**Picture Legends**

1. **Query Lab**: Scheme for progression of pre-mRNA splicing, highlighting the different conformations required for the first and second catalytic steps; modulation of transition between the two catalytic steps by spliceosomal mutations results in altered splicing fidelity and splice site choice.

2. **Fyodorov & Skoultchi Labs**: Drosophila melanogaster, a model system to study biochemistry and genetics of chromatin.

3. **Frenette Lab**: A whole-mount images of the bone marrow niche with 3D reconstruction. Arrowheads denote hematopoietic stem cells.

4. **Schildkraut Lab**: Fluorescent antibodies showing replication fork direction in single DNA molecules labeled with halogenated nucleotides.

5. **Skoultchi Lab**: ChIP-Seq – Chromatin immunoprecipitation followed by massive parallel sequencing reveals differences in the DNA binding patterns of transcription factor PU.1 in normal red blood cells (ES-EP) and malignant erythroleukemia cells (MEL).

6. **Kitsis Lab**: Cell death. Healthy (left) and dying (right) HEK293 cells. Blue - Hoechst 33342 staining of nuclei. Red-tetramethyl rhodamine ethyl ester reflecting electrical potential difference across the inner mitochondrial membrane.

7. **Warner Lab**: The structure of a yeast ribosome.

8. **Ye Lab**: Immunofluorescence staining reveals that transcription factors BCL6 (red) and STAT3 (green) are expressed in separate populations of B cells within the germinal center, a dynamic microenvironment critical for T-cell dependent antibody response.

9. **Kielian lab**: Assembly and budding of alphaviruses from the plasma membrane of infected host cells. The image is an overlay of correlated scanning electron microscopy and fluorescence images.

10. **Stanley Lab**: The Notch ligand Dll3 is upregulated in mid-hind brain of E8.5 mouse embryos lacking O-fucose glycans on Notch receptors.

11. **Kielian Lab**: The structure of the alphavirus membrane fusion protein, which mediates virus infection of host cells.

12. **Edelmann Lab**: Lgr5+ and Paneth cells form a stem cell niche in MMR-deficient intestinal tumors.
Welcome to the Albert Einstein College of Medicine and the Department of Cell Biology. Our department is focused on molecular mechanisms in many important areas of cell biology, ranging from stem cells to viruses, DNA replication to RNA processing, gene expression to immunology, glycobiology to cancer. We share many common interests and enjoy an interactive and scientifically stimulating atmosphere that makes the Cell Biology Department a great place to work.

Graduate students in Cell Biology participate in a variety of departmental activities. The department meets every Friday for a “work-in-progress” seminar in which post-doctoral fellows and graduate students describe the progress of their current research and discuss future directions. The department hosts a bi-weekly seminar program of invited outside speakers, with many opportunities for students and postdocs to meet the speaker for discussion and lunch. There is a departmental journal club series in which students present original articles and discuss over dinner. A Friday afternoon get-together encourages scientific interactions as well as social connections. Every few years, our departmental retreat takes us all to the seashore or mountains for a chance to talk about the big picture of our research, to enjoy poster presentations from students and postdocs, and to try to solve the zany puzzles organized by the skit committee.

On the following pages you will find information about the research programs of the individual faculty members, as well as listings of the current students and postdocs in the department. You can also find out more about the department on our web page at http://www.einstein.yu.edu/cellbiology. Feel free to contact any of us for further discussions.

Enjoy your first year!
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<th>Name</th>
<th>Location</th>
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<th>E-Mail</th>
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</thead>
<tbody>
<tr>
<td>Leonard Augenlicht (Joint appointment Medicine/Oncology)</td>
<td>Ullman 909A</td>
<td>4247</td>
<td><a href="mailto:leonard.augenlicht@einstein.yu.edu">leonard.augenlicht@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Barbara Birshtein, Professor</td>
<td>Chanin 403A</td>
<td>2291</td>
<td><a href="mailto:barbara.birshtein@einstein.yu.edu">barbara.birshtein@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Eric Bouhassira, Associate Professor (Joint appointment, Medicine/Hematology)</td>
<td>Ullman 903A</td>
<td>2188</td>
<td><a href="mailto:eric.bouhassira@einstein.yu.edu">eric.bouhassira@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Nicholas Chiorazzi, Adjunct Professor (Joint appointment Medicine)</td>
<td>North Shore LIJ</td>
<td></td>
<td><a href="mailto:nchizzi@NSHS.edu">nchizzi@NSHS.edu</a></td>
</tr>
<tr>
<td>Winfried Edelmann, Professor</td>
<td>Price Ctr 279</td>
<td>1086</td>
<td><a href="mailto:winfried.edelmann@einstein.yu.edu">winfried.edelmann@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Paul Frenette, Professor</td>
<td>Price Ctr 101</td>
<td>1255</td>
<td><a href="mailto:paul.frenette@einstein.yu.edu">paul.frenette@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Dmitry Fyodorov, Associate Professor</td>
<td>Chanin 414A</td>
<td>4021</td>
<td><a href="mailto:dmitry.fyodorov@einstein.yu.edu">dmitry.fyodorov@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Matthew Gamble (Joint appointment Molecular Pharm)</td>
<td>Golding 203</td>
<td>2942</td>
<td><a href="mailto:matthew.gamble@einstein.yu.edu">matthew.gamble@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Kira Gritsman, Associate Professor (Joint appointment Medicine)</td>
<td>Chanin 410</td>
<td>6707</td>
<td><a href="mailto:kira.gritsman@einstein.yu.edu">kira.gritsman@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Wenjun Guo, Assistant Professor Gottesman Stem Cell Institute</td>
<td>Price 122</td>
<td>1276</td>
<td><a href="mailto:Wenjun.guo@einstein.yu.edu">Wenjun.guo@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Keisuke Ito, Assistant Professor</td>
<td>Price 102</td>
<td>1278</td>
<td><a href="mailto:keisuke.ito@einstein.yu.edu">keisuke.ito@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Margaret Kielian, Professor</td>
<td>Chanin 515</td>
<td>3638</td>
<td><a href="mailto:margaret.kielian@einstein.yu.edu">margaret.kielian@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Richard Kitsis, Professor (Joint appointment, Medicine/Cardiology)</td>
<td>Forchheimer G46</td>
<td>2609</td>
<td><a href="mailto:richard.kitsis@einstein.yu.edu">richard.kitsis@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Charles Query, Associate Professor</td>
<td>Chanin 415A</td>
<td>4174</td>
<td><a href="mailto:charles.query@einstein.yu.edu">charles.query@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Matthew Scharff, Distinguished Professor</td>
<td>Chanin 403</td>
<td>3527</td>
<td><a href="mailto:matthew.scharff@einstein.yu.edu">matthew.scharff@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Carl Schildkraut, Professor</td>
<td>Chanin 416</td>
<td>2097</td>
<td><a href="mailto:carl.schildkraut@einstein.yu.edu">carl.schildkraut@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Robert Singer, Professor (Joint appointment, Anatomy &amp; Structural Biology)</td>
<td>Golding 601</td>
<td>8646</td>
<td><a href="mailto:robert.singer@einstein.yu.edu">robert.singer@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Arthur Skoultchi, Professor &amp; Chair</td>
<td>Chanin 402</td>
<td>2169</td>
<td><a href="mailto:arthur.skoultchi@einstein.yu.edu">arthur.skoultchi@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Pamela Stanley, Professor</td>
<td>Chanin 516</td>
<td>3346</td>
<td><a href="mailto:pamela.stanley@einstein.yu.edu">pamela.stanley@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Ulrich Steidl, Associate Professor</td>
<td>Chanin 601</td>
<td>3437</td>
<td><a href="mailto:ulrich.steidl@einstein.yu.edu">ulrich.steidl@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Jon Warner, Professor Emeritus</td>
<td>Chanin 413A</td>
<td>3022</td>
<td><a href="mailto:jon.warner@einstein.yu.edu">jon.warner@einstein.yu.edu</a></td>
</tr>
<tr>
<td>B. Hilda Ye, Associate Professor</td>
<td>Chanin 302C</td>
<td>3339</td>
<td><a href="mailto:hilda.ye@einstein.yu.edu">hilda.ye@einstein.yu.edu</a></td>
</tr>
</tbody>
</table>
Key Words: intestinal homeostasis and cancer, diet, mouse models, inflammation, stem cells

We are interested in cell autonomous effects and heterotypic cell interactions that maintain intestinal mucosal homeostasis, and environmental and genetic perturbations that disrupt this causing increased probability of tumor development. Experimental approaches use genetic and dietary mouse models, and intestinal organoids grown in three dimensional culture.

We demonstrated an orchestrated reprogramming of intestinal epithelial cells as they migrate from the progenitor cell compartment in the intestinal crypt and undergo maturation, eliminating cell cycling and promoting cell differentiation. We determined where key regulators of proliferation are active during this traverse of cells along the crypt-luminal axis, and effects of their disruption on mucosal homeostasis and tumor development.

