1. A wild type Drosophila eye anterioal disc stained for Emc (red), Da (green) and Sens (blue; Baker laboratory).

2. A mouse embryonic heart expresses green fluorescent protein in the endocardium (Zhou laboratory).

3. Cited3 functions in the survival of slow muscle cells in zebrafish embryo. S58 antibody specifically stains the slow-twitch muscle fiber specific myosin heavy chains in zebrafish embryo. The images are taken on the 3rd day-post-fertilization and correspond to the 17th-18th somites. Slow myofibers in wild-type embryos are well differentiated as shown in the left panel. When expression of cited3 is knockdown, however, the slow myofibers die due to apoptosis and hence the number of slow fiber is reduced as shown in the right panel. The myofibers’ lengths are shorter in the anterior-posterior direction; they are thinner and less in number. This results in drastic reduction in the dorsal-ventral width of somites. (Ozbudak laboratory).

4. Head of a live C. elegans hermaphrodite in which neurite specific heparan sulfate sugar structures are labeled (courtesy of Matthew Attreed, Buelow laboratory).

5. Spectral karyotyping of a mouse tumor metaphase (Montagna laboratory).

6. A composite image of a pancreatic neuroendocrine tumor (insulinoma) in an Men1 conditional knockout mouse. A PET scan showing the tumor in a live mouse and a confirmatory IHC section staining for insulin (red) and endothelial cells (green; Libutti laboratory).

7. Snapshot of a three dimensional model of three sex-specific neurons and their associated synapses in the C. elegans male tail. Volumetric reconstructions like the one above, along with wiring diagrams of the nematode nervous system, are used to address questions about nervous system development, synaptic specificity, the relationships between neuronal form and function, the neural circuits for goal-oriented behavior, and the genetics underlying these phenomena. (Emmons laboratory).

8. Fate mapping neural crest cells in Tbx1+/- embryo @ E10.5 (Morrow laboratory).

9. The HELP assay to study cytosine methylation genome-wide. Shown are data from mouse brain (red) and spermatogenic cells (green; Greally Laboratory).

10. The compound eye of Drosophila melano-gaster can be used as a powerful genetic tool. (Secombe laboratory).
Department of Genetics
## GENETICS FACULTY
### 2015-2016

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Room</th>
<th>Building</th>
<th>Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brett S. Abrahams</strong>, Assistant Professor</td>
<td>(secondary appointment, Neuroscience)</td>
<td>477</td>
<td>Price</td>
<td>310-347-9060</td>
</tr>
<tr>
<td><strong>Gil Atzmon</strong>, Assistant Professor</td>
<td>(primary appointment, Medicine/Endocrinology)</td>
<td>502B</td>
<td>Golding</td>
<td>430-3628</td>
</tr>
<tr>
<td><strong>Adam J. Auton</strong>, Assistant Professor</td>
<td>(secondary appointment, Epidemiology)</td>
<td>320</td>
<td>Price</td>
<td>678-1038</td>
</tr>
<tr>
<td><strong>Nicholas E. Baker</strong>, Professor</td>
<td>(secondary appointment, Developmental and Molecular Biology)</td>
<td>805</td>
<td>Ullmann</td>
<td>430-2854</td>
</tr>
<tr>
<td></td>
<td>(tertiary appointment, Ophthalmology and Visual Sciences)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nir Barzilai</strong>, Professor</td>
<td>(primary appointment, Medicine/Endocrinology)</td>
<td>701A</td>
<td>Belfer</td>
<td>430-3144</td>
</tr>
<tr>
<td><strong>Hannes Buelow</strong>, Associate Professor</td>
<td>(secondary appointment, Neuroscience)</td>
<td>709</td>
<td>Ullmann</td>
<td>430-3621</td>
</tr>
<tr>
<td><strong>Roy S. Chuck</strong>, Professor</td>
<td>(primary appointment, Chair, Ophthalmology and Visual Sciences)</td>
<td>3332 Rochambeau Ave., MMC</td>
<td>920-6665</td>
<td></td>
</tr>
<tr>
<td><strong>Ales Cvekl</strong>, Professor</td>
<td>(primary appointment, Ophthalmology and Visual Sciences)</td>
<td>123</td>
<td>Ullmann</td>
<td>430-3217</td>
</tr>
<tr>
<td><strong>Meelad Dawlaty</strong>, Assistant Professor</td>
<td></td>
<td>419</td>
<td>Price</td>
<td>678-1224</td>
</tr>
<tr>
<td><strong>Winfried Edelmann</strong>, Professor</td>
<td>(primary appointment, Cell Biology)</td>
<td>277</td>
<td>Price</td>
<td>678-1086</td>
</tr>
<tr>
<td><strong>Scott Emmons</strong>, Professor</td>
<td>(secondary appointment, Neuroscience)</td>
<td>703</td>
<td>Ullmann</td>
<td>430-3130</td>
</tr>
<tr>
<td><strong>Aaron Golden</strong>, Associate Professor</td>
<td>(joint appointment, Mathematical Sciences, YU)</td>
<td>353B</td>
<td>Price</td>
<td>678-1150</td>
</tr>
<tr>
<td><strong>John Greally</strong>, Professor</td>
<td>(secondary appointment, Medicine/Hematology)</td>
<td>322</td>
<td>Price</td>
<td>678-1234</td>
</tr>
<tr>
<td></td>
<td>(tertiary appointment, Pediatrics)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Susan Gross</strong>, Professor</td>
<td>(primary appointment, Clinical Obstetrics &amp; Gynecology and Women's Health)</td>
<td>509</td>
<td>Kennedy</td>
<td>430-3494</td>
</tr>
<tr>
<td></td>
<td>(secondary appointment, Pediatrics)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(tertiary appointment, Genetics)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Jean Hébert</strong>, Associate Professor</td>
<td>(primary appointment, Neuroscience)</td>
<td>104</td>
<td>Golding</td>
<td>430-3124</td>
</tr>
<tr>
<td><strong>Noboru Hiroi</strong>, Associate Professor</td>
<td>(primary appointment, Psychiatry &amp; Behavioral Sciences)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(secondary appointment, Neuroscience)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(tertiary appointment, Genetics)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
William R. Jacobs, Jr., Professor 555  Price 678-1079
(primary appointment, Microbiology & Immunology)

