it.

## What excites you the most for the future of science or your research and why?

Every time a group of great trainees leaves the lab, I go into a mini-depression thinking that there is no way we can surpass this. But I am constantly proven wrong. I feel fortunate to be able to still attract ambitious, curious trainees who also relish each other's company. Technical advancements have made it possible to now answer classic questions in genetics that I grew up with; I hope to answer some of these before I retire.



*I am especially grateful to the three senior scientists for their significant contributions to the success of my lab: Danielle Vermaak, Aida de la Cruz, and Janet Young.*



JOINED DIVISION IN 2003



Dr. Katie Peichel

## Peichel Lab

### Briefly tell us about your lab group's research.

We are interested in the genetic and genomic mechanisms that underlie evolutionary adaptation to divergent habitats and the formation of new species. Our main model system is a small fish called the threespine stickleback, which have adapted to a variety of marine and freshwater habitats across the Northern hemisphere since the end of the last ice age. Since then, they have evolved incredible diversity in behaviour, morphology, and life history, leading to reproductive isolation between closely related species. My group has been instrumental in the development of genetic and genomic tools for these fish, and we have used these tools to identify genetic changes that underlie adaptation and speciation, behavioural evolution, and sex chromosome evolution.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

My lab was probably the only lab at the Hutch in which fishing waders, seine nets, and minnow traps were essential lab equipment! But, we have always combined genetic and genomic approaches in the lab with evolutionary and ecological studies in the field to understand both the proximate mechanisms [i.e. molecular, developmental, neural, genetic and genomic] and the ultimate causes [i.e. selective forces] that lead to the spectacular phenotypic diversity we observe in nature. Despite the fact that my lab has always had people with diverse backgrounds and expertise, we have always been united by our love of science, each other, and good food.

### If you could take the lab back or forward to any point in time, when would it be and why?

Evolutionary biology is a historical science. We look at patterns that we see today, and try to infer something about how those patterns arose during evolution. So, I would love to go back in time to sample marine sticklebacks when they were first colonising new freshwater habitats at the end of the last ice age. Then, we could actually look at the genetic and phenotypic characteristics of these fish, as well as the ecological conditions at the time, which would allow us to better understand the patterns we see today. But, we might actually be able to recreate this evolutionary scenario...to see how, read on!

### What excites you the most for the future of science or your research and why?

We recently had the chance to put sticklebacks into empty lakes in Alaska, and we now have a chance to watch the evolution of their genomes and phenotypes, as well as the ecology of the lakes, in real time! We even plan to sequence the genomes of thousands of sticklebacks to see how their genomes evolve, something that would have been unimaginable just a few years ago. This real time evolutionary experiment in nature is going to keep me busy for a long time.



The Peichel Lab celebrated the successful PhD defense of our last UW student [Dr. Sophie Archambeault] in Seattle in the fall of 2019. It was a wonderful reunion, with former lab members coming from Seattle [Dr. Margaret Mills, Dr. James Urton, Dr. Anna Greenwood], Georgia [Dr. Mike White, Shaun McCann], and California [Dr. Jen Cech], and current lab members [Dr. Matt Zuellig] coming from Switzerland [and Skype] to celebrate.



The Peichel Lab found that the evolution of a fusion between the Y chromosome [labeled in green] and an autosome [labeled in purple] is associated with the evolution of different mating behaviors leading to reproductive isolation between two young stickleback species. Thanks to a collaboration between postdoc Dr. Jun Kitano and PhD student Dr. Joe Ross, this study brought together our interests in sex chromosome evolution, behavioral evolution, and speciation in an unexpected way.



Dr. Roger Brent

## Brent Lab

### Briefly tell us about the lab group's research.

We are interested in technologies and experimental designs that help scientists discover new knowledge. In one project, we try to understand causes of different kinds of non-genetic variation that contribute to variable phenotype in yeast and mammalian cells, establish the consequences of variation, and build means to suppress it. In a second, we are developing machine-vision-aided Augmented Reality [AR] to guide wet

lab experimentation. This project weaves together digital technology, machine learning, coordinate transformations, and empirical study of the human sensorium and human performance. Its goal is to develop interactive procedural guidance for the complex manual tasks that comprise labwork. The motivation for both projects is that helping scientists carry out more accurate experiments, learn to practice new methods, and work effectively with fewer mistakes should accelerate generation of biological knowledge over the course of the 21st century.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

In the scientific ecosystem, the lab occupies a place as a tolerated outlier and generator of new methods and ideas. After my graduate studies, the first prominent work was our use of LexA, a prokaryotic repressor we had shown repressed *E. coli* genes induced after DNA damage. We used LexA to repress transcription in a eukaryote *Saccharomyces cerevisiae*, and then to bring eukaryotic transcription regulators to specific sites on DNA. These experiments established operationally that DNA binding and activation/repression were separable functions carried out by different protein domains. They disproved some existing pictures of transcription regulation and helped spark a style school of naive protein engineering by bolting pieces of proteins together that continues to this day. My lab parlayed this work into broad scalable means to gain insight into gene function by identifying protein interactions [efficient two hybrid methods] and interfering with those interactions. This work included development of peptide aptamers isolated from combinatorial libraries to bind specific protein surfaces, and use of different peptide aptamer derivatives to break protein interactions, count proteins present in small numbers, change subcellular localization of target proteins, and trigger targeted protein posttranslational changes. Interaction methods continue to develop, and outgrowths of the aptamer work count as distant evolutionary ancestral contributions to contemporary methods including proximity ligation, and to therapeutic approaches including nanobody and targeted proteolysis. Our tireless evangelism for development and application of such broad approaches to gene function contributed to the late 20th century Zeitgeist.

However, during the late 1990s, we validated our outlier identity by executing a hard 90° turn in research direction. That work began at MSI, a small independent research institute we started with Sydney Brenner in Berkeley, California, and continues here. We advanced [or re-articulated] an operational definition of quantitative understanding of function a biological system, as ability to predict system output in response to defined perturbations, and set out to accomplish this goal for a prototype receptor-coupled signaling pathway in *Saccharomyces cerevisiae*. Although we fell short of that goal, we made a key finding, that the information the yeast system carries is the concentration of extracellular ligand, measured by the fraction of receptor that is bound by ligand, and that the system constantly adjusts its quantitative operation in order to maximize the precision with which this information is transmitted. Recent work by a collaborator has established a subtle mechanism for fractional receptor occupancy sensing by the yeast system. These "systems level" properties of fractional-occupancy sensing and constant adjustment are conserved throughout multicellular organisms, in different receptor-coupled signaling systems that operate by different biomedical mechanisms.

*continued >>*

# Brent Lab continued

The lab may be different in the degree to which it asks its researchers to consider how new scientific knowledge is generated, how the play of new methodologies, knowledge, and human institutions shapes problem choice and what knowledge that is generated, and how the increases in biological knowledge and capability [K&C] are shaping human affairs in the 21st century. We ask lab members to consider these issues in the context of their obligations as citizens, of existing, imperfectly democratic polities. We aspire to contribute to ethical thinking and practice that scientists (and others who help create the future) can use to inform and guide their future work.

## **If you could take the lab back or forward to any point in time, when would it be and why?**

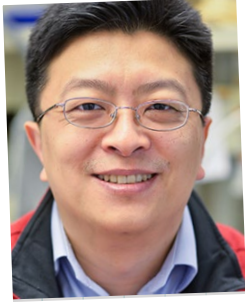
I'd take it forward, say to 2050. I want us to be able to see through the eyes of and experience the sensoria of researchers at work, to witness and understand how near future scientists combine physical experimentation and manipulation of virtual information to generate new knowledge.