Importance of the Intestinal Mucus Barrier:
In multiple mouse genetic models causing intestinal tumors, we showed decreased expression of the Muc2 gene that encodes the principal intestinal mucin. MUC2, synthesized and secreted by goblet cells, is the building block of mucus, forming a physical and chemical barrier between the mucosa and the intestinal lumen. Inactivation of Muc2 caused a loss of barrier function, inflammation and a detoxification response, and tumors developed throughout the intestinal tract, including the rectum – the first mouse model of rectal cancer, biologically and clinically distinct from colon cancer. We recently collaborated in showing that the mucus is fundamental in establishment of immune tolerance in the gut, forming a complex with luminal antigens necessary for their engulfment by dendritic cells and their presentation to T cells.

The Profound Role of Diet in Both Genetically Initiated and Sporadic Tumorigenesis:

The vast majority (~80%) of human colon tumors are sporadic, developing without known inherited genetic factors, and arising after 5-6 decades of life with incidence largely determined by long term dietary patterns. We modeled this in the mouse using a purified rodent diet (NWD1) that generates mouse consumption of a number of nutrients linked to colon cancer incidence at the same levels consumed by individuals in higher risk populations: higher fat, lower vitamin D₃, calcium, fiber and donors to the single carbon pool. NWD1 accelerated and amplified tumors in mouse genetic models of intestinal cancer, regardless of etiology, mechanism, or aggressiveness. Moreover, although none of the nutritional risk factors in NWD1 individually cause intestinal or colon tumors in wild-type mice, feeding of NWD1 for 1.5-2 years caused tumors in C57Bl6 mice with a lag, incidence, frequency and pathology similar to that of sporadic colon cancer in the human (1-2 tumors in 20% of after 2/3 of their lifespan). Long before tumors develop, there was macrophage infiltration into the mucosa, elevated serum cytokine levels, decreased secretory and increased absorptive cell marker expression; elevated Wnt signaling and ectopic Paneth cell marker expression throughout the intestinal and colonic mucosa. Moreover, the function of the intestinal Lgr5+ stem cell population is severely compromised in mice fed NWD1, which can be rescued by elevating dietary vitamin D₃ and calcium, and this is mimicked by inactivating the vitamin D receptor specifically in Lgr5+ cells. We are investigating: how diet recruits other, dormant stem cell populations; the mutational load and spectrum in different stem cell populations as a function of diet exposure over time; and the mechanisms by which the NWD1 causes a shift towards glycolytic metabolism in the mucosa (the “Warburg effect”) before tumors develop and the role of this metabolic shift in stem cell function.

Macrophages in the Inflammatory Response:

We investigated how the common feature of macrophage infiltration into the mucosa in tumor models can alter epithelial cell function. Colon epithelial cells secrete versican, a proteoglycan, when co-cultured with macrophages. This stimulates Stat1 activation in the macrophages, causing synthesis and secretion of a number of cytokines. IL-1β from the macrophages then stimulates Wnt signaling in the epithelial cells, via an NFκβ-AKT-GSK3β pathway, causing epithelial cell proliferation, inhibition of the extrinsic apoptotic pathway, and an epithelial-mesenchymal transition, and also stimulates the synthesis of versican, completing a self-amplifying loop between the two cell types. Other work developed a mouse model of colitis (inflammation) associated colon cancer by inactivating Stat3 in macrophages, and showed that inflammation caused by inhibition of Notch signaling, which stimulates massive secretory cell hyperplasia and mucin secretion, causes dysplasia and tumor development.

Selected Publications:


Regulation of Antibody Heavy Chain Gene Rearrangements and Expression by the 3’ Regulatory Region

The immune system is our spacesuit for life in an environment containing enormous numbers of infectious agents. An essential part of the immune system is the B cell, which is the only cell type that produces antibodies. Antibody (Ig) genes are constructed via a series of DNA rearrangements. Occasionally, mistakes occur during antibody construction, which activate oncogenes and lead to cancers. My long term goal has been to understand the mechanisms that initiate and control antibody gene rearrangements within the 3 megabase heavy chain gene (IgH) locus.

Our experiments have focused on a complex 3’ IgH regulatory region that lies immediately downstream of the antibody heavy chain gene cluster in mouse and humans. This region has recently been identified as a “super-enhancer” by Richard Young's laboratory. The ~50 kb 3’ IgH regulatory region (3’ RR) that contains multiple regulatory elements, a 1 kb intronic enhancer, and two small elements in the diversity DH gene region are the only currently known regulatory regions for the IgH locus. We have identified an extension of the 3’ RR (hs5, 6, 7, 8), which like the other 3’ enhancers, has binding sites for Pax5, a transcription factor essential for B cell development. In addition, the 3’ RR extension contains insulator activity, i.e. prevention of communication between an enhancer and its target promoter. This is associated with multiple binding sites for CTCF, a protein identified in all mammalian insulators. Chromatin analysis shows that the 3’ RR extension is likely to be active throughout B cell development while other 3’ RR segments become progressively and stage-specific active.

Murine germline IgH locus, with variable (VH), diversity (DH), joining (JH) and constant region genes (, , , ). Regulatory elements, Eμ and the 3’ regulatory region (3’RR) are depicted. Two additional elements in the DH segment are important for VDJ joining.

The 3’ RR has been shown to be critical both for class switch recombination that affects expression of virtually all antibody classes and for somatic hypermutation of the heavy chain variable region. In addition, the 3’ RR regulates high levels of expression of antibodies in fully differentiated plasma cells. A major goal of our laboratory has been to understand the mechanisms by which the 3’ RR functions in both mouse and human, both by acting on the IgH locus and by insulating the locus from its non-Igh neighboring genes. CTCF binding sites are anticipated to play a major role in these activities by promoting interactions between distal DNA sequences through loop formation.

We have been analyzing the extent of B cell-specific regulation of the IgH locus, by studying DNA demethylation, histone modifications in and the binding of CTCF and Pax5, and other factors to 3’ RR sequences during B cell development and class switching. Furthermore, we have examined the interaction of the 3’ RR with target sequences within the IgH locus, as assessed by the chromosome capture conformation technique (3C). Together, these approaches have been...
designed to understand how the 3’ RR facilitates molecular acrobatics necessary for the immunoglobulin heavy chain locus without their intrusion on downstream non-IgH genes, or resulting in chromosomal translocations involved in malignancies.

Publications:


HUMAN EMBRYONIC STEM CELLS, EPIGENETICS AND REPROGRAMMING:
Epigenetic is the study of mitotically or meiotically heritable changes in gene function not associated with changes in DNA sequence. Epigenetic regulations are mediated by changes in chromatin structure that alter access of transcription factors to their cognate binding sites, and therefore, expression levels of genes and transgenes. Understanding these regulations is critical for gene therapy, cancer therapy and generally to gain a greater ability to modify mammalian genomes. The main focus of my lab is to understand the molecular bases of some of these epigenetic regulations. We are particularly interested in using massively parallel sequencing technologies to understand the mechanisms of establishment, maintenance, and inheritance of chromatin structures. We have recently developed a method termed TimEX to determine the timing of DNA replication genome-wide. We are using TimEX in conjunction with Chip-Seq and RNA-seq to study epigenome organization.

The second major focus of the lab is to use the epigenetic information obtained above to improve the reprogramming of somatic cells into induced pluripotent stem cells and to develop methods to reprogram somatic cells into other stem or progenitor cells by over-expression of transcription factors without reverting to an embryonic state.

Finally, we are currently developing a system to produce normal human red blood cells with embryonic, fetal or adult characteristics by forced differentiation of human ES cells using a genetic approach. The goal is to generate large amount of genetically homogenous, genetically modifiable normal erythroid cells at different stages of differentiation. This system could allow us to produce red cells for transfusion medicine, to study the silencing of the gamma-globin gene, to develop silencing resistant gene therapy cassettes that will be useful to cure the hemoglobinopathies, and to generally study the establishment and maintenance of epigenetic signals directly in untransformed human cells. We also have active research projects on the role of DNA methylation, DNA replication, histone modification, linker histones, and transcriptional interferences in the determination of expression levels.