Andreas Jenny, Associate Professor 503  Chanin 430-4183
(primary appointment, Developmental and Molecular Biology)

Ganjam V. Kalpana, Professor 823  Ullmann 430-2354
(secondary appointment, Microbiology & Immunology)

Herb Lachman, Professor 103  Forchheimer 430-2428
(primary appointment, Psychiatry and Behavioral Sciences)
(secondary appointment, Medicine/Hematology)
(tertiary appointment, Genetics)

Jack Lenz, Professor 717  Ullmann 430-3715
(secondary appointment, Microbiology & Immunology)

Steven K. Libutti, Professor 3400 Bainbridge Ave., MMC 920-4231
(primary appointment, Vice-Chair, Surgery)

Wei Liu, Assistant Professor 117A  Ullmann 839-7926
(primary appointment, Ophthalmology and Visual Sciences)

Sridhar Mani, Professor 302D-1  Chanin 430-2871
(primary appointment, Medicine/Oncology)

Cristina Montagna, Associate Professor 401  Price 678-1158
(secondary appointment, Pathology)

Bernice Morrow, Professor 402  Price 678-1121
(secondary appointment, Obstetrics & Gynecology and Women’s Health)
(tertiary appointment, Pediatrics)

Ertuğrul M. Özbudak, Associate Professor 711  Ullmann 430-3241

Jayanta Roy-Chowdhury, Professor 523  Ullmann 430-2265
(primary appointment, Medicine/Gastroenterology & Liver Diseases)

Namita Roy-Chowdhury, Professor 523  Ullmann 430-2254
(primary appointment, Medicine/Gastroenterology & Liver Diseases)

Nicole Schreiber-Agus, Assistant Professor 623  Block (Mazer) 639-7911
(secondary appointment, Obstetrics & Gynecology and Women’s Health)

Julie Secombe, Associate Professor 809  Ullmann 430-2698

Simon D. Spivack, Professor 274  Price 678-1040
(primary appointment, Medicine/Pulmonary Medicine)
(secondary appointment, Epidemiology & Population Health)
(tertiary appointment, Genetics)

Yousin Suh, Professor 475  Price 678-1111
(secondary appointment, Medicine/Endocrinology)

Jan Vijg, Professor and Chair 450  Price 678-1151
(secondary appointment, Ophthalmology & Visual Sciences)
Daniel Weiser, Assistant Professor  
(primary appointment, Pediatrics)  
813  
Ullmann  
430-2181

Zev Williams, Assistant Professor  
(primary appointment, Obstetrics & Gynecology and Women's Health)  
475  
Price  
914-997-060

Zhengdong Zhang, Assistant Professor  
353A  
Price  
678-1139

Deyou Zheng, Associate Professor  
(primary appointment, Neurology)  
(tertiary appointment, Neuroscience)  
320  
Price  
678-1217

Bin Zhou, Professor  
(secondary appointment, Pediatrics)  
(tertiary appointment, Medicine/Cardiology)  
420  
Price  
678-1067
# RESEARCH FACULTY

## Department of Genetics

**2015-2016**

<table>
<thead>
<tr>
<th>Name (Mentor)</th>
<th>Title</th>
<th>Room</th>
<th>Building</th>
<th>Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brent Calder (Vijg)</td>
<td>Associate</td>
<td>B01</td>
<td>Van Etten</td>
<td>839-7225</td>
</tr>
<tr>
<td>Robert Dubin (Grealy)</td>
<td>Associate</td>
<td>353</td>
<td>Price</td>
<td>678-1166</td>
</tr>
<tr>
<td>Silvia Gravina (Vijg)</td>
<td>Associate</td>
<td>468</td>
<td>Price</td>
<td>678-1135</td>
</tr>
<tr>
<td>Tingwei Guo (Morrow)</td>
<td>Research Asst. Prof.</td>
<td>402</td>
<td>Price</td>
<td>678-1122</td>
</tr>
<tr>
<td>Hwa Jin Jung (Suh)</td>
<td>Associate</td>
<td>475</td>
<td>Price</td>
<td>678-1112</td>
</tr>
<tr>
<td>Stephan Knierer (Ozbudak)</td>
<td>Associate</td>
<td>711</td>
<td>Ullmann</td>
<td>430-2770</td>
</tr>
<tr>
<td>Xingyin Liu (Secombe)</td>
<td>Associate</td>
<td>809</td>
<td>Ullmann</td>
<td>430-4463</td>
</tr>
<tr>
<td>Shahina Maqbool (Grealy)</td>
<td>Research Asst. Prof.</td>
<td>157</td>
<td>Price</td>
<td>678-1163</td>
</tr>
<tr>
<td>Alexander Maslov (Vijg)</td>
<td>Research Asst. Prof.</td>
<td>468</td>
<td>Price</td>
<td>678-1153</td>
</tr>
<tr>
<td>Jorge Blanco Mendana (Baker)</td>
<td>Associate</td>
<td>805</td>
<td>Ullmann</td>
<td>430-2855</td>
</tr>
<tr>
<td>Wilbur Quispe (Mazlov)</td>
<td>Associate</td>
<td>468</td>
<td>Price</td>
<td>678-1135</td>
</tr>
<tr>
<td>Silvia Racedo (Morrow)</td>
<td>Research Asst. Prof.</td>
<td>402</td>
<td>Price</td>
<td>678-1122</td>
</tr>
<tr>
<td>David Reynolds (Morrow)</td>
<td>Associate</td>
<td>1203</td>
<td>Ullmann</td>
<td>929-246-6735</td>
</tr>
<tr>
<td>Michael Sagle (Montagna)</td>
<td>Associate</td>
<td>413</td>
<td>Price</td>
<td>678-1159</td>
</tr>
<tr>
<td>Jidong Shan (Montagna)</td>
<td>Research Asst. Prof.</td>
<td>413</td>
<td>Price</td>
<td>678-1155</td>
</tr>
<tr>
<td>Masako Suzuki (Grealy)</td>
<td>Research Asst. Prof.</td>
<td>319</td>
<td>Price</td>
<td>678-1571</td>
</tr>
<tr>
<td>Cagdas Tazeerslan (Suh)</td>
<td>Associate</td>
<td>475</td>
<td>Price</td>
<td>678-1112</td>
</tr>
<tr>
<td>Lan-hsin Wang (Baker)</td>
<td>Associate</td>
<td>805</td>
<td>Ullmann</td>
<td>430-2855</td>
</tr>
<tr>
<td>Bingruo Wu (Zhou)</td>
<td>Principal Associate</td>
<td>420</td>
<td>Price</td>
<td>678-1551</td>
</tr>
</tbody>
</table>
# POSTDOCTORAL FELLOWS