## **What excites you the most for the future of science or your research and why?**

After what seemed to be a lull, circa 2000-2014-ish, I am ecstatic that the pace of discovery of new biological knowledge once again seems fast and seems likely stay fast for some time. Given that one way that new biological knowledge impacts human events is its application to human health, I am equally excited about the pace of applied work, how the massive increase in opportunities suggested by new biological knowledge [i.e. targetable processes and targets] is being matched by an ever- growing array of possible therapeutic and genomic modalities. These include but are not limited to, human mastery of antibody drugs, the development of degraders and other bifunctional molecules, the current crazy embarrassment of possible cell therapies, the continued development of all kinds of DNA and RNA therapies, the steady progress in de novo protein design and small molecule drugs, and the real prospect of targeted germline genomic interventions during this century. Yet another reason for excitement is the maturation of a generation of researchers, which, for all that its composition may fall short of optimal, is certainly the most demographically inclusive the world has known, and all of whose are comfortable using the new methods and platforms and Information and Communication Technologies [ICTs] that make the methods work.



JOINED DIVISION IN 2011



Dr. Jihong Bai

## Bai Lab

### Briefly tell us about the lab group's research.

The Bai lab investigates neuronal mechanisms that determine how we move, how we figure out the surroundings, and how we remember the past. These physiological activities, controlled by the brain, are fundamental to human health. To understand how the brain works, research in the Bai lab focuses on principles that govern neuron communication at the molecular, cellular, and circuit levels. We use a combination of genetic, biochemical, imaging, and electrophysiological techniques to listen to and

to guide conversations among neurons. Our current projects are the following: 1) Mechanisms that control the quality of synaptic vesicles – Synaptic vesicles store and release neurotransmitters. They serve as morphological counterparts of the neurotransmitter quanta. Disruptions in vesicle property create deficits in neuronal communication and cause various forms of neurological and psychiatric disorders. 2) Neuromodulation pathways and their links to behavior – Neuromodulatory signals [such as monoamines and neuropeptides] play important roles in tuning the property of synapses and neurons, which consequently lead to behavior flexibility with changing environmental stimuli. How environment and past experience shape neuromodulatory signaling remains largely unknown. 3) Sensory integration and plasticity – Neural circuits do not work in isolation. Instead, they interact and influence each other's performance through reciprocal modulation and plasticity. We are interested in molecular and circuitry mechanisms that coordinate different brain circuits and govern brain-wide plasticity for shaping our sensation and behavior. Elucidation of the mechanisms outlined above are expected to provide crucial insights into brain function, and into dysfunction associated with neurological disorders.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

Members in the Bai lab come together with diverse cultural and educational backgrounds. Some of us are immigrants or members of minority groups. Diverse life experiences make the lab an inclusive place for research. We also make efforts to provide lab opportunities to encourage the growth of future scientists [high school and undergraduate students]. We are very glad to see that some of our high school interns in the past are now in graduate schools.

### If you could take the lab back or forward to any point in time, when would it be and why?

We would like to see the future when people are free from neurological diseases and mental disorders.

### What excites you the most for the future of science or your research and why?

Watching neurons in conversation, predicting their action based on their dialogue, understanding group discussions among neural circuits, and rebuilding damaged neuronal connections using engineered synapses.

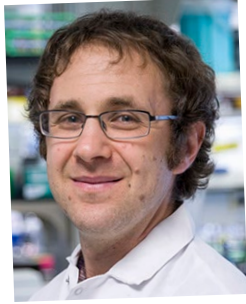


First Bai Lab activity in 2011



First lab gathering after full vaccination in 2021

JOINED DIVISION IN 2011

*Dr. Jesse Bloom*

# Bloom Lab

**Briefly tell us about your lab group's research.**

My lab studies the evolution of viruses. We're especially interested in using new computational approaches to understand evolution at a quantitative molecular level and use the resulting insights to inform vaccines and therapeutics.

**What is/was a distinguishing feature of your lab? What made your lab stand out?**

A feature of my lab is that we've been fortunate to have lab members with a great mix of expertise in evolution, virology, and computation. That has allowed us to combine these approaches in new way—which has been really fun!

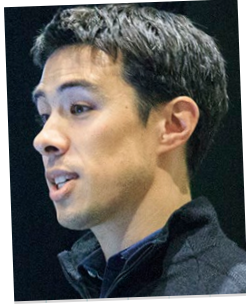
**If you could take the lab back or forward to any point in time, when would it be and why?**

I actually feel like right now is the perfect and most exciting time for our research. Genomic techniques mean that there is lots of data about how viruses are evolving in nature, and new vaccine techniques mean there is the potential to take public-health action based on insights about viral evolution. So right now is a very exciting time to be understanding how mutations observed in viral genomics affect vaccines.

**What excites you the most for the future of science or your research and why?**

I'm really excited how evolutionary biology is becoming an increasingly applied field, with various methods to use evolutionary insights directly in public-health contexts. This means that evolutionary concepts—which I think are some of the most interesting parts of biology—are becoming increasingly relevant.

JOINED DIVISION IN 2011



Dr. Robert Bradley

## Bradley Lab

### Briefly tell us about the lab group's research.

Almost all human genes are alternatively spliced, thereby allowing one gene to give rise to multiple distinct proteins. Although RNA splicing has long been recognized as a critical step in eukaryotic gene expression, the discovery that alternative splicing is regulated across most biological states and correspondingly dysregulated in disease came only within the last ten years. These discoveries coincided with the development of high-throughput sequencing, and together transformed the study of splicing.

My lab is interested in understanding fundamental molecular mechanisms governing RNA splicing regulation, how dysregulated splicing contributes to tumorigenesis, and how correcting splicing errors can yield new therapies for both genetic diseases and cancers. We are particularly interested in understanding how recurrent mutations in several RNA splicing factors cause myelodysplastic syndromes and cancers.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

We use an unusually broad combination of different methods and technologies, including functional genomics, statistics, genetics screens, biochemistry, and other techniques. People who work in my lab tend to become jacks of all trades.

### If you could take the lab back or forward to any point in time, when would it be and why?

I'd like to jump forward to a time when there are many splicing-directed therapeutics in use in the clinic. There has been enormous progress in the past decade toward development splicing-directed therapies, and I believe that we will see much more progress within the coming years.

### What excites you the most for the future of science or your research and why?

I'm excited about the close links that are becoming established between basic science and translational research in my field. There are now lots of labs like my own, where we work across the research spectrum, ranging from fundamental basic science to preclinical studies.



The Bradley Lab celebrating Rob Bradley's promotion to full professor.



The Bradley Lab celebrating Qing Feng receiving the Weintraub Graduate Student Award



JOINED DIVISION IN 2015



Dr. Rasi Subramaniam

**Briefly tell us about your lab group's research.**

Our lab studies molecular mechanisms of mRNA translation. We study the role of ribosome stalling in regulation of gene expression using *S. cerevisiae* and human cells as model systems.

**What is/was a distinguishing feature of your lab? What made your lab stand out?**

We use a combination of computational modeling and high throughput approaches to understand mRNA translation. This has given us unique insights that would not have been possible without this integrated approach. For example, we were able to identify a critical role for ribosome collisions at stalls using experimental data to constrain kinetic models of gene expression.

**If you could take the lab back or forward to any point in time, when would it be and why?**

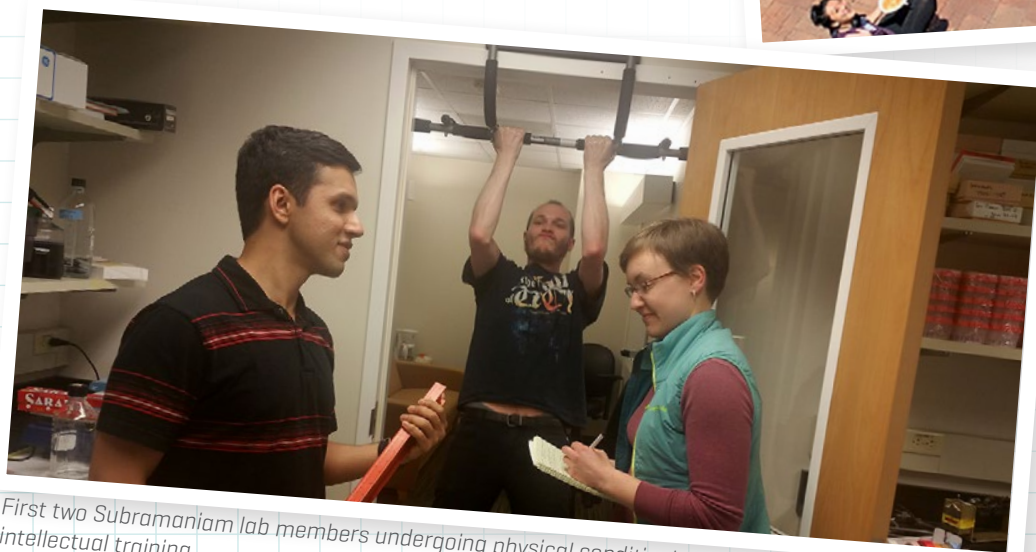
I look forward to a time when biochemistry and molecular biology research is routinely done with the precision that is common in the physical sciences. How cool will it be if Fig. 7 of a paper has an interactive simulation of the mechanism proposed in a paper instead of a cartoon model?