FOR MORE DETAILS: http://cellbio.aecom.yu.edu/Lab/Bouhassira/

Selected References:
The maintenance of genomic integrity in all organisms requires multiple DNA repair pathways that are involved in the processes of DNA replication, repair and recombination. Perturbations in these pathways can lead to increased mutation rates or chromosomal rearrangements that ultimately result in cancer. MMR is one of the repair systems that mammalian cells employ to maintain the integrity of its genetic information by correcting mutations that occur during erroneous replication. Mutations in MMR genes are linked to one of the most prevalent human cancer syndromes, Lynch syndrome and a significant number of sporadic colorectal cancers. At the molecular level tumors that develop in these patients display increased genomic mutation rates as indicated by increased instability at microsatellite repeat sequences (termed microsatellite instability, MSI). MMR in eukaryotes is complex and involves several homologs of the bacterial MutS and MutL proteins. In mammals, the initiation of the repair process requires two complexes formed by three different MutS homologs (MSH): A complex between MSH2-MSH6 for the recognition of single base mismatches and a complex between MSH2-MSH3 for the recognition of insertion/deletions. The repair reaction also requires a complex between the two MutL homologs MLH1 and PMS2 that interacts with the MSH complexes to activate subsequent repair events which include the excision of the mismatch carrying DNA strand and its re-synthesis. In addition to correcting DNA mismatches, the MMR system mediates an apoptotic response to DNA damage and both of these functions are thought to be important for genome maintenance and tumor suppression. We have generated gene targeted mouse lines with inactivating mutations in all the different MutS and MutL homologs, and also in genes that function in the later MMR steps to study their roles in genome maintenance and tumor suppression. In addition, we have generated knock-in mouse lines with missense mutations and conditional knockout mouse lines that inactivate specific MMR functions and/or model mutations found in humans. Our studies indicate that specific MMR functions play distinct roles in maintaining genome stability and that defects in these functions have important consequences for tumorigenesis. We are currently studying the functions of MMR in intestinal stem cells and cancer stem cells and how loss of MMR in stem cells affects tumorigenesis and the response of tumors to chemotherapeutic treatment. Our studies have also revealed that some of the MMR proteins play essential roles in class switch recombination and somatic hypermutation during antibody maturation and the control of meiotic recombination in mammals.

**Selected References:**


Our laboratory has three areas of interest:

A) We are interested in the biology of hematopoietic stem cells (HSCs) with a focus on microenvironment cues that promote their survival, differentiation and self-renewal. We have identified novel niche constituents and novel regulatory mechanisms using genetically engineered mice and whole-mount imaging of the bone marrow.

Key primary references:

B) We have ongoing projects on the mechanisms of vaso-occlusion in sickle cell disease. We have identified activated neutrophils as a key promoter of vaso-occlusion by interacting with circulating sickle erythrocytes.

Key primary references:


B) Based on our finding of an important role of neural signals in regulating hematopoiesis, we are investigating the role of peripheral nerves in hematologic malignancies and prostate cancer.

Key primary references:


BIOCHEMISTRY AND GENETICS OF CHROMATIN ASSEMBLY

In the eukaryotic nucleus, hundreds of millions of base pairs of DNA are packed into chromosomes. Chromatin, the central nucleoprotein filament of a chromosome, has many forms and organization levels. Chromatin is the natural state of DNA in the nucleus and the native substrate for nuclear reactions, such as DNA replication, recombination, repair and transcription. The assembly of DNA into chromatin and dynamic conversion between its different forms are critical steps in the maintenance and regulation of the eukaryotic genome. The ultimate goal of our research is to understand how chromosomes are assembled and how chromatin assembly regulates the structure and activity of eukaryotic chromosomes. The crucial first step in this direction is a systematic study of factors that mediate this process. To this end, we use biochemical approaches to analyze mechanisms of chromatin assembly by histone chaperones and ATP-dependent enzymes. We also dissect their function in vivo by methods of Drosophila genetics. Thus, we are trying to uncover the network of chromatin assembly factors and to elucidate their roles in hierarchical organization of the chromosome.

1. Molecular mechanisms of nucleosome assembly

ACF (ATP-utilizing chromatin assembly factor) was identified on the basis of its ability to mediate ATP-dependent reconstitution of chromatin in vitro. ACF consists of two subunits, a SNF2-like ATPase ISWI and another evolutionary conserved polypeptide, termed Acf1. In the presence of a core histone chaperone NAP-1, ACF mediates deposition of histone octamers onto DNA and forms arrays of regularly spaced nucleosomes. We study ACF and ISWI as prototype factors to elucidate elementary molecular events that take place during ATP-dependent formation of nucleosomes. Upon reaction initiation, ACF commits to the DNA template and assembles nucleosomes as a processive, ATP-driven, DNA-translocating motor. Multiple conserved domains of Acf1 and ISWI are required for this activity.

2. Biological functions of chromatin assembly factors

ACF is the major ATP-dependent chromatin assembly factor in Drosophila. To expose its biological functions, we study fly mutants that do not express ACF. ACF-deficient animals have multiple defects of chromatin organization. However, ACF is not essential for fly viability due to the presence of additional, redundant ACF-like factors. We discovered novel ISWI-containing complexes ToRC (comprising Tou, ISWI and CtBP) and RSF (comprising Rsf1 and ISWI) that can functionally substitute ACF in vivo. Our genetic and cytological analyses implicate the network of ATP-dependent, ISWI-containing chromatin assembly factors in diverse, partially redundant pathways of regulation of chromatin structure and activity.

SNF2-like protein CHD1 is another ATP-dependent nucleosome assembly factor. We disrupted Chd1 in flies and discovered that CHD1 is required for replication-independent deposition of histones into chromatin in vivo. Specifically, CHD1 is essential during early embryonic development for deposition of replacement histone H3.3 into paternal chromatin.

3. Higher-order chromatin forms

ACF can mediate deposition of both core and linker histones (H1) in vitro. Thus, it can assemble the 30 nm chromatin fiber in a defined system. To reconstitute other higher-order chromatin structures, we incorporate modified core histones, histone variants and heterochromatin proteins. In vitro assembled chromatin vectors can turn into useful tools in research and therapy. Among other outcomes, these studies will eventually lead to the discovery of techniques to reconstitute functional metazoan chromosomes.

To better understand the biology of H1 deposition into chromatin, we decided to first analyze the processes that are associated with elimination of H1 from chromatin in vivo. In collaboration with the lab of Dr. A. Skoultchi, we began to examine phenotypes of animals in which H1 is depleted in vivo by RNAi or genetic approaches. We discovered that H1 is the major component of heterochromatin and is required to establish its biochemical identity and functional properties. For instance, H1 recruits histone methyltransferase Su(var)3-9, which mediates dimethylation of lysine 9 of histone H3, a signature heterochromatin-specific epigenetic mark.
In sperm, DNA is compacted with protamines to form enzymatically static sperm “chromatin”. We have begun to analyze protein factors that mediate protamine deposition during spermatogenesis and their removal from DNA after fertilization. It turns out that sperm chromatin assembly and remodeling is mediated by a group of factors that are similar to core histone chaperones.

**Publications**


THE ROLE OF MACRODOMAIN-MEDIATED REGULATION OF CHROMATIN STRUCTURE AND FUNCTION DURING CANCER AND SENESCENCE

Macrodains are found in several histone variants, chromatin remodelers, and other transcriptional coregulators (e.g. macroH2A, PARP14, CHD1L) with roles in cancer progression, senescence, innate immune responses, and viral pathogenesis. These protein modules function, in part, as ligand binding domains for NAD+-derived poly(ADP-ribose), ADP-ribose, and O-acetyl-ADP-ribose. The ability of macrodomains to bind these ligands links the function of macrodomain-containing proteins (MDCPs) to NAD+-dependent signaling events catalyzed by enzymes such as PARP-1, PARG and SIRT1. Our laboratory employs a variety of cell-based, genomic and biochemical techniques to explore the role of macrodomains, their ligands and the NAD+-utilizing enzymes that produce them in transcriptional regulation and DNA damage responses.

The histone variant macroH2A is an MDCP of particular interest to our group. MacroH2A1 incorporates into nucleosomes found in large chromatin domains that occupy a quarter of the human genome. MacroH2A1 exists as one of two splice variants, macroH2A1.1 which can bind to NAD+-derived ligands, and macroH2A1.2 which cannot associate with these small molecules. Interestingly, while both macroH2A1 variants are present in normal adult cells, macroH2A1.1 splicing is decreased in a variety of human cancers including endometrial, lung, breast, ovarian, testicular, colon, and bladder cancer. Additionally, macroH2A1.1 can trigger an innate tumor suppressive pathway called oncogene-induced senescence. We are currently exploring the mechanisms that regulate macroH2A1 splicing, the specific roles of each macroH2A variant in transcriptional regulation and DNA damage responses, and how these processes are perturbed during oncogenesis.

Selected References:


The PI3 kinase Signaling Pathway in Adult Blood Development and Leukemia

My lab studies the signal transduction pathways that affect the early fate decisions of adult hematopoietic stem cells (HSCs) as they progress from an undifferentiated multipotent state to the generation of differentiated blood cells. When these early fate decisions go awry, this can lead to the formation of leukemia-initiating cells.

Roles of the PI3 kinase isoforms in adult blood development

PI3 kinase (PI3K) is a lipid kinase that is important for the regulation of metabolism, the cell cycle, apoptosis, and protein synthesis. In hematopoietic cells, there are four isoforms of the catalytic subunit of PI3K, each encoded by a separate gene. Emerging evidence suggests that these isoforms have unique functions in normal and cancer cells, but may substitute for each other in some contexts. We have generated a series of mouse knockout models that allow us to study the roles of each of these isoforms individually in adult hematopoiesis. For example, we have found that the p110alpha isoform is most important for red cell development, but is not required in normal blood stem cells. We have now also generated compound knockout mice to determine the redundant roles of the PI3K isoforms in blood development. We are studying how deletion of PI3K will impact normal HSC function, including self-renewal, proliferation, and differentiation along different blood lineages.