Department of Genetics

2015-2016

<table>
<thead>
<tr>
<th>Name (Mentor)</th>
<th>Telephone</th>
<th>Lab Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susmita Bagchi (Montagna)</td>
<td>678-1159</td>
<td>407 Price</td>
</tr>
<tr>
<td>Danny Ben-Avraham (Atzmon)</td>
<td>430-3628</td>
<td>502B Golding</td>
</tr>
<tr>
<td>Claude Bherer (Aouto)</td>
<td>678-1251</td>
<td>353 Price</td>
</tr>
<tr>
<td>John-Paul Bukowski (Dawlaty)</td>
<td>678-1210</td>
<td>413 Price</td>
</tr>
<tr>
<td>Ruben Nogales Cadenas (Zhang)</td>
<td>862-7224</td>
<td>B01 Van Etten</td>
</tr>
<tr>
<td>Xiao Dong (Vijg)</td>
<td>678-1135</td>
<td>468 Price</td>
</tr>
<tr>
<td>Coralie Drelon (Secombe)</td>
<td>430-4463</td>
<td>809 Ullmann</td>
</tr>
<tr>
<td>Simon Johnson (Suh)</td>
<td>678-1112</td>
<td>469 Price</td>
</tr>
<tr>
<td>Yoshiki Katsumi (Kalpana)</td>
<td>430-2404</td>
<td>823 Ullmann</td>
</tr>
<tr>
<td>Sevdenur Keskin (Ozbudak)</td>
<td>430-2770</td>
<td>711 Ullmann</td>
</tr>
<tr>
<td>Byunghyuk Kim (Emmons)</td>
<td>430-2249</td>
<td>703 Ullmann</td>
</tr>
<tr>
<td>Marianthi Kiparaki (Baker)</td>
<td>430-2855</td>
<td>805 Ullmann</td>
</tr>
<tr>
<td>Amit Kumar (Baker)</td>
<td>430-2855</td>
<td>805 Ullmann</td>
</tr>
<tr>
<td>Chang Hyun Lee (Baker)</td>
<td>430-2855</td>
<td>805 Ullmann</td>
</tr>
<tr>
<td>Run Lei (Dawlaty)</td>
<td>678-1210</td>
<td>413 Price</td>
</tr>
<tr>
<td>Jhih-Rong Lin (Zhang)</td>
<td>862-7224</td>
<td>B01 Van Etten</td>
</tr>
<tr>
<td>Pengfei Lu (Zhou)</td>
<td>430-1551</td>
<td>414 Price</td>
</tr>
<tr>
<td>Elaine Maggi (Montagna)</td>
<td>678-1159</td>
<td>407 Price</td>
</tr>
<tr>
<td>David Rhee (Golden)</td>
<td>678-1150</td>
<td>353B Price</td>
</tr>
<tr>
<td>Hanae Sato (Greally)</td>
<td>678-1570</td>
<td>314 Price</td>
</tr>
<tr>
<td>Yidong Wang (Zhou)</td>
<td>678-1551</td>
<td>414 Price</td>
</tr>
<tr>
<td>Donghong Zhang (Zhou)</td>
<td>678-1551</td>
<td>414 Price</td>
</tr>
<tr>
<td>Lei Zhang (Vijg)</td>
<td>678-1135</td>
<td>468 Price</td>
</tr>
<tr>
<td>Quanwei Zhang (Zhang)</td>
<td>862-7224</td>
<td>B01 Van Etten</td>
</tr>
<tr>
<td>Wen Zhang (Zhang)</td>
<td>862-7224</td>
<td>B01 Van Etten</td>
</tr>
</tbody>
</table>
# GRADUATE STUDENTS