**What excites you the most for the future of science or your research and why?**

Academic science is rapidly losing its traditional silos and boundaries, and this has allowed outsiders to bring fresh perspectives to longstanding problems. I think this trend is exciting and is only going to accelerate in the future.



Celebrating 5 years  
of Subramaniam lab  
at the Hutch.



First two Subramaniam lab members undergoing physical conditioning to complement the intellectual training.

JOINED DIVISION IN 2016



Dr. Emily Hatch

# Hatch Lab

## Briefly tell us about the lab group's research.

Changes in the shape of the cell nucleus have long been used to diagnose cancer from biopsies and are associated with a large group of human genetic diseases, called laminopathies. However, the reasons for these changes and how they contribute to disease have remained mysterious. Recently, our lab and others discovered that these morphology changes can be correlated with an even more extreme phenomenon: nucleus rupture. During nucleus rupture, critical functions are impaired, and the DNA is exposed to a damaging cellular environment. Amazingly, nuclei can repair after these events and the cells continue to proliferate. However, our work demonstrated that when small nuclei, called micronuclei, form after DNA damage or defective cell division, they rupture at a high frequency and cannot repair. This leads to massive changes in the structure of the DNA that are frequent in many types of cancer. In addition, rupture in micronuclei and nuclei can induce inflammation and increase cell invasion. My lab is focused on understanding why nuclear rupture occurs, why these ruptures can only sometimes be repaired, and how nucleus rupture affects gene expression and cell behavior in cancer.

## What is/was a distinguishing feature of your lab? What made your lab stand out?

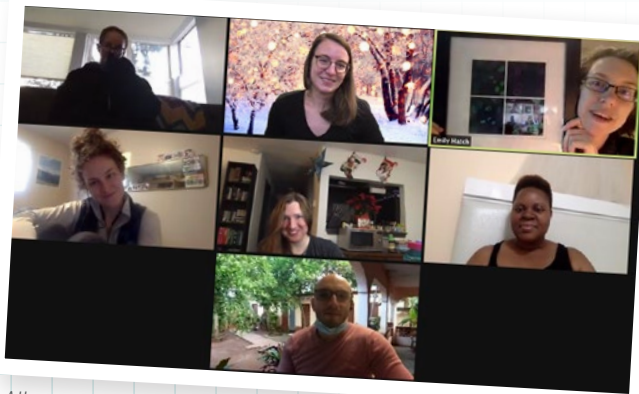
We are studying a relatively new topic using the most cutting-edge microscope technology available. Our research relies on observing live cells over many hours and leads to some fantastic movies. These movies not only lead to new insights into the dynamics of the human nucleus, but also give us great material for talks. My favorite is when we start presenting our videos at meetings and someone in the audience gasps. We have also started several collaborations to bring new imaging technologies to our field that I hope will become a distinguishing feature of the lab!

## If you could take the lab back or forward to any point in time, when would it be and why?

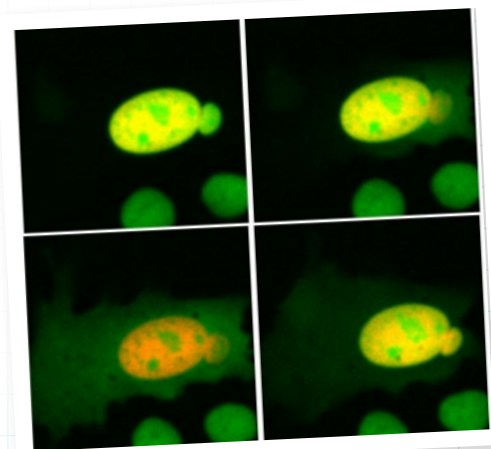
Definitely forward to when we can visualize all of the major structures in the cell at once in real time for a long time. It will be fascinating to see how all of these parts of the cell we study in isolation interact to cause complex cell behaviors.

## What excites you the most for the future of science or your research and why?

The most exciting thing about science for me is that just when we think we've dug down as deep as we can in a cellular process, a new technology comes along and we get to become explorers all over again. Models in the field that we thought were fixed are tweaked or overturned and there's a sense of excitement in the whole community. To me, being a cell biologist is a lot like re-reading a favorite book, each time you look at the same text but discover new meanings that only become apparent because you're looking at them in a new way.



*Alli party: Team Hatch Lab celebrates together (virtually) to say goodbye to a lab mate moving onto the next phase of her career*



*The Hatch Lab studies nucleus rupture and repair in human cells.*

JOINED DIVISION IN 2016



Dr. Akhila Rajan

## Rajan Lab

### Briefly tell us about your lab group's research.

We study how fat stores talk to the brain to regulate physiological decisions on a number of critical processes, including hunger, cognition, sleep, and immunity—dysregulation of fat-brain communication results in obesity and chronic metabolic conditions. Surprisingly, fruit flies and humans exhibit a high degree of conservation in both lipid biology and the brain circuits that receive fat signals to control behavior. This allows us to take advantage of the sophisticated genetic tool kit of *Drosophila* to uncover the underpinnings of fat-brain communication; our discoveries have the potential to treat obesity and its associated complications.

### What is/was a distinguishing feature of your lab? What made your lab stand out?

The questions that we ask in the lab involving fat-brain communication require us to take a broad inter-disciplinary approach. We use various techniques ranging from traditional fly genetics to assays that analyze feeding motivation and cognition. Moreover, we have to adapt and deploy emerging technologies, including proximity proteomics and super-resolution imaging. This multi-scale approach is challenging to execute, as every study that my lab conducts demands us to chart new routes to the answers we seek. Despite these challenges, when we finally get the answers, we are rewarded with original biological insights that connect sub-cellular mechanisms to organismal level behavior.

### If you could take the lab back or forward to any point in time, when would it be and why?

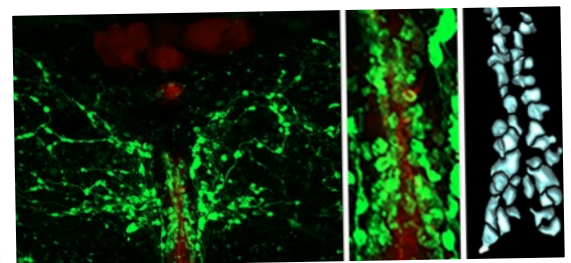
If there were a time machine, I would like to take my lab back to the year 1665 and sit in as a fly on the wall [no pun intended] on Royal Society meetings where a scientific discovery was live performance art. Peer-reviewers, far from being anonymous, participated in a lively debate of ideas with the scientist presenting the discovery. In 1665, Robert Hooke presented the first micrographs of landmark drawings made using a microscope to the Royal Society. It allowed the definition of what we now call a "cell". Incidentally, 1665 was also the year when— in sessions of the Royal Society—peer-review as we know it took shape. It was also the year when Antoni van Leeuwenhoek described "little animals" under a microscope and convinced observers of the existence of microorganisms. Today, we take for granted the "scientific process". How we make a scientific "story" and get our work funded and published is now codified and systematized. While this allows for increased productivity and important developments, and to some extent, provides the rigor needed to make science what it is, the process often diminishes excitement and curiosity. So, I would like to take my lab back in time to experience the age of wonder, and perhaps we may end up liking today better.