Roles of the PI3 kinase isoforms in leukemia

Acute myeloid leukemia (AML) is a genetically diverse disease, but activation of the PI3K pathway has been reported in up to 80% of cases. A subset of AML cell lines and AML patient samples respond to PI3K pathway inhibitors, but it is unclear how patients should be selected for potential response to these inhibitors. We found that RAS-mutated myeloid leukemias are particularly dependent on the p110alpha isoform of PI3K, and that pharmacologic inhibition of p110alpha can be used to treat both RAS-mutated cell lines and RAS-mutated leukemia in mice. Our future work will be focused on generating a more comprehensive understanding of the molecular determinants for PI3K dependence in hematologic malignancies. Furthermore, we plan to use cell lines, patient samples, and mouse models of leukemia to investigate the mechanisms of resistance to PI3K inhibition, with the goal of identifying new drug targets and designing new combination treatments for leukemia that incorporate PI3K inhibitors.

Selected Publications


Kharas, M.G. and Gritsman, K. Akt: A Double-Edged Sword for Hematopoietic Stem Cells. *Cell Cycle* 2010; Vol 9; Issue 7

Key Words: mammary gland, breast cancer, stem cells, metastasis

My lab is interested in two interlocking areas of stem cell biology: the molecular pathways that regulate the normal stem-cell state in the mammary gland, and the role of these pathways in the regulation of breast cancer stem cells.

Regulators of mammary stem cells

We have developed sensitive and specific mammary stem cell assays. Using these assays, we aim to identify novel markers and regulators of mammary stem cells.

In this effort, we identified two key transcription factors of mammary stem cells, Slug and Sox9. Both factors are necessary for maintaining endogenous mammary stem cells. Furthermore, ectopic expression of these factors efficiently converts differentiated mammary epithelial cells into long-term gland-regenerating stem cells. We are now investigating the mechanism of action by which these factors induce stem cells and regulate the epithelial cell hierarchy in the mammary gland.

Function of stem-cell pathways in breast cancer

Emerging evidence suggests that normal stem-cell pathways often get activated aberrantly in cancers and contribute to aggressive cancer behaviors. Identification of key normal stem cell regulators provides us a framework to understand how breast cancer stem cells are regulated. We are particularly interested in understanding the role of stem-cell factors in regulating metastatic colonization, a rate-limiting step of the metastatic cascade that involves cancer stem cells. In addition, we are interested in how cancer stem cells are regulated by the tumor microenvironment.

Selected Publications


Key Words: Hematopoietic stem cell, Leukemia, Myelodysplastic syndrome

Our research interests have focused on biomedical research aiming toward the development of stem cell therapies. In keeping with this commitment, our team’s long-term research goals are to define the critical regulatory pathways in the controlled equilibrium of stem cells, findings which will be relevant to therapy.

One of our main projects is to illuminate through both genetic and pharmacological approaches the role of one such potential regulatory element, cellular metabolism, in the cell fate decisions of hematopoietic stem cells (HSCs). Various molecular metabolisms have recently come into focus as novel regulatory elements of stem cell maintenance. Another study in the laboratory is investigating the pathogenesis of an incurable stem cell disorder, myelodysplastic syndrome (MDS). Our lab has devised a plan to identify key mechanisms of MDS pathogenesis for the development of targeted therapies to combat the disease more effectively.

Selected Original research and Theoretical treatises;


Selected Invited articles and Review articles


Molecular Mechanisms of Virus Entry and Exit.

For more information please see our lab homepage:

https://sites.google.com/site/kielianlab/

During infection all enveloped viruses use the essential steps of membrane fusion to enter a cell, and membrane budding to produce infectious progeny viruses. Molecular information on these processes is critical to understanding the infection pathways of enveloped viruses and as a key model for cellular membrane fusion and budding reactions.

Our research focuses on the molecular mechanisms of virus-membrane fusion and virus budding using alphaviruses and the closely related virus Rubella virus, and flaviviruses such as dengue virus (DENV). The flaviviruses and alphaviruses include many important human pathogens such as dengue, West Nile, and Chikungunya viruses, which cause millions of human infections each year. There are currently no vaccines or antiviral therapies for these viruses, and new strategies are urgently needed.

Alphaviruses, Rubella virus and flaviviruses enter cells by endocytic uptake and then fuse their membrane with the endosome membrane in a reaction triggered by the low pH of the endocytic vesicle. The membrane fusion proteins of these viruses are structurally related proteins and refold during fusion to a homotrimer conformation that mediates virus fusion and infection. In collaboration with Dr. Félix Rey, we determined the structure of the homotrimer of the alphavirus fusion protein E1. This structure is strikingly similar to the DENV homotrimer. Using the structures as a guide, our lab developed fragments of the alphavirus and DENV fusion proteins that act as dominant-negative inhibitors of virus fusion and infection. We have reconstituted trimer formation in vitro on target membranes using purified proteins.

Many important questions on the molecular mechanism of membrane fusion remain. We are investigating the mechanism of fusion protein insertion into the target membrane using in vitro reconstitution and fluorescent labeling approaches. Cooperative interactions occur between trimers in vitro but their functional role is controversial and untested. We seek to define these E1 contacts and to determine if they play a critical role for alphaviruses and for other fusion proteins. We are investigating the novel calcium requirement for the insertion of the Rubella virus fusion protein into target membranes.

During alphavirus and flavivirus biogenesis, a companion protein forms a closely-associated dimer with the fusion protein, and protects it from low pH and premature fusion during exocytic transport. This companion protein must then dissociate to permit virus fusion. We are studying these key pH protection and dissociation steps. The pH protection mechanisms for many other viruses are unknown, and we are using Rubella virus as a system to define novel mechanisms of pH protection.

Alphaviruses exit by budding through the plasma membrane of the infected host cell. Little is known about the budding of either alphaviruses or flaviviruses, although it is clear that budding is highly specific (excluding host proteins) and produces very organized virus particles. How does this happen and what are the roles of cellular and viral factors? We have developed fluorescently tagged alphaviruses to follow virus assembly and budding in real time in infected cells. We are investigating how the virus spreads from cell to cell, how the internal RNA-capsid core is recruited to the site of budding, and how the envelope proteins exclude host proteins from the budding site.
The cell plasma membrane and cytoskeletal network are extensively remodeled during budding and we are defining the mechanisms and signaling pathways that mediate remodeling. We carried out a genome-wide RNAi screen to identify host factors involved in alphavirus entry and exit, and we are currently defining the role of these novel proteins in the virus lifecycle.

Our lab uses a wide variety of approaches including molecular biology, virus genetics, protein biochemistry, live cell imaging, cell biology, fluorescence spectroscopy, small molecule and RNAi screens, and structural biology.

Potential research projects include: use of fluorescently tagged viruses to follow steps in virus assembly and budding, characterization of the role of viral and cellular factors in virus entry and exit, mutagenesis of virus infectious clones to characterize specific steps in fusion and pH protection.

Selected references:


Key Words: cell death/apoptosis/necrosis/heart disease/cancer/diabetes

Professional Interests

Cell Death: Fundamental Mechanisms and Roles in Human Disease

The most basic decision that any cell makes is to grow, differentiate, or die. Our laboratory is interested in basic mechanisms of cell death, and the roles of cell death in normal biology and human disease.

Basic Science

From a fundamental perspective, we are particularly interested in how different cell death pathways interconnect. In previous and ongoing work, we have explored this question using ARC, an endogenous inhibitor of apoptosis with the unusual property of inhibiting both extrinsic (death receptor) and intrinsic (mitochondrial/ER) apoptosis pathways (see Nam et al. Molecular Cell, 2004; Foo et al. PNAS, 2007; and others below). Our basic interests are currently focused on understanding how the pathways that mediate apoptotic and non-apoptotic cell death interconnect in what may be a unified program of cell death. In particular, we would like to understand the factors that determine whether a cell dies by apoptosis versus necrosis in the mitochondrial death pathway (see Whelan et al. PNAS, 2012). These studies involve a wide array of approaches including molecular and cellular biology, biochemistry, and chemical, mouse, and lower organism genetics.

Translational Science

Although our disease-related interests have ranged from cancer (see Wu et al. JBC, 2010; Medina-Ramirez et al. Cancer Res, 2011) to diabetes (see McKimpson et al. Diabetes, 2012), our major contributions involve heart disease, including myocardial infarction (“heart attack”) and heart failure (see reviews Whelan et al. Annu Rev Physiol, 2010; Kung et al. Circ Res, 2011; Konstantinidis et al. Arterioscler Thromb Vasc Biol, 2012). In collaboration with Dr. Evripidis Gavathiotis (Department of Biochemistry), we are employing a powerful combination of chemical biology, structural biology, biochemistry, molecular and cellular biology, and small and large animal in vivo models in an attempt to translate basic insights into cardiac cell death mechanisms into novel small molecule therapies to decrease heart damage during heart attacks.