Department of Genetics

2015-2016

<table>
<thead>
<tr>
<th>Name (Mentor)</th>
<th>Telephone</th>
<th>Lab Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maria Aivalioti (Baker)</td>
<td>430-2855</td>
<td>805 Ullmann</td>
</tr>
<tr>
<td>Grasiella Andrian (Montagra)</td>
<td>678-1159</td>
<td>407 Price</td>
</tr>
<tr>
<td>Erika Blumen (Kalpana)</td>
<td>430-2404</td>
<td>823 Ullmann</td>
</tr>
<tr>
<td>Ying Cai (Zhang)</td>
<td>862-7224</td>
<td>B01 Van Etten</td>
</tr>
<tr>
<td>Christopher Campbell (Autcn)</td>
<td>839-7223</td>
<td>B01 Van Etten</td>
</tr>
<tr>
<td>Kevin Celestrin (Buelow)</td>
<td>430-3622</td>
<td>709 Ullmann</td>
</tr>
<tr>
<td>Jonathan Chung (Morrow)</td>
<td>678-1122</td>
<td>408 Price</td>
</tr>
<tr>
<td>Steven Cook (Emmons)</td>
<td>430-2249</td>
<td>703 Ullmann</td>
</tr>
<tr>
<td>Brenda Gonzalez (Suh)</td>
<td>678-1112</td>
<td>469 Price</td>
</tr>
<tr>
<td>Kimberly Hammond (Suh)</td>
<td>678-1112</td>
<td>469 Price</td>
</tr>
<tr>
<td>Raven G. Harris* (Liu)</td>
<td>839-7926</td>
<td>117 Ullmann</td>
</tr>
<tr>
<td>Erica Hasten (Morrow)</td>
<td>678-1122</td>
<td>408 Price</td>
</tr>
<tr>
<td>Lourdes Martin Hernandez (Buelow)</td>
<td>430-3622</td>
<td>709 Ullmann</td>
</tr>
<tr>
<td>Qiyuan Hong (Ozbudak)</td>
<td>430-2770</td>
<td>711 Ullmann</td>
</tr>
<tr>
<td>Zhejun Ji (Baker)</td>
<td>430-2855</td>
<td>805 Ullmann</td>
</tr>
<tr>
<td>Andrew Johnston* (Greally)</td>
<td>678-1570</td>
<td>319 Price</td>
</tr>
<tr>
<td>Yu Kong (Auron)</td>
<td>839-7223</td>
<td>B06 Van Etten</td>
</tr>
<tr>
<td>Maria Lazaro-Pena (Emmons)</td>
<td>430-2249</td>
<td>703 Ullmann</td>
</tr>
<tr>
<td>Annelena LaPorte (Kalpana)</td>
<td>430-2404</td>
<td>823 Ullmann</td>
</tr>
<tr>
<td>Ke Li (Baker)</td>
<td>430-2855</td>
<td>805 Ullmann</td>
</tr>
<tr>
<td>Saima Limi (Cvekl)</td>
<td>430-3218</td>
<td>123 Ullmann</td>
</tr>
<tr>
<td>Mingyan Lin (Zheng)</td>
<td>430-2769</td>
<td>915 Kennedy</td>
</tr>
<tr>
<td>Wendy Lui (Zhau)</td>
<td>678-1077</td>
<td>414 Price</td>
</tr>
<tr>
<td>Albert Lowe (Liu)</td>
<td>839-7926</td>
<td>117 Ullmann</td>
</tr>
<tr>
<td>Stephanie Macchiarulo (Morrow)</td>
<td>678-1122</td>
<td>408 Price</td>
</tr>
<tr>
<td>Sheila Lola MacRae (Vijg and Singer)</td>
<td>678-1135</td>
<td>468 Price</td>
</tr>
<tr>
<td>Virginia Fagado Marco (Baker)</td>
<td>430-2855</td>
<td>805 Ullmann</td>
</tr>
<tr>
<td>Brandon Milholland (Vijg and Suh)</td>
<td>678-1112</td>
<td>469 Price</td>
</tr>
<tr>
<td>Julie Nadel (Greally)</td>
<td>678-1571</td>
<td>319 Price</td>
</tr>
<tr>
<td>Rebecca Nebel (Abrahams)</td>
<td>678-1203</td>
<td>469 Price</td>
</tr>
<tr>
<td>Danielle Pasquel (Mani)</td>
<td>430-2871</td>
<td>302 Chalin</td>
</tr>
<tr>
<td>Nelson Ramirez (Buelow)</td>
<td>430-3622</td>
<td>709 Ullmann</td>
</tr>
<tr>
<td>Kristian Said (Buelow)</td>
<td>430-3622</td>
<td>709 Ullmann</td>
</tr>
<tr>
<td>Kevin Shieh* (Golden)</td>
<td>862-7227</td>
<td>B01 Van Etten</td>
</tr>
<tr>
<td>Jian Sun (Cvekl)</td>
<td>430-3218</td>
<td>123 Ullmann</td>
</tr>
<tr>
<td>Archana Tare (Suh)</td>
<td>678-1112</td>
<td>469 Price</td>
</tr>
<tr>
<td>Jessica Tozour* (Greally)</td>
<td>678-1571</td>
<td>319 Price</td>
</tr>
<tr>
<td>Ryan White (Vijg)</td>
<td>678-1135</td>
<td>468 Price</td>
</tr>
<tr>
<td>Neil A. Wijetunga* (Greally)</td>
<td>678-1571</td>
<td>319 Price</td>
</tr>
<tr>
<td>Young Jae Woo (Abrahams)</td>
<td>678-1203</td>
<td>469 Price</td>
</tr>
<tr>
<td>Yizhou Zhu (Suh)</td>
<td>678-1112</td>
<td>475 Price</td>
</tr>
<tr>
<td>Sumaira Zamurrod (Secombe)</td>
<td>430-4483</td>
<td>809 Ullmann</td>
</tr>
</tbody>
</table>

*M.D./Ph.D. Students*
Neurodevelopmental Disease: From Human Genetics to Personalized Treatment

Efforts in our group are aimed at improving our understanding of disorders of human cognition and achieving better outcomes in patients. A key focus of the lab is the study of a four gene region on Chromosome 15. Risk for schizophrenia, epilepsy, dyslexia and developmental delay are increased in individuals with deletions at the 15q11.2 region. Reciprocal duplications may increase risk for autism.

Social media has allowed us to recruit 15q11.2 deletion and duplication families from all over the world into research and novel online phenotyping has identified domain specific cognitive impairments in deletion carriers. We are evaluating now whether internet delivered behavioral intervention is able to ameliorate the deficits we observe. Complementary investigations making use of MRI and iPSC technologies are providing key insights into mechanisms, and have given rise to an assay system that will enable rapid and cost effective identification of compounds tailored to benefit individuals in our cohort.

Website: http://www.einstein.yu.edu/labs/brett-abrahams/default.aspx?id=28778

Key Publications:


GIL ATZMON, Ph.D.

Epigenetic Profiling in Healthy Aging and Exceptional Longevity

Examples of epigenetic regulation of genome architecture and gene expression are paved across the evolutionary lineage. Even if only a small proportion of human genes are subject to similar effects, they may still play a major role in the phenotypic variation and susceptibility to diseases. My long-term research goal is to investigate changes in the epigenetic control of gene expression which may be one of the central mechanisms by which aging predisposes to many age-related diseases and therefore lifespan.