### What excites you the most about the future of science or your research and why?

Dementia is the collateral damage of our society's triumphs on increased lifespan. The cognitive decline associated with dementia robs people of loved ones even when they are alive. It is one of the hardest conditions to treat. So, I am excited for the time when we will develop effective treatments to manage or even cure dementia. One key impediment to progress is the challenge of delivering drugs to the central brain. We hope that by studying how peripheral signals from fat reach the central brain, we may uncover novel strategies for delivering therapies to the brain. That is an aspiration that drives some of the work in my lab.



Ava Brent, a founding member of the lab, "graduated" after her important work on identifying how bodyweight set-points are regulated.



This image of the adult *Drosophila* brain's pars intercerebralis region shows the Upd2/Leptin target energy-sensing neurons (left, green), the Insulin-producing cells (left, red), and the point of synaptic contact between them (middle). Segmentation analysis of contacts (right) allows for determining the extent to which the energy-sensing neurons modulate the activity of the Insulin-producing cells.



JOINED DIVISION IN 2018



Dr. Meghan Koch

# Koch Lab

## Briefly tell us about the lab group's research.

We are interested in understanding how maternal-offspring interactions regulate neonatal physiology, with a specific interest in immunity, the gut microbiota, and metabolism. Current efforts are aimed at understanding how breastfeeding regulate offspring health in the short- and long-term. We have identified maternal antibodies, transmitted via breastfeeding, as a key regulator of host-microbiota interactions in neonates. We are defining the mechanisms by which these different maternal antibody isotypes temper immune responses to commensal microbes, help select for a beneficial gut microbiota, and promote nutrient absorption and weight gain in early life. We are also assessing how certain types of breastmilk antibodies subvert protective immune responses to gut pathogens in order to temper inflammatory responses to commensal bacteria. Finally, we are determining how perturbations in early life host-microbiota interactions, triggered by deficiencies in breastmilk antibodies, cause durable impairments in gut health and enhance susceptibility to intestinal inflammation in the long-term.

## What is/was a distinguishing feature of your lab? What made your lab stand out?

We are not afraid to tackle a new research direction and/or method. Sometimes we are too ambitious, but usually it is worth it! We take pride in our mouse manipulation skills – from setting up wild breeding schemes and mix-and-match fostering experiments to harvesting tiny tissues from newborn mice. We've even learned how to milk mice!

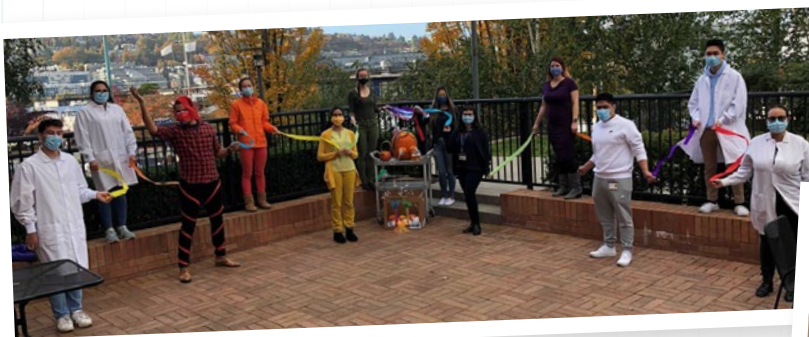
## If you could take the lab back or forward to any point in time, when would it be and why?

I've always wanted to use tiny robots – a la 'The Magic School Bus' – to really SEE what's going on inside our bodies. How are immune responses pathogens mobilized? Who interacts with who? And where? And how?

This might require venturing to an alternate reality, rather than forward in time...

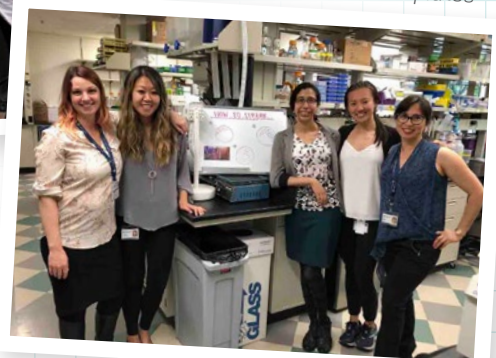
## What excites you the most for the future of science or your research and why?

I'm just excited to be part of this rich and collaborative community of research in the biological sciences. I'm excited for the new, unexpected, stories I'll hear from other researchers, the new, unexpected research paths my group will engage in, and all the collaboration and communication along the way. I'm also excited about better NIH paylines [please?]



Halloween 2020, we dressed up as a Rainbow

The core group at a fundraiser – we taught donors how to streak bacteria on plates



JOINED DIVISION IN 2018



Dr. Aakanksha Singhvi

# Singhvi Lab

## Briefly tell us about your lab group's research.

We study glia: cells that make up half of the human brain but are not well-understood. Glia work hand-in-hand with neurons, and communicate constantly with them via molecular signals, to enable all nervous system functions. This is how we are able to interact with the world around us. In fact, defects in this communication underlie many neurological diseases, from Autism to Alzheimer's. Our goal is to define these glia-neuron conversations in molecular detail, so we can better understand nervous system health, disease and aging.

## What is/was a distinguishing feature of your lab? What made your lab stand out?

We are a crazy bunch of neuroscientists from different parts of the world and varied backgrounds. We love chatting with each other as much as we love to listen in on glia-neuron conversations. Only, our chats often involve mimosas and cake! [Also, btw, we've taken Fred Hutch's "Most Horrific Pumpkin" title 3 years running...so yeah, we can also be scary like that :) ..]

## If you could take the lab back or forward to any point in time, when would it be and why?

Going back would be Nobel laureate Santiago Ramón y Cajal's drawing studio in the late 1800s, when he stained and drew glial cells for the first time.

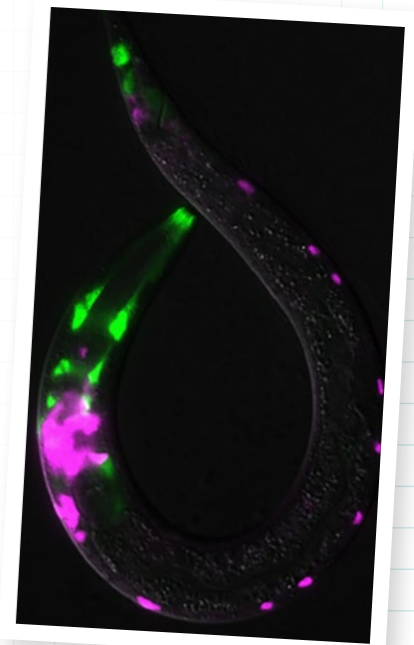
To the future, it will be to witness a time when both molecular neuroscience research and technology are sufficiently advanced that they together enable personalized medicine for neurological diseases.

## What is the role of basic science for society?

Basic science is the foundation for our future society. In practice, it seeds all future technological and medical advances. More philosophically, basic science is rooted in empirical derivation of objective facts. This approach, and the results, are what lead us to a deeper understanding of ourselves and the world around us.

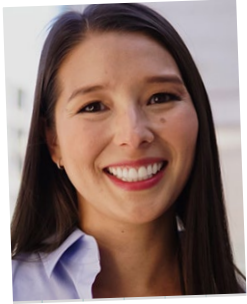


The Singhvi Lab



A transgenic *C. elegans* animal with its entire nervous system labeled with fluorescent reporters (green glia, magenta neurons).