Selected Publications


Mechanisms of RNA Processing

Intron removal, a defining feature of eukaryota, is catalyzed by the spliceosome, a 50-60S complex composed of five snRNAs and >100 proteins. Our laboratory investigates spliceosome assembly and catalysis and mechanisms of snRNP quality control. We formulated a model of spliceosome function based on thermodynamic equilibrium, which impacts our understanding of substrate selectivity, and we have developed orthogonal (or ‘designer’) spliceosomes to facilitate investigation of core RNA-RNA interactions.

Orthogonal systems for in vivo investigation of catalytic center interactions. During pre-mRNA splicing, the branch site (BS) base pairs with a phylogenetically invariant sequence in U2 snRNA, an interaction essential for spliceosome assembly and first-step catalysis. Investigation of the BS-U2 duplex was previously limited by the deleterious nature of mutations that disrupt BS-U2 pairing. We developed an orthogonal system wherein a dedicated second-copy U2 with grossly substituted BS-binding mediates splicing of a cognate reporter gene. This orthogonal BS-U2 pair produces a non-essential second spliceosome that allows in vivo characterization of the BS-U2 helix, first-step nucleophile positioning, and interaction with the spliceosome core, with few constraints. These properties allowed us to demonstrate that the BS-U2 structure exists at the time of first-step catalysis.

What is the second-step catalytic core? We used our orthogonal systems to elucidate the 3’S binding site within the second-step core, demonstrating that the branch structure formed in the first step translocates on a triplet repeat sequence in U2 (GUAGUA) and the 3’S then binds in a geometry analogous to that of the first-step nucleophile.

Do variant snRNAs make variant spliceosomes? One of the great ‘black holes’ in RNA biology is the identification of RNAs between 50 and 300 nts, which are simply missing in all modern-day sequencing datasets. Vertebrate genome sequences reveal hundreds of snRNA gene loci; however, with few exceptions, only the most abundant canonical snRNAs have been investigated. We are sequencing the snRNA transcriptome, asking which variants are expressed and if variant expression changes during development and impacts spliceosome function.

Also ongoing: Do miRNAs contribute to snRNA biogenesis? Do miRNA-snRNA interactions provide a Quality Control Mechanism for snRNP assembly? What are the mechanistic consequences of disease-related mutations in spliceosomal factors? What is the role of pseudouridine-modified nucleobases in the spliceosome core? How are conformational transitions of the spliceosome mediated?
Recent Publications
Our laboratory is studying how antibody-forming cells respond to antigen by undergoing somatic hypermutation and class switch recombination so that they can produce higher affinity antibodies with more useful effector functions. The molecular and biochemical mechanisms of antibody variable region hypermutation and class switch recombination is being studied in mice that have mutations in various repair proteins in collaboration with Dr. Winfried Edelmann. In order to examine detailed molecular mechanisms, we are also studying how mutation is targeted to antibody genes and some oncogenes in human Burkitt’s lymphoma cell lines which are undergoing variable region mutation in culture. These cell lines and genetically defective mice are being used to study the role of activation induced deaminase (AID), mismatch repair and error prone polymerases in the variable region hypermutation and isotype switching. The analysis of these events also involves the examination of AID activity biochemically and, in collaboration with Drs, Aviv Bergman and Thomas MacCarthy, computationally to analyze and simulate the details of the mutational activity. The highly mutagenic processes required to generate antibody diversity also leads to B cell lymphomas so we are trying to understand how AID causes mouse B cell lymphomas and human Chronic Lymphocytic Leukemia (in collaboration with Dr. Nicholas Choirazzi) and how mismatch repair protects B cells from undergoing malignant transformation while also contributing to the generation of antibody diversity.

We are also using somatic mutation and isotype switching to generate better monoclonal antibodies that will protect the host from lethal toxins and emerging infections.

Selected References:


Our laboratory is a part of the Einstein Center for Human Embryonic Stem Cell Research and the Cancer Center.

**Genome instability, cancer and aging disorders related to trinucleotide repeat expansion and telomere replication**

**Long term interests:**
- Genome protection by telomeres.
- Triplet nucleotide expansion diseases and aging.
- Role of common Fragile sites in human cancer.
- Regulation and reprogramming of DNA replication of human embryonic stem (ES) cells and induced pluripotent stem cells (iPS).

**Current projects include a wide range of interests:**
- Understanding trinucleotide repeat expansion and telomere maintenance to gain insights into aging related disorders.
- Defining mechanisms that ensure proper telomere replication to prevent telomere dysfunction that results in cellular senescence and cancer-promoting genetic instability.
- Mechanisms leading to breaks at common fragile sites that result in chromosomal rearrangements frequently detected in cancer cells.
- Triplet nucleotide expansion diseases. The fragile X premutation expansion to 55 – 200 CGGs affects ~ one in 200 women resulting in serious fertility problems and ataxia.
- Study of human ES cell DNA replication dynamics. Thorough understanding of replication programs to advance the availability of immunologically compatible hES cells for patients.

**SELECTED PUBLICATIONS:**


Our work is focussed on the travels of RNA within the cell: from the site of its birth to its ultimate biological destiny in the cytoplasm where it makes proteins in specific locations. All we have learned results from the development of new technology, known as in situ hybridization, to visualize specific nucleic acid sequences within individual cells. Using our approach, synthetic nucleic acid probes are labeled with a variety of detectors such as fluorochromes or antigens. Subsequently these molecules are hybridized to the cell and detected using high resolution digital imaging microscopy. This enables the detection of specific nucleic acid molecules within the structural context of the cell. We have developed imaging algorithms capable of detecting a single RNA molecule within a cell. As a result of this approach, we have found that specific RNA sequences are located in particular cellular compartments. An example is the messenger RNA for beta-actin which is located in the periphery of the cell where actin protein is needed for cell motility. These transcripts are not free to diffuse. The transcripts may be associated with a cellular matrix or skeleton from the moment of their synthesis through translation. We are investigating how this spatial information is encoded within the gene and how the RNA transcript is processed within the nucleus and then transported to its correct compartment in the cytoplasm resulting in asymmetric protein distribution. RNA localization also occurs in yeast. During budding, a nuclear factor represses mating type switching asymmetrically, only in the daughter cell. This is because the factor is synthesized only in the bud because the mRNA was transported there by an actomyosin system. This discovery allows us to investigate the genetic mechanism responsible for this RNA’s travels. In addition, we have constructed genetically modified yeast and mice carrying chimeric genes using recombinant DNA techniques to allow single mRNAs to be observed in living cells and tissues. In particular, we are focused on neuronal regulation of mRNA localization and translation. In this way the kinetics of the entire life cycle of an mRNA can be characterized, from birth to death.

Selected References:


Key Words: Chromatin, epigenetics, transcription, proliferation, differentiation, leukemia

Our laboratory is interested in understanding the mechanisms controlling mammalian development and cell differentiation. We study the epigenetic functions of chromatin proteins and transcription factors in control of gene expression in embryonic stem cells, in red blood cells, and in Drosophila. Our approaches involve directed gene inactivation and transgenesis in mice and Drosophila. We also study control of proliferation and differentiation in red blood cell progenitors and in leukemia cells in which normal development is disrupted. Currently there are two major projects underway in the lab.

Role of H1 Linker Histones and Chromatin Remodeling Factors in Chromatin Structure, DNA Methylation, the Histone Code, Gene Expression and Development in Mice and Drosophila. Recent studies show that posttranslational modifications of core histones (H2A, H2B, H3, H4) (the Histone Code) play a very important role in control of gene expression. The H1 linker histones are more diverse than the core histones. Mice contain 8 H1 histone subtypes including differentiation-specific and tissue-specific subtypes, whereas Drosophila has only one type of H1. H1’s are thought to be responsible for the final level of packaging DNA into the compact chromatin structure but we know very little about their role in gene expression and development. We are studying the functional roles of H1 linker histones by inactivating (knocking-out) specific H1 genes in mice and the single H1 in Drosophila. We are also reintroducing mutant H1 linker histones into H1 depleted mouse cells and flies, to perform structure-function studies. We have also established a new role for H1 histone in DNA methylation, genomic imprinting and establishment of the histone code. We are also studying the chromatin remodeling factor that assembles H1 histone into chromatin.

Control of Proliferation and Differentiation in Normal and Leukemic Blood Cells: In this project we are investigating how cell proliferation and differentiation are coordinated in normal blood cell development and how this coordination is disrupted in leukemia. We have investigating the molecular mechanisms for the cross talk between these two cellular programs in normal and leukemic blood cells. Our studies are focused on the relationships between the master transcription factors that control blood cell development and the cell cycle regulators (cyclins, cyclin-dependent kinases (cdks), cdk inhibitors and RB) that regulate the cell division cycle proliferation. This project includes genome-wide approaches involving chromatin immunoprecipitation and high throughput sequencing (ChIP-Seq) and gene expression profiling by RNA-Seq.