Despite some early work, the role of epigenetics in human life span and age related diseases has remained unexplored. Discovering that methylated loci are involved in the genetic control of cellular existence, modify the risk for age-related disease and influence mortality is a novel and extremely important concept that would significantly enhance our understanding of the biology of aging. In addition, accumulating evidence supports the notion that major age-associated diseases (such as diabetes, metabolic syndrome and cancer) are regulated by epigenetic alterations. Epigenetic changes may provide information on the pivotal points between healthy and sick stages in the lifespan of an individual. Hence, epigenetic changes could serve as landmarks of events such as onset of disease and these events can be tracked long after its occurrence (forms of epimutation and the Barker theory).

To test our hypothesis, we propose to employ a novel high-throughput genome-wide methylation assay, HELP-tag. Additionally, we will utilize a combination of large-scale epigenomic analysis (EWAS) to identify the most distinctive epigenetic loci that show greatest differential methylation. We will then perform Multi-locus validation for methylation status using MassARRAY. We will test expression of candidate loci to explore possible mechanisms of methylation regulation. We will combine these results with whole genome sequences to assess the interaction between the genetic blueprint and the environment as it manifested through epigenetic changes.

This research will further our understanding of the complexity of healthy lifespan process by identifying loci that when altered epigenetically have important ramifications for age-related diseases and lifespan. Validating the genes whose function is modulated epigenetically could lead to interventions to delay or even prevent the development of age-associated diseases.

Recent Publications:
ADAM AUTON, D.Phil.

Statistical and Population Genetics

As the price of DNA sequencing technologies continues to fall, large population genetic datasets are becoming available. One of the main interests of the lab is application of these large next-generation DNA sequencing datasets for the better understanding of the properties and evolution of the human genome. Our lab has been closely involved with the 1000 Genomes Project, which aims to construct a near-complete catalogue of common human genetic variation via low coverage, whole-genome sequencing of thousands of individuals from multiple populations around the world. We develop statistical models of evolutionary history to investigate the forces that have shaped genetic diversity in the modern human population. Of particular interest is the use of such models to understand how genetic recombination has shaped the patterns of genetic and haplotype diversity throughout the genome.

For more details of our research, please see our website: http://autonlab.einstein.yu.edu/

Recent Publications:

NICHOLAS E. BAKER, Ph.D.

Fundamental mechanisms of growth and development

Development requires the control of growth and morphogenesis in addition to cell type specification. Growth stops with terminal cell cycle exit and must be up-regulated for regeneration, tissue regulation, or response to damage. Many diseases involve disorders in these events. To study these processes in intact animals, we molecular and genetic manipulation of the fruitfly *Drosophila melanogaster*, which permits in vivo studies not yet possible in most organisms. We are also employing mathematical models to understand cell-cell interactions fully.

Current projects include:
1) ‘Cell competition’ is a process that occurs between cells that differ in growth, for example because of different expression levels of ribosomal protein genes or of the proto-oncogene myc. It is thought that cell competition may exist to identify and eliminate aneuploid cells, or progenitor cells with reduced fitness, and that cell competition suppresses cancer and genome damage during aging. We have identified multiple genes that are required for cell competition and are studying the molecular mechanisms of this process and its contributions to aging and cancer in flies and mice.
2) HLH proteins represent a well-known class of transcription factors that are important in development. Their ubiquitously-expressed heterodimer partners are implicated in a very wide variety of diseases. We are studying how they are controlled both to allow differentiation and to promote or suppress progenitor cell proliferation, processes that underly human diseases such as Pitt-Hopkins Syndrome, schizophrenia, Fuchs corneal dystrophy, Rett syndrome, and atherosclerosis.

These basic processes that balance growth against terminal differentiation are so fundamental to multicellular organisms that they contribute to understanding many normal and pathological processes. The processes we study are relevant to human diseases including many cancers, cellular senescence, diabetes, Diamond Blackfan Anemia, neuronal dendrite development, multiple neurodegenerative diseases, polycystic kidney disease, Sjogren’s Syndrome, and developmental changes associated with pregnancy and lactation.

For more details, and complete list of publications, please see our website at http://fruitfly4.aecom.yu.edu/index.html

Selected recent publications


NIR BARZILAI, M.D.

Searching for Longevity Genes in Humans

Why do some people live much longer than others? What allows these individuals to escape age-associated diseases that contribute to mortality in the elderly? Is this a result of favorable genes or merely a healthy lifestyle? If the genome does play a role, what are the mechanisms?

To address these questions, we recruited over 1500 Ashkenazi Jews. The Ashkenazi Jewish population is unique as it is derived from a small number (several thousands) of founders and therefore it is genetically homogeneous. This population has been utilized for identification of several genes, a prominent example being the breast cancer gene. The subjects fall into three groups; probands, subjects with exceptional longevity (1:10000 in the general population); their offspring; and a control group consisting of spouses of the offspring and other Ashkenazi Jewish people recruited from the Einstein Aging Study.

Studying the clinical and metabolic phenotype, revealed certain physiological characteristics in the centenarians and their offspring such as high levels of high-density lipoprotein (HDL), high adiponectin levels, and high IGF-1 levels. In collaboration with Dr. Atzmon and Suh, we showed that each of those phenotype is now associated with a genotype that has a functional meaning, and each of those genotypes have been validated independently in at least one other population of centenarians. One of the genotypes is also specifically protective from cognitive decline, and this was also validated as an Alzheimer’s protective gene. We studied telomere length demonstrating longer telomeres in our longest living subjects and their offspring compared to control. These findings may indicate longer telomeres at birth or slower attrition rate in their length, and this was associated with a specific haplotype of the telomere gene. Most important, since the trait of longer telomeres is associated with protective lipoprotein profile and less age-related disease, this test may be used as a predictor for longevity.

Using an un-biased approach we have employed an Affimetrix 6.0 platform with almost 2MM markers and across the genome. Comparing the centenarian genotype to a younger un-related control, we established 35 genotypes that increase monotonically with aging (from age 60 to 112) and were linked significantly (p<10-6) to genes that have not been previously linked to aging. In collaboration with Drs. Greally and Atzmon, we have used high throughput methylation assay (HELP) to demonstrate that centenarians methylation pattern across the genome is significantly different than in younger un-related subjects.