JOINED DIVISION IN 2020



Dr. Melody Campbell

# Campbell Lab

## Briefly tell us about the lab group's research.

Our lab is focused on understanding how cells communicate and interact with their surroundings. We study integrins, a family of receptors that are critical for accurate cell communication. These receptors transverse the cell membrane and relay external signals into the cell, as well as internal signals out. Many integrins recognize and bind an array of different ligands, are implicated in multiple different signaling pathways, and are known to undergo significant conformational changes. Therefore, this family of proteins is strictly regulated: dysregulation is associated with a myriad of pathologies including autoimmune, cardiac, pulmonary and blood diseases as well as cancer and infectious diseases. Our lab utilizes a broad range of strategies in biophysics (including cryo electron microscopy [cryo-EM]), protein engineering, biochemistry, and cell biology to shed light on how integrins function at a molecular level.

## What is/was a distinguishing feature of your lab? What made your lab stand out?

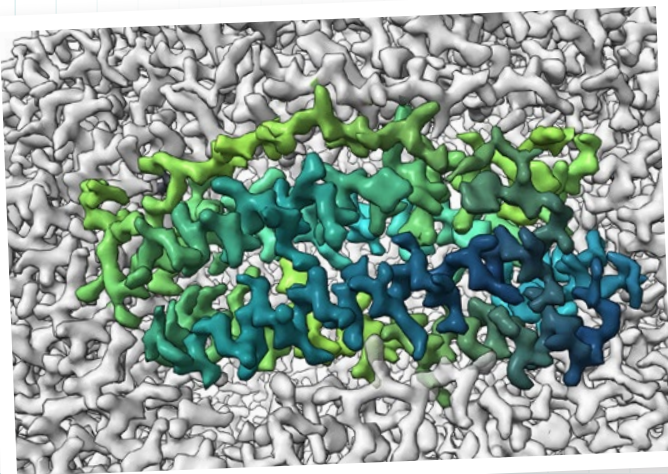
We're been here under a year in and just getting started! For now, the lab is young and full of energy: the experiments are shiny and new and no idea seems too big or too unattainable. I'm backed by an outstanding group of people who are brilliant, accomplished, and kind and I'm hoping to carry this boundless fearless energy and optimism forward so that one day it will be the distinguishing feature that makes our lab stand out.

## If you could take the lab back or forward to any point in time, when would it be and why?

I'd just skip ahead a couple months [assuming no severe new SARS-CoV2 variants emerge] so that we can finally start having meetings and doing presentations in person again, but other than that I'm good. It's an exciting time to be doing research and I don't want to miss any of the smaller discovers as they build up to the big ones [nor do I want to go back in time and struggle with issues that have since been solved]!

## What excites you the most for the future of science or your research and why?

As science progresses and experiments become faster and more straightforward it will allow us to tackle bigger broader and more comprehensive questions and I'm here for it.



The first high resolution structure determined using the Fred Hutch Cryo-EM Shared Resource: a 2.4 Å map of Apoferritin.



The group celebrates both rotation students joining at its first outing at Golden Gardens in June of 2021. L to R: Rachel, Melody, Jeremy, Adam, & Caleigh.



JOINED DIVISION IN 2021



Dr. Manu Setty

# Setty Lab

## Briefly tell us about your lab group's research.

How a cell decides its lineage fate is a long-standing and enigmatic question in biology. Our multi-disciplinary research aims to decipher the cell autonomous gene regulatory mechanisms and non-autonomous cell communication mechanisms that drive cellular lineage decisions in development, and the dysregulation of these mechanisms in cancer. We investigate these questions in close collaborative partnerships. High throughput single-cell genomics technologies have revolutionized the study of developmental and disease trajectories, offering an unprecedented scale and resolution. We employ cutting-edge analysis tools and develop novel machine learning methods to leverage these technologies and better characterize mechanisms driving these trajectories.

Cell autonomous gene regulatory networks are the primary drivers of lineage decisions in developmental trajectories. We are developing methods to integrate multiple single-cell modalities to infer the regulatory network reconfigurations that drive cell state transitions and cell-fate choices along trajectories. Gene regulatory networks invariably are downstream of cell communication and signaling mechanisms. We are developing algorithms to model cell-cell communication and how they shape developmental trajectories. Mutations in regulators have been demonstrated to be key drivers in many cancers. As with development, cell communication with the microenvironment also plays a central role in disease progression. We are interested in using the developmental / healthy system as a reference and develop methods to understand the disruption and dysregulation of these mechanisms in disease initiation, progression, and transformation.

## What is/was a distinguishing feature of your lab? What made your lab stand out?

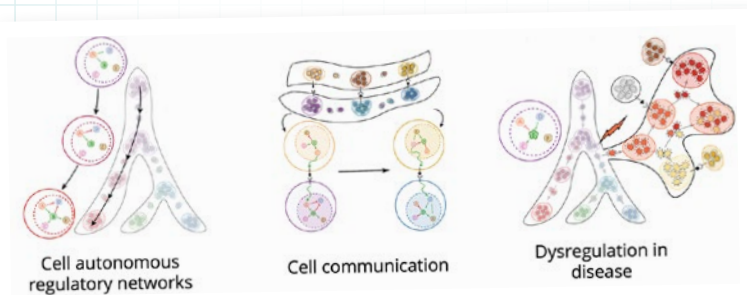
We are an inter-disciplinary group with backgrounds spanning developmental biology to mathematics. This diverse expertise and interests shape all our conversations, making it a stimulating research environment.

## If you could take the lab back or forward to any point in time, when would it be and why?

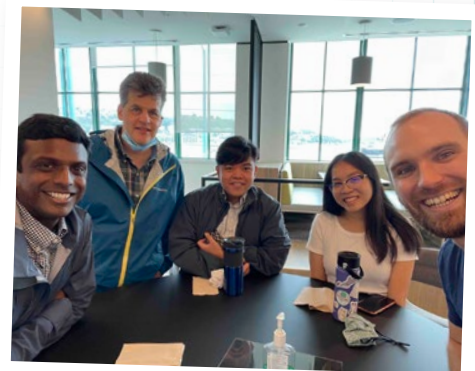
I would take it forward to a time where we can record molecular information about individual cells in space and time as they differentiate given our interest in understanding mechanisms of cell-fate choices.

## What excites you the most for the future of science or your research and why?

Single-cell and spatial technologies are evolving at an astonishingly rapid pace. These technologies allow data generation for many fundamental questions that could not be posed before, providing exciting opportunities for computationally unravel cell-fate choice mechanisms.



The Setty Lab uses single-cell technologies to investigate developmental trajectories and their dysregulation in disease.



The first Setty Lab lunch at the Steam Plant building.

JOINED DIVISION IN 2021



Dr. Nic Lehrbach

# Lehrbach Lab

## Briefly tell us about the lab group's research.

Abnormal protein homeostasis is a feature of aging, cancer, adult-onset neurodegenerative diseases, and many rare genetic conditions. In neurodegeneration, failure to degrade aberrant proteins leads to cellular dysfunction; whereas cancer cells are able to survive and proliferate despite producing abnormal and damaged proteins at high levels. Most cellular protein degradation is carried out by a multi-subunit protease called the proteasome. My lab uses genetic approaches in the nematode *C. elegans* to discover

how cells regulate the proteasome to ensure efficient protein degradation and understand the mechanisms that contribute to proteasome misregulation in disease. We have developed fluorescent protein-based reporters and simple phenotypic assays that allow us to monitor proteasome levels and activity in live animals. We use these tools to discover new regulators of protein degradation and examine their roles in aging, neurodegeneration and cellular resistance to cancer chemotherapeutics. We hope that this work will eventually reveal ways to therapeutically manipulate the proteasome to improve human health.

## What is/was a distinguishing feature of your lab? What made your lab stand out?

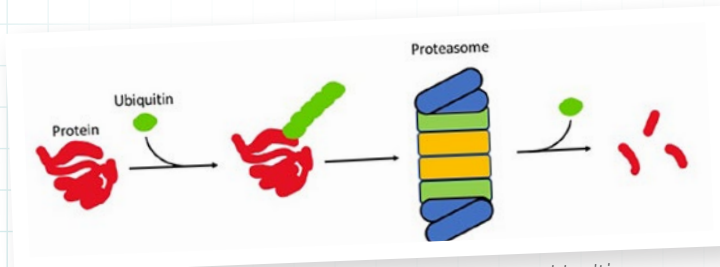
Right now my lab stands out as the newest lab in the division! I hope that my lab will distinguish itself by developing and using creative genetic approaches to answer complex questions in protein homeostasis.