Selected Publications:


Glycan Functions in Development, Spermatogenesis and Notch Signaling

Glycosylation is the most abundant and varied post-translational modification of proteins and is a critical factor in regulating their biological functions. The complement of glycans that may be produced by an organism is called the GLYCOME. Changes in glycans expressed on the cell surface occur during development and differentiation. Specific glycans on Notch receptors modulate signal transduction by Notch ligands. This is a novel paradigm of signal transduction whereby the transfer of a single sugar residue alters the ability of Notch receptors to signal. We are using cell-based glycosylation mutants, Notch signaling assays, glycosyltransferase gene knockout mice, and biochemical approaches including MALDI-TOF mass spectrometry, to identify biological functions of growth factor receptor and Notch glycans, and the underlying mechanisms by which glycans mediate biological events.

Notch receptors span the cell membrane. When a Notch ligand like Delta or Jagged on an apposing cell binds to a Notch receptor, it induces cleavage of Notch extracellular domain, followed by a second cleavage that releases Notch intracellular domain. The Notch intracellular domain goes to the nucleus and activates target genes that ultimately lead to a change in cell fate or cell growth control. Using a CHO glycosylation mutant that adds few O-fucose glycans to Notch extracellular domain, we showed that Notch signaling is markedly reduced when fucose is limiting. Using a panel of different CHO glycosylation mutants developed in this lab, we showed that inhibition of Notch signaling by the Fringe glycosyltransferase requires the addition of a Gal residue to O-fucose glycans on Notch. We are continuing to use Notch signaling assays to define the mechanisms of action of Fringe and other glycosyltransferases that modulate Notch signaling. We are also targeting glycosyltransferase genes that encode enzymes that modify Notch in the mouse, and generating Notch mutants that cannot accept an O-fucose glycan at a specific site in Notch. Mice lacking O-fucose in the ligand binding domain have defective T cell development and are being investigated for other immunological defects. Mice lacking the three Fringe activities are affected in T and B cell development. The most recent modification of Notch is by O-GlcNAc and we are now exploring its functions in the regulation of Notch signaling in mammals.

We are also investigating a novel inhibitor of complex N-glycan synthesis that we discovered. It is expressed mainly in testicular germ cells in a highly regulated manner during spermatogenesis. Expression of this gene causes cells to bind strongly to Sertoli cells and we predict that it will be important for germ-Sertoli cell interactions necessary for spermatogenesis. We are testing this hypothesis by conditional deletion of the inhibitor in spermatogonia. We have also found that complex N-glycans are essential for male fertility and are testing the hypothesis that they play an important role in spermatid/Sertoli cell interactions.

Finally, Chinese hamster ovary (CHO) cell glycosylation mutants developed in this laboratory continue to be used as hosts to characterize orphan glycosyltransferases identified in genome databases. The genome encodes ~200 glycosyltransferase genes, many conserved through evolution, and the reactions they catalyze are not known for a significant orphan subgroup. We also use the CHO mutants to develop new methods such as a novel approach to tracking glycan epitopes on the cell surface.
Selected References


Transcriptional and Epigenetic Regulation of Pre-Cancerous and Cancer Stem Cells in Hematopoiesis and Leukemogenesis

Hematopoiesis maintains a life-long supply of the entire spectrum of highly specialized blood cells dependent on systemic needs. This process relies on a tightly regulated balance of self-renewal, commitment, and differentiation of a small number of pluripotent hematopoietic stem cells (HSC).

Recent experimental evidence has shown that acute myeloid leukemias (AML) and myelodysplastic syndromes (MDS) arise from transformed immature hematopoietic cells following the accumulation of multiple stepwise genetic and epigenetic changes in HSC and committed progenitors. The series of transforming events initially give rise to pre-leukemic stem cells (pre-LSC), preceding the formation of fully transformed leukemia stem cells (LSC). Pre-LSC as well as LSC are characterized by a relative resistance to chemotherapy and thereby contribute to treatment failure. As a consequence, and despite the established use of poly-chemotherapy and the development of new agents that transiently reduce the tumor burden, relapse continues to be the most common cause of death in most subtypes of AML and MDS. Defining the molecular characteristics and regulatory mechanisms in pre-LSC and their progression to fully transformed LSC is critical to understanding the genesis of leukemia and to developing therapeutic strategies by which these cells can be eradicated.

Recent findings from our own group and others have demonstrated a critical role of key transcriptional regulators, chromatin-remodeling factors, and mediators of aberrant signaling in the genesis and function of pre-LSC and LSC in AML and MDS in mouse and human model systems. The goal of our research is to delineate critical mechanisms in HSC that drive formation and function of pre-LSC and LSC. To identify and functionally study implicated pathways we are utilizing rigorously defined stem and progenitor cell subsets isolated by means of multi-parameter high-speed fluorescence-activated cell sorting (FACS). Identified target genes are biochemically and functionally tested. We utilize lentiviral gene transfer allowing for forced expression or shRNA-mediated knockdown, followed by in vitro as well as in vivo assays for stem and progenitor cell functions including murine transplantation models. This allows for assessing the function of candidate genes in normal and leukemic stem cells. We are studying murine genetic models as well as primary human samples from patients with leukemia. Our studies ultimately aim at the development of targeted, pre-LSC- and LSC-directed therapies.

Projects in the lab include:

- Studies of the function and mechanism of action of the non-clustered homeobox transcription factor HLX, and its therapeutic targeting for the treatment of AML and MDS.
- Study mechanisms of how reduced levels of PU.1 lead to pre-LSC formation, subclonal diversification, and progression to fully transformed LSC.
- Identification and study of novel genes/pathways governing normal and malignant hematopoiesis.
- Studies of the role of transcriptionally dysregulated genes in stem cells in AML patients (e.g. IL1RAP, PAK1, PU.1) and their suitability as therapeutic and prognostic targets (“stem cell MRD (minimal residual disease)").
- Development and preclinical testing of novel drugs/compounds targeting transcriptional and epigenetic regulators in pre-LSC in AML and MDS.
Selected publications:


Transcription Regulation and Cell Signaling Control in Normal and Lymphoma B cells

Molecular pathogenesis of lymphomas situates at the crossroad of B cell differentiation, cancer genetics, transcription regulation, and cell signaling. Thus, we constantly draw upon the most recent advances in these perspective fileds to address the mechanisms responsible for lymphoma initiation and development. As each lymphoma entity often corresponds to a specific lymphocyte activation/differentiation state that is phenotypically “frozen” by the malignant transformation process, our lymphoma-related studies also provide valuable insights to the regulatory mechanisms that govern the normal immune system. Our research has three major goals: to better understand mature B cell development in molecular terms, to decipher how this process is perturbed during lymphomagenesis, and to help develop better lymphoma therapy.

The germinal center (GC) response is a T-cell dependent B cell activation, expansion, and maturation process that has the unique property of generating high affinity antibodies and B cell memory. Because dysregulated GC responses contribute to the development of B cell lymphomas and autoimmune diseases, in-depth understanding of the control mechanisms governing the GC response has both immunological and clinical implications. GCs are dynamic and specialized structures in the secondary lymphoid organs where the B cell genome is subject to two types of genetic alterations catalyzed by AID (activation induced cytidine deaminase), e.g. Ig class switch recombination and somatic hypermutation. Prior to their GC exit, B cells bearing mutated surface Ig molecules undergo positive and negative selections through interaction with two other types of cells in the GC, e.g. follicular dendritic cells and follicular T helper cells. As a result, only those B cells with the proper Ig specificity and affinity are allowed to escape the fate of apoptosis or anergy, gaining license to terminally differentiate into memory or plasma cells. At the single cell level, the acquisition and termination of GC phenotype is the coordinated transcriptional response to various extracellular and intracellular stimuli; yet the precise sequence and nature of events that orchestrate this process is incompletely understood. We are particularly interested in the roles played by two transcriptional factors, BCL6 and STAT3. BCL6 coordinates the initiation of GC response and maintains the GC phenotype by regulating an extensive gene expression program which restricts B cell responsiveness to activation signals, genotoxic stress, and terminal differentiation potential. In the late phase of GC response, BCL6 downregulation triggers the rise of STAT3 expression and activity, which then collaborate with IRF4 to control the commitment step to the plasma cell fate.