Our lab has trained many graduates and post-docs, and the latest graduate, Reid Thompson, MD/Ph.D. student, can be a reference. We offer a clinical platform for variety of genomic studies in collaboration with many of the Einstein faculty.

Recent Publications:
HANNES E. BUELOW, Ph.D.

Genetics of Nervous System Development

My lab uses the small nematode C. elegans with its simple and well characterized nervous system as a genetic model. We are trying to understand how growing axons and dendrites navigate the extracellular space to connect to their partners and be appropriately patterned.

The extracellular space is filled with a complex mixture of proteins and proteoglycans e.g. heparan sulfate (HS) proteoglycans which are a particular focus of the lab. We are asking how specific modification patterns of the polysaccharide HS determine the path of developing axons. For instance, we have shown that distinct modification patterns in HS serve specific and instructive functions during neural development leading us to formulate the ‘HS code’ hypothesis. We propose that defined combinations of modifications in the sugars of HS contain information and generate a molecular map that helps shape the nervous system. Our goal is to decipher the information contained in HS, determine the factors that create and modulate it and describe the genes that respond to it. We are also investigating a pathological dimension of HS by studying Kallmann Syndrome, a human genetic disease with specific neurological defects in which we have identified mutations in HS genes.

In another project we are studying the development of dendrites in polymodal multidendritic neurons of C. elegans. We are aiming to understand how the complex dendritic arbors that resemble menorah-like candelabras are patterned. In summary, we are using genetic approaches coupled with biochemical and advanced imaging approaches to understand the function of genes involved in development and disease of the nervous system.

Recent Publications:


Roy S. Chuck, MD, PhD

Ocular Surface Disease and Repair

My team has developed a unique mouse model of human dry eye syndromes via blockade of neurotransmission in tear production within the lacrimal gland. To accomplish this goal, we use botulinum toxin (the same compound used to remove facial wrinkles!). The resulting dry eye at the ocular surface mimics that found in humans and allows simple high throughput testing of preclinical therapeutics and devices for dry eye. In extreme dry eye damage states, the ocular surface can become stem cell deficient. Because my group is one of but a few that performs corneal epithelial stem cell replacement surgery regularly in humans, utilization of this titratable animal model of ocular surface damage will allow for better understanding of human stem cell deficiency as it affects ocular surface disease. The other arm of my team's research program employs our expertise in bioengineering to create new tools and devices for laboratory investigation and surgical therapy. Among the devices which we have developed are a non-invasive microscopic tool for mitochondrial detection and potential stem cell isolation, laser systems for corneal transplantation currently in early clinical use, an implantable intraocular pressure monitor which would allow for continuous monitoring of intraocular pressure, and the Trabectome, a new and increasingly popular surgical approach for glaucoma treatment now in widespread clinical use in the United States.

Recent Publications:
ALEŠ CVEKĻ, Ph.D.

Genetic and Epigenetic Regulatory Mechanisms in Mammalian Eye Development and Ocular Diseases

We are studying molecular mechanism of temporal and spatial regulation of expression of tissue-specific genes during mammalian development. We use an integrative approach to identify and characterize specific DNA-binding transcription factors and their co-activators interacting with proximal and distal regulatory regions of genes whose expression is coordinately regulated during development. We also study the dynamics of covalent modifications of core histones associated with these genes. Finally, we are interested in the developmental roles of ATP-dependent chromatin remodeling enzymes Brg1 and Snf2h and histone acetyltransferases CBP and p300, and somatic variants of linker histone H1.

Our prevailing model system is the ocular lens. Because of its unique morphology, lens is an advantageous tissue to study molecular mechanisms of embryonic induction, cellular differentiation, intercellular signaling and aging. Lens progenitor cells are formed as a result of multiple signals exchanged between the head surface ectoderm surrounding the anterior neural plate, the pre-placodal region, and lateral mesoderm. Lens precursor cells and terminally differentiated lens cells are marked by the expression of crystallin genes. Lens development as well as lens expression are regulated by a sparse number of genes encoding transcription factors such as Pax6, c-Maf, Gata3, Hsf4, Prox1, Six3, Sox1 and Sox2 expressed in the lens. These genes act in concert with various signal transduction pathways notably FGFs, BMPs/TGF-β and Wnts. These genes either control the entire process of eye development (Pax6) or its specific stages. Mutations in these genes are responsible for a wide spectrum of human congenital eye diseases (aniridia, early onset cataract, and glaucoma). Our primary focus is on the Pax6-dependent gene regulatory network. Pax6 is considered a "master" gene for eye development. Thus, studies on Pax6 are both important for understanding of eye development and evolution of visual systems.

To study mechanisms of human eye diseases, we employ human ES cell differentiation towards lens and retinal organoids, and retinal pigmented epithelium (RPE). We developed a procedure to generate large quantities of lens progenitor cells from human ES cells. This finding allows us to investigate the molecular mechanisms of lens lineage formation and to develop procedures to differentiate these cells into lentoid bodies. We are also interested to employ retinal pigment epithelial cells from age-related macular degeneration patients and probe function of genes, which provide anti-stress and anti-inflammatory responses. Our long-term goal is to identify novel genes and pathways involved in this disease and identify genes with protective roles in age-onset cataract and in age-related macular degeneration.

Recent Publications:
MEELAD DAWLATY, Ph.D.

Investigating the epigenetics of stem cells, development and cancer using genetically modified pluripotent stem cells and mice

Our research focuses on understanding the epigenetic mechanisms governing the biology of stem cells, development and cancer with an emphasis on the role of DNA modifying enzymes DNMTs and Tets in DNA (de)methylation and hydroxymethylation in pluripotent, multipotent and germ cells. We utilize embryonic stem cells, induced pluripotent stem cells and mice as model systems to study how these enzymes reshape the epigenome and regulate development and cancer. The lab specializes in state-of-the-art technologies of genome engineering in mouse and human embryonic stem cells and iPSCs and generating complex strains of conditional, inducible, transgenic and knockout mice to dissect epigenetic pathways and mechanisms in vitro and in vivo. For more details on our research see previous work (Dawlaty et al Cell Stem Cell 2011, Dawlaty et al Developmental Cell 2013, Dawlaty et al Developmental Cell 2014, Rudenko & Dawlaty et al Neuron 2013, Cimmino and Dawlaty et al Nature Immunology 2015).