## If you could take the lab back or forward to any point in time, when would it be and why?

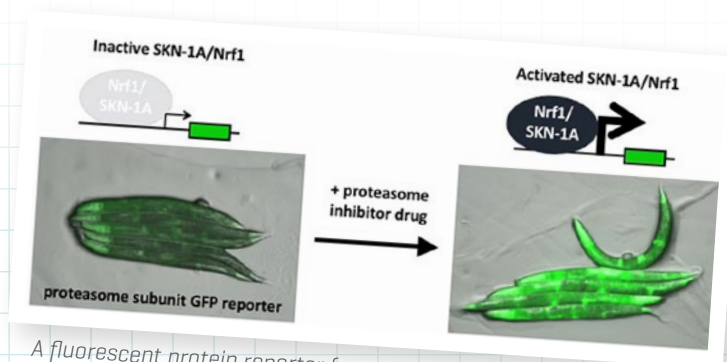
I would take the lab forward to a time when sequencing the [100 million base pair] worm genome takes minutes and costs pennies.

## What excites you the most for the future of science or your research and why?

Rapid advances in technologies for sequencing, synthesizing and manipulating DNA are opening up many new and exciting avenues for genetics research.



The Lehrbach lab studies protein degradation by the ubiquitin-proteasome system.



A fluorescent protein reporter for proteasome regulation used in the Lehrbach lab.

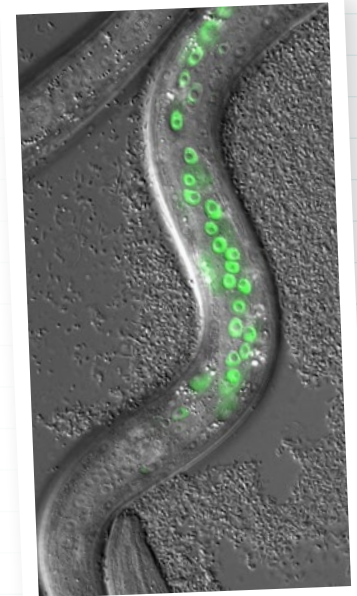


Image showing localization of a GFP-tagged protein involved in proteasome regulation.

JOINED DIVISION IN 2021



Dr. Jimmy Talbot

## Talbot Lab

### Briefly tell us about your lab group's research.

Our lab studies how interactions between neurons and immune cells in the gut can help maintain intestinal health. The gut balances two competing needs: bringing nutrients in and keeping pathogens out. We showed that in the presence of food, certain gut neurons can increase nutrient absorption by reining in the activity of a specialized subset of immune cells that act to increase the gut wall's barrier function by decreasing its permeability. Our work reveals how changes in the diet or the intestinal microbiota may lead to immune and nutritional dysfunctions and how microbes can hijack neuron-immune interactions to enable infections.

### What is/was a distinguishing feature of your lab?

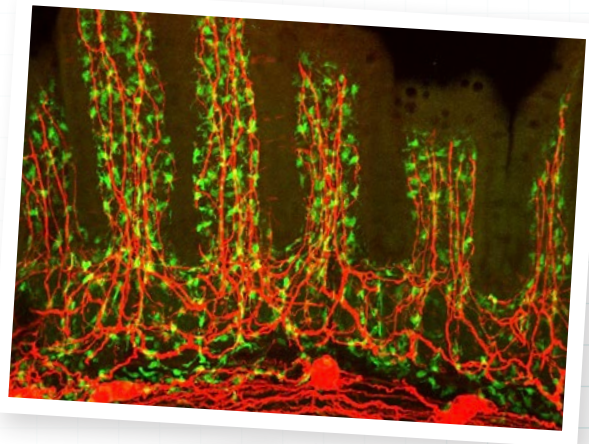
We are very interested in the crosstalk between different cell systems in mammals, systems that otherwise are studied as separate entities [e.g., brain, gut, immune cells, microbiota]. Our lab works to understand how these systems come together to establish basic physiological functions. We focus on the gut as the organ we study since there is a convergence of all these systems there. We have already found that multidirectional crosstalk between the nervous system and the immune system is important for controlling how much nutrients we absorb from the diet.

### What excites you the most for the future of science or your research and why?

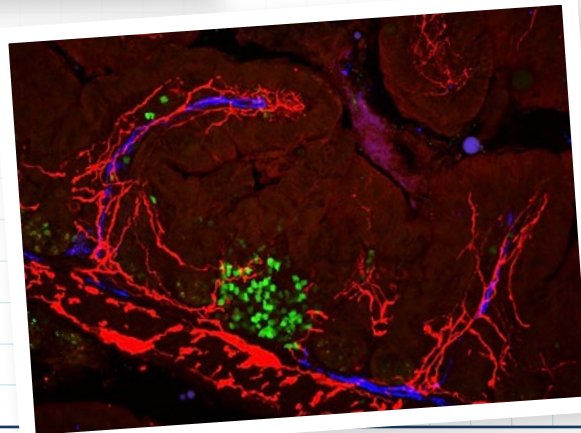
Since I just started my lab in July 2021, all the new directions in my research seem very exciting, although risky. Trying to bridge different areas of research is not an easy task. But interdisciplinarity seems to be more of a common theme than an exception in all the labs in the Basic Science Division. Right now, seeing all the past successful endeavors of risky approaches developed by labs here gives me confidence and excites me.



Electron Microscopy of the small intestine of a mice. One can clearly see the villi, finger-like structures of the intestine responsible for nutrient absorption. You can also see the commensal microbiota (non-pathogenic microbes) attached to the villi of the small intestine.



Gut neurons and macrophages (immune cells) interact in the intestine of a mice



Neuronal innervation of lymphocyte cluster in the small intestine of a mice.



JOINED DIVISION IN 2021



Dr. Richard Adeyemi

# Adeyemi Lab

## Briefly tell us about the lab group's research.

My group is interested in understanding how the integrity of our genomes are maintained. Our cells are constantly exposed to agents that damage DNA, for example from radiation exposure, chemical agents and even microbial infections. In addition, a number of errors arise spontaneously during cell duplication. Failure to properly take care of these errors can lead to a lot of problems including cancer. My lab employs genetic, molecular biology and cell biology approaches to understand how these processes affect our DNA and how our cells respond to adequately and effectively preserve our genomic code.

## What is a distinguishing feature of your lab? What made your lab stand out?

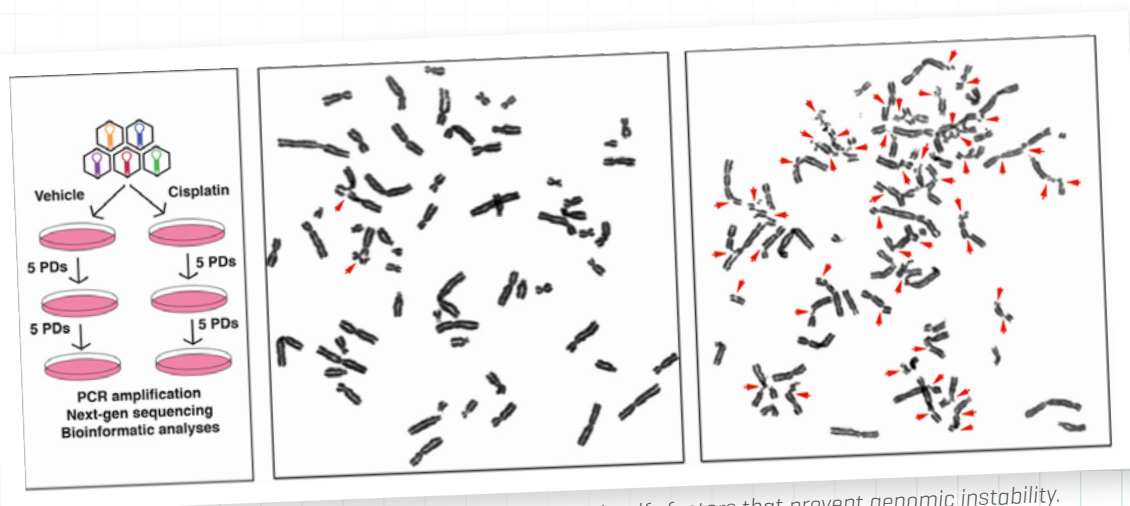
Following up and coupling high-throughput big data genomic screening approaches with detailed biochemical, molecular and cellular biology characterization of novel genes.