Non-Hodgkin’s lymphoma (NHL) is the 5th most common type of cancer in the U.S. Many NHLs have a B cell phenotype and are transformed from normal GC B cells. It is well-documented that not only is AID responsible for Ig CSR and SHM, but its mutagenic action in non-Ig loci can cause tumorigenic mutations and chromosomal translocations in many B cell lymphomas. BCL6, in fact, was initially cloned through its involvement in lymphoma-associated chromosomal translocations and is the most frequently targeted proto-oncogene in NHL. Another important characteristic of mature B cell lymphomas is its heterogeneity. We are particularly interested in diffuse large B cell lymphoma (DLBCL), a heterogeneous type of NHL that accounts for 30-40% of
newly diagnosed NHL cases in the U.S. Based upon their gene expression similarities to either normal GC B cells or in vitro activated peripheral blood B cells, DLBCLs are subdivided into 3 groups: the GCB-DLBCL, ABC-DLBCL and an unclassified type III. In general, the GCB group expresses high levels of BCL6 and tends to respond better to conventional chemotherapy, while the ABC group has lower levels of BCL6, constitutively activated NF-κB and STAT3, and tends to be refractory to chemotherapeutic treatment. The distinct immunophenotypic and cell signaling properties of the two DLBCL subtypes have important implications in understanding their transformation pathways as well as facilitating development of biology-based, targeted lymphoma therapies. Our recent studies have focused on the role of STAT3 in post-GC plasma cell differentiation and novel roles in ABC-DLBCL pathogenesis and therapeutic response.

**Ongoing studies are designed to address the following questions:**
1. What are the cause and consequence of constitutively activated STAT3 in ABC-DLBCL?
2. What is the mechanistic basis underlying the survival disparity between the two DLBCL subtypes? Can a better understanding here lead to improved treatment strategies for ABC-DLBCL patients?
3. How is the expression status of BCL6 coupled to B cell differentiation control?
4. The role of Bcl6 as a mechatoblic regulator in the liver.