Lab website: http://dawlatylaboratory.weebly.com/

Selected publications:
WINFRIED EDELMANN, Ph.D.

Genomic Instability and Cancer

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, MIN). 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. These steps are carried out by exonucleases, polymerases and a number of replication associated proteins. In addition to correcting DNA mismatches, the MMR system mediates an apoptotic response to DNA damage and suppresses recombination between non-identical sequences in mammalian genomes. All of these functions are thought to be important for genome maintenance and tumor suppression. We have generated knockout mouse lines with inactivating mutations in all the different MMR 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 and the response of tumors to chemotherapeutic treatment. They have also revealed that some of the MMR proteins play essential roles in the control of meiotic recombination in mammals.

Selected References:
SCOTT W. EMMONS, Ph.D.

Development and Function of Neural Circuits, Connectomics

How complex neural circuits form and how they function are major unsolved problems in neurobiology. The field of connectomics is emerging as a significant focus of today’s neuroscience research. We determine connectivity in the nervous system of the nematode Caenorhabditis elegans using serial section electron microscopy. We have established one of a small number of connectomics centers nationally with state-of-the-art sectioning and microscopy capabilities. The new technology allows us to determine complete animal connectomes much more rapidly than before. We have determined the connectome (complete wiring diagram) of the C. elegans adult male and have reinterpreted previously-published micrographs (by others) of the hermaphrodite. Our data allows quantitative analysis of patterns of connectivity using analytical methods from network and graph theory. Future studies will focus on the connectomes of larval stages and the possibility that experience modifies connectivity.

The patterns of neural connections revealed by the electron microscopic reconstructions pose a challenge for the geneticist and developmental biologist to understand how such a complex structure is encoded in the genome and built during development. We are interested in identifying the elusive class of proteins that encode the molecular determinants of synaptic specificity. Our strategy is to determine the expression patterns of neural cell adhesion and recognition genes across a neural network of known connectivity. We postulate that correlations between the expression patterns and connectivity will reveal clues as to the identities of the cell labels that allow for programmed cell-cell recognition for synapse formation. These clues will be tested in genetic experiments making use of transgenes that express fluorescent proteins targeted to specific synapses.

Visit our website: www.worms.aecom.yu.edu and www.wormwiring.org

Selected Recent Publications:
AARON GOLDEN, Ph.D.

Genome, Epigenome and Microbiome Informatics

The lab is focused on the application of novel informatics techniques to contemporary problems in the 'omics domain. These range from new methods of visualizing and representing complex datasets to more efficient approaches to “stream” process information as it is being generated, and involve the use of machine learning algorithms and accelerated hardware environments. This emphasis on technological innovation also applies to working with other groups on campus in the development of novel RNA therapeutic structures, the optimization of biomedical imaging algorithms and the identification of biomarkers amongst diverse empirical datasets.

Projects are also underway on the development of new approaches to data warehouse clinical genomics datasets, the use of national cyberinfrastructure resources to process the largest datasets, and an examination of how the oral and gastrointestinal microbiome responds to external perturbations, such as radiation and chemotherapy.

The ‘lab’ consists of the school’s High Performance Computing cluster, and in particular, Leo, a supercomputer which possesses 2 B of RAM and a cluster of graphics processing units capable of 2 Teraflops sustained computation. We speak Python, R, C, C++, Java and, under duress, Perl. For more details of our research, please see our website: http://goldenlab.einstein.yu.edu/

Selected Recent Publications


JOHN M. GREALLY, M.B., B.Ch., Ph.D.

Epigenomics in Human Disease

The genome is used in different ways in multicellular organisms to establish and to maintain cellular differentiation and fates. Transcriptional programming of this type requires some ability to maintain a memory of a differentiation state through cell division, a property usually described as epigenetic. The mediators of such epigenetic regulation potentially include the positioning, types and post-translational modifications of histones within nucleosomes, the methylation of DNA, the influence of short RNAs and chromatin looping in three dimensions.

The malleability of the epigenetic and transcriptional programs in the cell allow adaptation to the environment. However, the same adaptive and flexible processes used to the cell’s advantage can acquire errors and lead to pathological changes. As a consequence, genome-wide epigenetic studies (referred to as epigenomic studies) can give insights into disease states, originally exemplified by cancer, but now including everything from diabetes mellitus to Alzheimer’s disease.

The Greally lab has interests in both basic science and clinical research, focusing on epigenomic processes. We have a long-standing interest in cytosine methylation, having developed genome-wide assays that interrogate not only promoters of genes but also the other genomic contexts that are usually ignored, finding patterns of regulation in normal cells that serve to guide understanding of changes observed in human disease states. The question of how this methylation mark is read by the cell has prompted us to initiate a program in structural epigenomics with colleagues in Biochemistry, and the development of a new approach to identify R-loop forming DNA in mammalian cells. Our human disease interests include type 2 diabetes mellitus arising as a consequence of intrauterine growth restriction, chronic kidney disease, Huntington’s disease, asthma and allergy, breast cancer, and viral infection of cells.

We recognize that computational skills are now an essential part of epigenomics research, making this a major focus of the lab. The same combination of molecular and computational approaches to study basic science and clinically-relevant questions defines Einstein’s Center for Epigenomics, directed by the PI, bringing new technological and computational resources to Einstein as a whole.

Recent Publications:
JEAN HÉBERT, Ph.D.