## If you could take the lab back or forward to any point in time, when would it be and why?

So many to choose from. I guess I would take them back to the late 19th century, when the germ theory was being advanced and finally replaced the miasma theory that had been accepted as dogma for centuries. There was so much potential for discoveries during this period and this led to a boom in science. It also coincides with rapid advances in other areas of science as well.

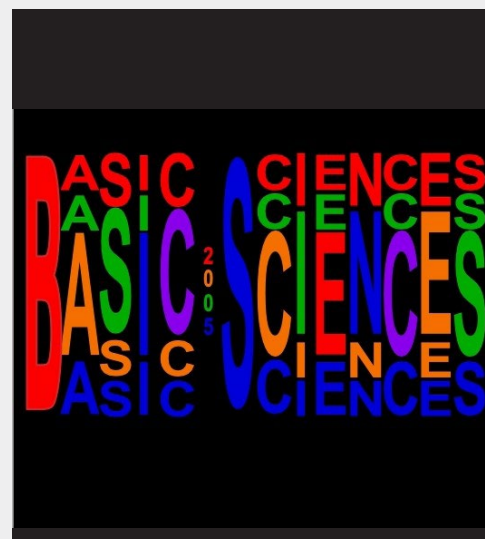
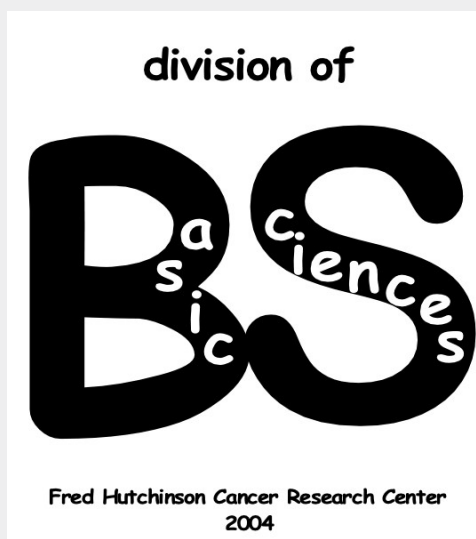
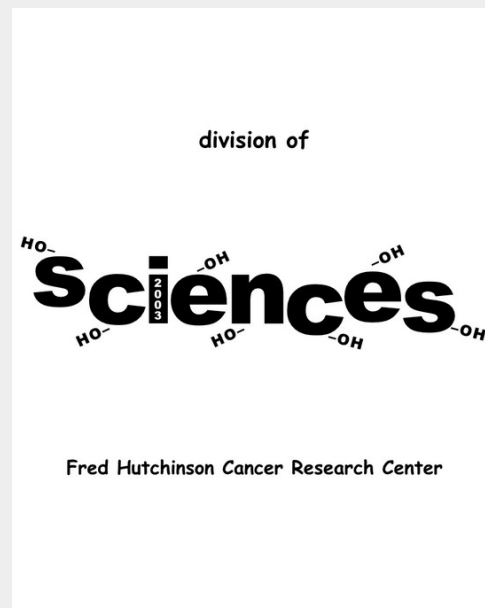
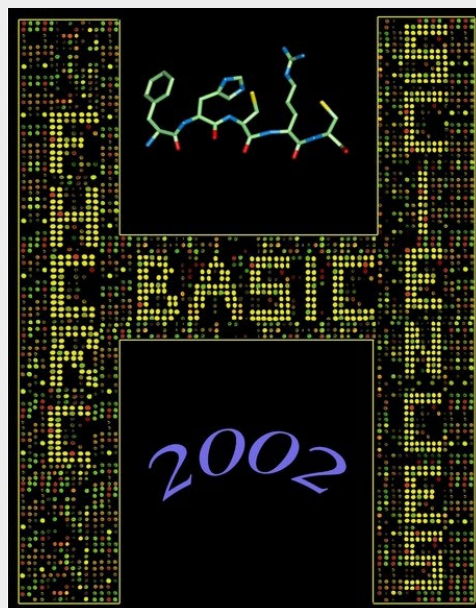
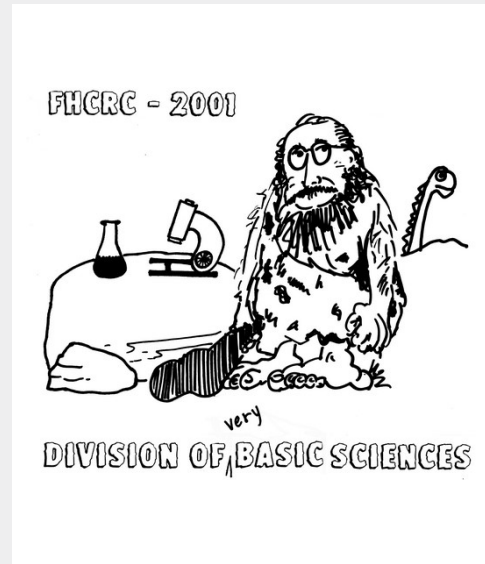
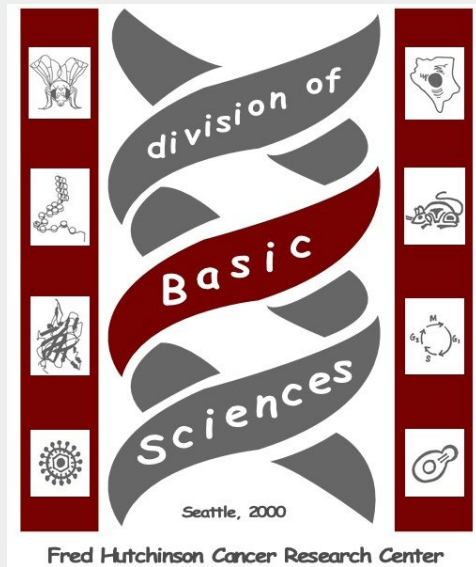
## What excites you the most for the future of science or your research and why?

Several things excite me! The development of new tools for rapid and high throughput genetic manipulation of mammalian cells using CRISPR and similar approaches, the increased appreciation and advancement of inter-disciplinary approaches for solving long-standing biomedical problems including the rise of bioinformatics and the potential for personalized medicine afforded by reduced cost of genome sequencing. Even the pandemic presents us with a silver lining in the form of advances in mRNA therapeutics. It is an exciting time to be a scientist!