**Selected Publications:**


# JUNIOR FACULTY

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<td><strong>RESEARCH ASSISTANT PROFESSOR</strong></td>
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<tr>
<td>Boris Bartholdy (Steidl)</td>
<td>417</td>
<td>Chanin</td>
<td>7938</td>
<td><a href="mailto:boris.bartholdy@einstein.yu.edu">boris.bartholdy@einstein.yu.edu</a></td>
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<td><strong>ASSOCIATES</strong></td>
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<tr>
<td>Alexander Emelyanov (Fyodorov)</td>
<td>414</td>
<td>Chanin</td>
<td>4022</td>
<td><a href="mailto:alexander.emelyanov@einstein.yu.edu">alexander.emelyanov@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Srikanta Ghosh (Skoultchi)</td>
<td>402</td>
<td>Chanin</td>
<td>2168</td>
<td><a href="mailto:Srikanta.ghosh@einstein.yu.edu">Srikanta.ghosh@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Harry Hou (Bouhassira)</td>
<td>911</td>
<td>Ullman</td>
<td>2188</td>
<td><a href="mailto:harry.hou@einstein.yu.edu">harry.hou@einstein.yu.edu</a></td>
</tr>
<tr>
<td>KyeRyoung Lee (Edelmann)</td>
<td>269</td>
<td>Price</td>
<td>1087</td>
<td><a href="mailto:kyeryoung.lee@einstein.yu.edu">kyeryoung.lee@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Colette Prophete (Frenette)</td>
<td>107</td>
<td>Price</td>
<td>1204</td>
<td><a href="mailto:colette.prophete@einstein.yu.edu">colette.prophete@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Katie Stiles (Kielian)</td>
<td>515</td>
<td>Chanin</td>
<td>3639</td>
<td><a href="mailto:katie.styles@einstein.yu.edu">katie.styles@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Dr. Daqian Sun (Steidl)</td>
<td>601</td>
<td>Chanin</td>
<td>3551</td>
<td><a href="mailto:daqian.sun@einstein.yu.edu">daqian.sun@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Shanzhi Wang (Scharff)</td>
<td>403</td>
<td>Chanin</td>
<td>3504</td>
<td><a href="mailto:shanzi.wang@einstein.yu.edu">shanzi.wang@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Yong Wei Zhang (Edelmann)</td>
<td>269</td>
<td>Price</td>
<td>1087</td>
<td><a href="mailto:yongwei.zhang@einstein.yu.edu">yongwei.zhang@einstein.yu.edu</a></td>
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<td>416</td>
<td>Chanin</td>
<td>3193</td>
<td><a href="mailto:william.drosopoulos@einstein.yu.edu">william.drosopoulos@einstein.yu.edu</a></td>
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<tr>
<td>Britta Will (Steidl)</td>
<td>601</td>
<td>Chanin</td>
<td>3786</td>
<td><a href="mailto:britta.will@einstein.yu.edu">britta.will@einstein.yu.edu</a></td>
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<tr>
<td>Jeannine Gerhardt (Schildkraut)</td>
<td>416</td>
<td>Chanin</td>
<td>3193</td>
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<td>601</td>
<td>Chanin</td>
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<td><a href="mailto:ileana.antony-debre@einstein.yu.edu">ileana.antony-debre@einstein.yu.edu</a></td>
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<tr>
<td>Noboru Asada (Frenette)</td>
<td>101</td>
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<td>1204</td>
<td><a href="mailto:noboru.asada@einstein.yu.edu">noboru.asada@einstein.yu.edu</a></td>
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<tr>
<td>Travis Bernardo (Skoultchi)</td>
<td>402</td>
<td>Chanin</td>
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<td><a href="mailto:travis.bernardo@einstein.yu.edu">travis.bernardo@einstein.yu.edu</a></td>
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<tr>
<td>Alexander Birbrair (Frenette)</td>
<td>101</td>
<td>Price</td>
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<td><a href="mailto:alexander.birbrair@einstein.yu.edu">alexander.birbrair@einstein.yu.edu</a></td>
</tr>
<tr>
<td>Barnali Biswas (Stanley)</td>
<td>516</td>
<td>Chanin</td>
<td>3470</td>
<td><a href="mailto:barnali.biswas@einstein.yu.edu">barnali.biswas@einstein.yu.edu</a></td>
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<tr>
<td>Massimo Bonora (Ito)</td>
<td>102</td>
<td>Price</td>
<td>1279</td>
<td><a href="mailto:massimo.bonora@einstein.yu.edu">massimo.bonora@einstein.yu.edu</a></td>
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<tr>
<td>Philip Boulaïs (Frenette)</td>
<td>101</td>
<td>Price</td>
<td>1204</td>
<td>philip.boulaï<a href="mailto:s@einstein.yu.edu">s@einstein.yu.edu</a></td>
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<tr>
<td>Rebecca Brown (Kielian)</td>
<td>515</td>
<td>Chanin</td>
<td>3639</td>
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<tr>
<td>Luis Carvajal (Steidl)</td>
<td>601</td>
<td>Chanin</td>
<td>3786</td>
<td><a href="mailto:luis.carvajal@einstein.yu.edu">luis.carvajal@einstein.yu.edu</a></td>
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<tr>
<td>Xenia (Zhi) Duan (Scharff)</td>
<td>403</td>
<td>Chanin</td>
<td>3504</td>
<td><a href="mailto:zhi.duan@einstein.yu.edu">zhi.duan@einstein.yu.edu</a></td>
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<tr>
<td>Loïc Etienne (Kielian)</td>
<td>515</td>
<td>Chanin</td>
<td>3639</td>
<td><a href="mailto:loic.etienne@einstein.yu.edu">loic.etienne@einstein.yu.edu</a></td>
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<td>Patrick Ferrell (Steidl)</td>
<td>601</td>
<td>Chanin</td>
<td>3786</td>
<td><a href="mailto:patrick.ferrell@einstein.yu.edu">patrick.ferrell@einstein.yu.edu</a></td>
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<tr>
<td>Imit Kaur (Gritsman)</td>
<td>410</td>
<td>Chanin</td>
<td>6707</td>
<td><a href="mailto:imit.kaur@einstein.yu.edu">imit.kaur@einstein.yu.edu</a></td>
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<td>Vivek Kumar (Stanley)</td>
<td>516</td>
<td>Chanin</td>
<td>3470</td>
<td><a href="mailto:vivek.kumar@einstein.yu.edu">vivek.kumar@einstein.yu.edu</a></td>
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<td>Advaitha Madireddy (Schildkraut)</td>
<td>416</td>
<td>Chanin</td>
<td>3193</td>
<td><a href="mailto:advaitha.Madireddy@einstein.yu.edu">advaitha.Madireddy@einstein.yu.edu</a></td>
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<td>Maria Marianovich (Frenette)</td>
<td>101</td>
<td>Price</td>
<td>1204</td>
<td><a href="mailto:maria.marianovich@einstein.yu.edu">maria.marianovich@einstein.yu.edu</a></td>
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<td>Meng Liang (Stanley)</td>
<td>516</td>
<td>Chanin</td>
<td>3470</td>
<td><a href="mailto:meng.liang@einstein.yu.edu">meng.liang@einstein.yu.edu</a></td>
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<tr>
<td>Yun Mai (Ye)</td>
<td>413</td>
<td>Chanin</td>
<td>3339</td>
<td><a href="mailto:yun.mai@einstein.yu.edu">yun.mai@einstein.yu.edu</a></td>
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<td>Guadalupe (Maria) Martinez (Kielian)</td>
<td>515</td>
<td>Chanin</td>
<td>3639</td>
<td><a href="mailto:guadalupe.martinez@einstein.yu.edu">guadalupe.martinez@einstein.yu.edu</a></td>
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<td>Wendy McKimpson (Kitsis)</td>
<td>G01</td>
<td>Golding</td>
<td>2613</td>
<td><a href="mailto:wendy.mckimpson@phd.einstein.yu.edu">wendy.mckimpson@phd.einstein.yu.edu</a></td>
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<tr>
<td>Avital Mendelson (Frenette)</td>
<td>101</td>
<td>Price</td>
<td>1204</td>
<td><a href="mailto:avital.mendelson@einstein.yu.edu">avital.mendelson@einstein.yu.edu</a></td>
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<tr>
<td>Fumio Nakahara (Frenette)</td>
<td>101</td>
<td>Price</td>
<td>1204</td>
<td><a href="mailto:fumio.nakahara@einstein.yu.edu">fumio.nakahara@einstein.yu.edu</a></td>
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<tr>
<td>Sandra Pinho (Frenette)</td>
<td>101</td>
<td>Price</td>
<td>1204</td>
<td><a href="mailto:sandra.pinho@einstein.yu.edu">sandra.pinho@einstein.yu.edu</a></td>
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<tr>
<td>Hugo Pinto (Skoultchi)</td>
<td>402</td>
<td>Chanin</td>
<td>2168</td>
<td><a href="mailto:hugo.pinto@einstein.yu.edu">hugo.pinto@einstein.yu.edu</a></td>
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<td>Elena Tosti (Edelmann)</td>
<td>269</td>
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<td>1087</td>
<td><a href="mailto:elena.tosti@phd.einstein.yu.edu">elena.tosti@phd.einstein.yu.edu</a></td>
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<td>Shweta Varshney (Stanley)</td>
<td>516</td>
<td>Chanin</td>
<td>3470</td>
<td><a href="mailto:shweta.Varshney@einstein.yu.edu">shweta.Varshney@einstein.yu.edu</a></td>
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<td>Dagmar Walter (Steidl)</td>
<td>601</td>
<td>Chanin</td>
<td>3786</td>
<td><a href="mailto:dagmar.walter@einstein.yu.edu">dagmar.walter@einstein.yu.edu</a></td>
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<td>Qian Wang (Ito)</td>
<td>102</td>
<td>Price</td>
<td>1279</td>
<td><a href="mailto:qian.wang@einstein.yu.edu">qian.wang@einstein.yu.edu</a></td>
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<td>Chunhui Wang (Guo)</td>
<td>108</td>
<td>Price</td>
<td>1277</td>
<td><a href="mailto:chunhui.wang@einstein.yu.edu">chunhui.wang@einstein.yu.edu</a></td>
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<td>Qiaozhi Wei (Frenette)</td>
<td>101</td>
<td>Price</td>
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<td>Chuliang Xu (Frenette)</td>
<td>101</td>
<td>Price</td>
<td>1204</td>
<td><a href="mailto:chuliang.xu@einstein.yu.edu">chuliang.xu@einstein.yu.edu</a></td>
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<td>Zheng “Jim” Zhang (Guo)</td>
<td>108</td>
<td>Price</td>
<td>1277</td>
<td><a href="mailto:zheng.zhang@phd.einstein.yu.edu">zheng.zhang@phd.einstein.yu.edu</a></td>
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<td>G01</td>
<td>Golding</td>
<td>2613</td>
<td><a href="mailto:Dulguun.amagalan@phd.einstein.yu.edu">Dulguun.amagalan@phd.einstein.yu.edu</a></td>
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<tr>
<td>Stephen Braigen (Query)</td>
<td>415B</td>
<td>Chanin</td>
<td>4175</td>
<td><a href="mailto:stephen.braigen@phd.einstein.yu.edu">stephen.braigen@phd.einstein.yu.edu</a></td>
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<tr>
<td>Emily Byrd (Kielian)*</td>
<td>515</td>
<td>Chanin</td>
<td>3639</td>
<td><a href="mailto:emily.byrd@med.einstein.yu.edu">emily.byrd@med.einstein.yu.edu</a></td>
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<tr>
<td>Jiahao Chen (Steidl)</td>
<td>601</td>
<td>Chanin</td>
<td>3786</td>
<td><a href="mailto:jiahao.chen@phd.einstein.yu.edu">jiahao.chen@phd.einstein.yu.edu</a></td>
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<tr>
<td>John Christin (Guo)</td>
<td>108</td>
<td>Price</td>
<td>1277</td>
<td><a href="mailto:john.christin@phd.einstein.yu.edu">john.christin@phd.einstein.yu.edu</a></td>
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<td>Amanda Grieco (Bouhassira)</td>
<td>911</td>
<td>Ullman</td>
<td>3119</td>
<td><a href="mailto:amanda.grieco@phd.einstein.yu.edu">amanda.grieco@phd.einstein.yu.edu</a></td>
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<tr>
<td>Sean Healton (Skoultschi)*</td>
<td>402</td>
<td>Chanin</td>
<td>2168</td>
<td><a href="mailto:sean.healton@med.einstein.yu.edu">sean.healton@med.einstein.yu.edu</a></td>
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<tr>
<td>Dayle Hodge (Guo)*</td>
<td>108</td>
<td>Price</td>
<td>1277</td>
<td><a href="mailto:dayle.hodge@med.einstein.yu.edu">dayle.hodge@med.einstein.yu.edu</a></td>
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<tr>
<td>Ruth Howe (Steidl)*</td>
<td>601</td>
<td>Chanin</td>
<td>3786</td>
<td><a href="mailto:ruth.howe@med.einstein.yu.edu">ruth.howe@med.einstein.yu.edu</a></td>
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<td>Yun-Ruei Kao (Steidl)</td>
<td>601</td>
<td>Chanin</td>
<td>3786</td>
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<td>Halley Ketchum (Frenette)</td>
<td>107</td>
<td>Price</td>
<td>1204</td>
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<td>Brian Kosmyna (Query)</td>
<td>415B</td>
<td>Chanin</td>
<td>4175</td>
<td><a href="mailto:brian.kosmyna@phd.einstein.yu.edu">brian.kosmyna@phd.einstein.yu.edu</a></td>
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<td>Saima Limi (Skoultschi)</td>
<td>402</td>
<td>Chanin</td>
<td>2168</td>
<td><a href="mailto:saima.limi@phd.einstein.yu.edu">saima.limi@phd.einstein.yu.edu</a></td>
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<tr>
<td>Kelly Mitchell (Steidl)</td>
<td>601</td>
<td>Chanin</td>
<td>3786</td>
<td><a href="mailto:kelly.mitchell@phd.einstein.yu.edu">kelly.mitchell@phd.einstein.yu.edu</a></td>
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<tr>
<td>Richard Piszczatowski (Steidl)*</td>
<td>601</td>
<td>Chanin</td>
<td>3786</td>
<td><a href="mailto:richard.piszczatowski@med.einstein.yu.edu">richard.piszczatowski@med.einstein.yu.edu</a></td>
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<tr>
<td>Susana Rodriguez-Santiago (Query)</td>
<td>415B</td>
<td>Chanin</td>
<td>4175</td>
<td><a href="mailto:susana.rodriguezsantiago@phd.einstein.yu.edu">susana.rodriguezsantiago@phd.einstein.yu.edu</a></td>
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<tr>
<td>Robert Stanley (Steidl)*</td>
<td>601</td>
<td>Chanin</td>
<td>3786</td>
<td><a href="mailto:robert.f.stanley@med.einstein.yu.edu">robert.f.stanley@med.einstein.yu.edu</a></td>
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<td>Judy Wan (Kielian)</td>
<td>515</td>
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<td>Justin Wheat (Steidl)*</td>
<td>601</td>
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<tr>
<td>Cary Weiss (Ito)*</td>
<td>102</td>
<td>Price</td>
<td>1279</td>
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<td>Michael Willcockson (Skoultschi)*</td>
<td>402</td>
<td>Chanin</td>
<td>2168</td>
<td><a href="mailto:michael.willcockson@med.einstein.yu.edu">michael.willcockson@med.einstein.yu.edu</a></td>
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<tr>
<td>Eva Yang (Frenette)*</td>
<td>107</td>
<td>Price</td>
<td>1204</td>
<td><a href="mailto:eva.yang@med.einstein.yu.edu">eva.yang@med.einstein.yu.edu</a></td>
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<tr>
<td>Ali Zahalka (Frenette)*</td>
<td>107</td>
<td>Price</td>
<td>1204</td>
<td><a href="mailto:ali.zahalka@med.einstein.yu.edu">ali.zahalka@med.einstein.yu.edu</a></td>
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<tr>
<td>Dachaun Zhang (Frenette)</td>
<td>107</td>
<td>Price</td>
<td>1204</td>
<td><a href="mailto:dachaun.zhang@phd.einstein.yu.edu">dachaun.zhang@phd.einstein.yu.edu</a></td>
</tr>
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</table>

*MD/PhD Student