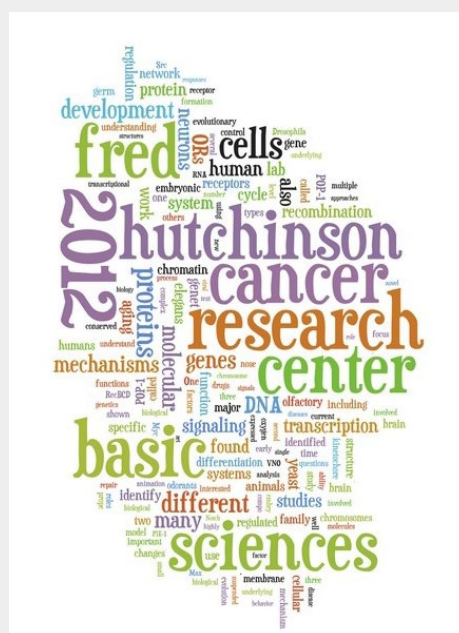
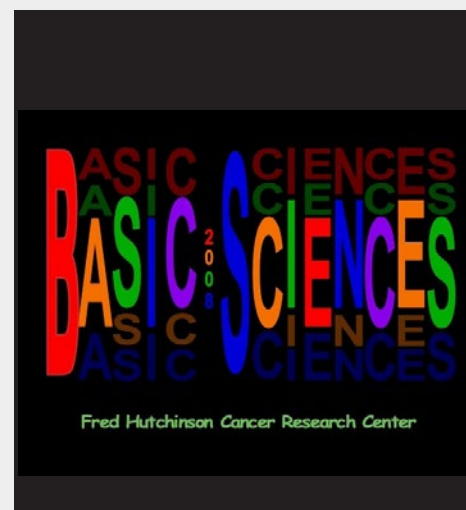
The lab employs high throughput genetic approaches to identify factors that prevent genomic instability.

## BASIC SCIENCE RETREAT COVERS - 2000-2005



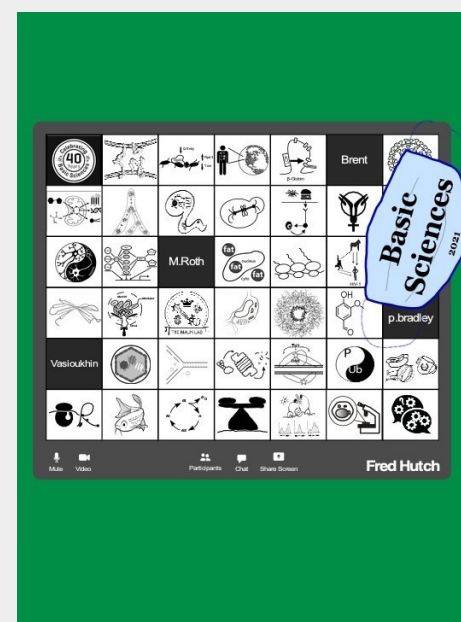
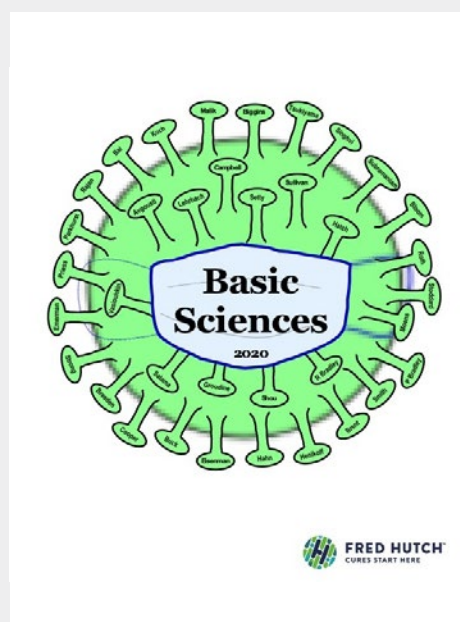
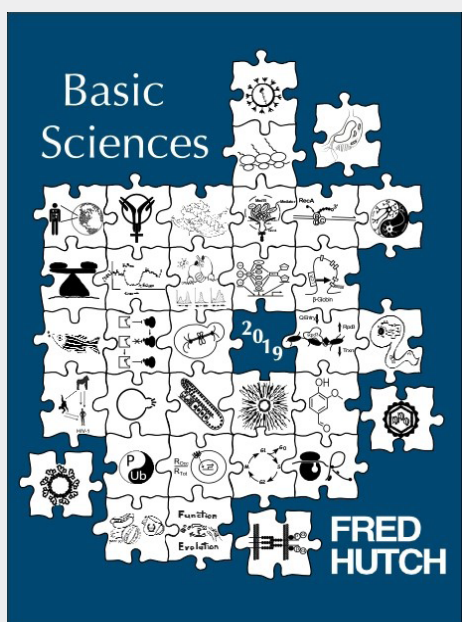
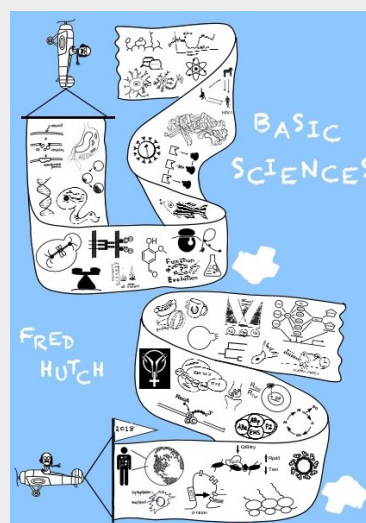
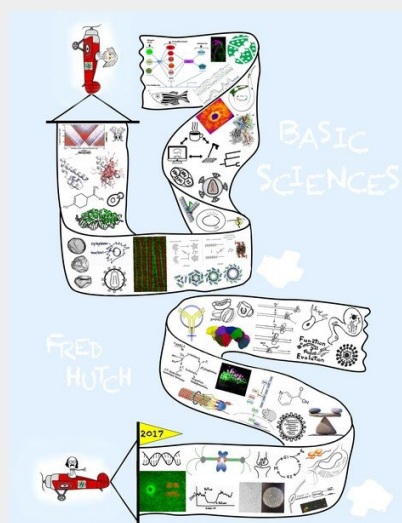
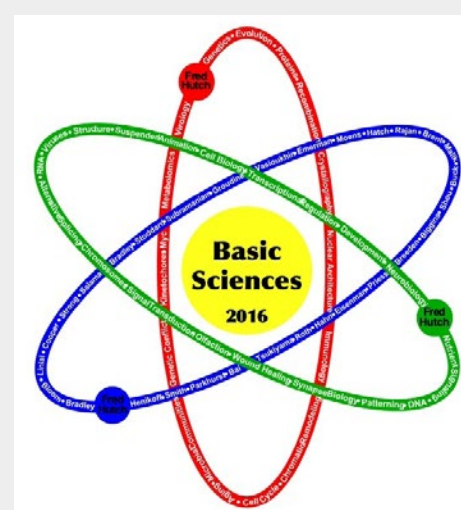
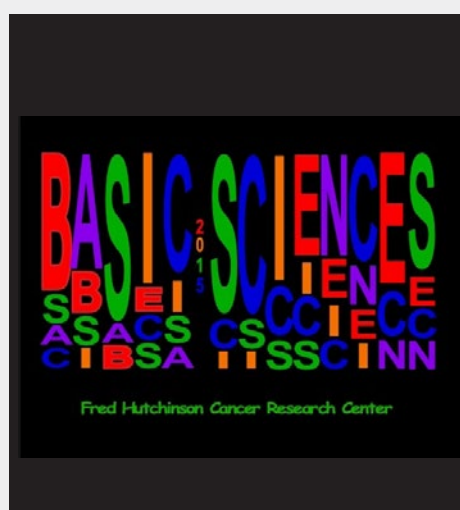
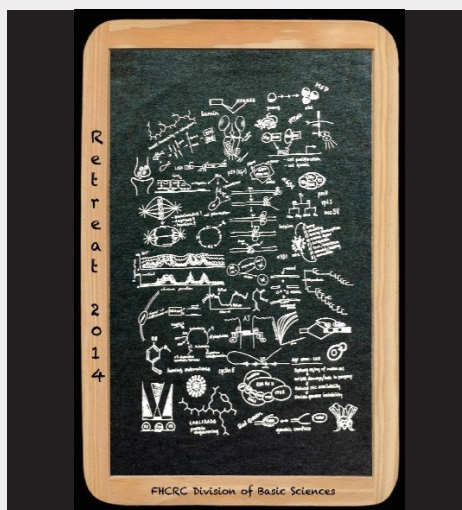


## BASIC SCIENCE RETREAT COVERS - 2006-2013





## BASIC SCIENCE RETREAT COVERS - 2014-2021





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