Generating and Regenerating the Neocortex

The Hébert lab has two main focuses: first, understanding how a simple sheet of neuroepithelial cells early in embryogenesis develops into the adult neocortex, the part of our brains that we use for our highest cognitive and perceptual functions; and second, devising methods for regenerating the principle neurons of the adult neocortex when they are lost. For both interests, we use primarily molecular genetic techniques to manipulate the expression of regulatory genes in neural precursor cells in mice. More specifically, our two main goals are: 1) to understand how one class of genes, those that encode components of the FGF signaling pathway, regulate the behavior of neural precursor cells during development and in the adult forebrain; and 2) to establish paradigms for regenerating widely dispersed glutamatergic neurons in the adult neocortex using engineered neural precursor cells. As a secondary focus, we are also exploring the long-term effects of inner ear defects on forebrain function.

Selected Publications


NOBORU HIROI, Ph.D.

Genetic Bases of Nicotine Addiction and Developmental Neuropsychiatric Disorders

The primary aim of this laboratory is to more fully understand the genetic bases of nicotine dependence and 22q11 syndrome.

**Nicotine dependence:** Among those who initiate smoking, only one-third develop dependence and addiction. Individuals who develop dependence often exhibit pre-existing behavioral traits. There are many genes that likely contribute, in complex ways, to individual variations in the development of nicotine dependence. Identification of such genes has been difficult in humans. Nicotine dependence includes tolerance, withdrawal, cue reactivity, and many other elements. These elements are likely to have distinct neural and genetic substrates. Additionally, it is thought that multiple genes affect nicotine dependence in a complex way. Mouse models provide a unique opportunity to examine the precise ways that individual genes alter different elements of nicotine dependence. We use diverse behavioral paradigms to examine how specific genes contribute to elements of nicotine dependence in genetically engineered mice. Our studies have revealed that the transcription factor FoxB, monoamine oxidase A, and cGMP-dependent protein kinase (PKG) are required for nicotine cue reactivity and stress-related behavioral traits. We are currently using lentiviral vectors to identify specific brain regions in which genes mediate the expression of nicotine cue reactivity.

**22q11 and neuropsychiatric disorders:** The human genome includes many variations, ranging from duplications and deletions of full chromosomes to single nucleotide polymorphisms. Moreover, a large number of kilo- to mega-base copy number variations (CNVs) are associated with autism spectrum disorder, mental retardation, and schizophrenia. Human chromosome 22q11.2 contains CNVs. Children and adolescents with 22q11.2 duplications and deletions consistently exhibit these neuropsychiatric disorders, along with associated cognitive and intellectual impairments during development. However, the diagnosis of these neuropsychiatric disorders is challenged by variations in diverse cognitive and intellectual capacities. Thus, patients with the same diagnosis may vary greatly in specific symptoms. Moreover, because duplications and deletions of 22q11.2 encompass 1.5 Mb or larger regions, it is not possible to determine whether segments or single genes are responsible for specific phenotypes in humans. To circumvent these obstacles, our laboratory examines the role of individual 22q11 genes in distinct aspects of behavior in genetically engineered mice. We have identified two small human 22q11.2 segments whose over-expression during development causes behavioral phenotypes consistent with neuropsychiatric disorders. Our current work examines the role of each of the genes encoded in the segments in behavioral phenotypes relevant to neuropsychiatric disorders in mice.

**Recent Publications:**


Extensively Drug-Resistant *Mycobacterium tuberculosis*: The Death Defying Pathogen

Tuberculosis, caused by *Mycobacterium tuberculosis*, causes one in four avoidable deaths in the Third World and kills more adults than malaria, AIDS, and all tropical diseases combined. In recent years, there has been a dramatic increase in the number of new TB cases worldwide - one of the consequences of the AIDS epidemic. In addition to these increasing incidences of TB, there has been an emergence of *M. tuberculosis* strains that are resistant to all seven anti-tuberculosis agents. These alarming trends have caused the World Health Organization to declare tuberculosis a global health emergency, a distinction never accorded another disease. My laboratory has focused on developing systems to genetically manipulate mycobacteria, particularly *M. tuberculosis*. These tools have allowed us to 1) develop the luciferase reporter phage assay for rapid assessment of drug susceptibilities; 2) analyze the genes involved in resistance to tuberculosis drugs such as isoniazid, ethionamide, ethambutol, and pyrazinamide, 3) to identify specific phenotypic properties associated with tuberculosis pathogenesis, and 4) develop recombinant mycobacteria vaccines. Current research efforts are employing a newly developed transposon mutagenesis system to identify genes of *M. tuberculosis* that are required for growth and persistence in mice. Additionally we have developed a high-throughput system for knocking out each gene in *M. tuberculosis*. This set of knockouts is a valuable resource for understanding important pathways and gene functions in *M. tuberculosis*. This knowledge should lead to the development of novel tuberculosis drugs and attenuated mutants of *M. tuberculosis* that can be used as live-cell tuberculosis vaccines. In addition, we have used genes from mycobacteriophages to make *Plasmodium falciparum*, the causative agent of malaria, more genetically tractable.


Recent Publications:


ANDREAS JENNY, Ph.D.

Canonical and non-canonical Wnt signaling: patterning and cell polarization

Wnt/Wingless (Wg) growth factors commonly signal through either the canonical Wnt (Wg)-Frizzled (Fz)/β-catenin pathway or through non-canonical Wnt pathways such as the Wnt/Fx-planar cellular polarity (PCP) pathway, resulting the polarization of cells within the plane of the epithelium. These two pathways are highly conserved between humans, mice, fish, and flies. Canonical Wnt/β-catenin signaling is essential for many aspects of development. For example in vertebrates, it controls the specification of the dorsal-ventral (D-V) embryonic axis, cell proliferation in many tissues, and the maintenance of stem cells and during vascularization. In addition, aberrant canonical Wnt signaling in humans causes cancer. Our lab studies the function of Wnk kinases, for which we have identified a novel role in Wnt signaling in addition to their well-known role in the regulation of ion homeostasis in the kidney, where their lack causes hypertension (Gordon syndrome).

Non-canonical Wnt signaling established polarity within the plane of an epithelium, commonly referred to as epithelial planar cell polarity (PCP) and allows a cell to form structures that require not only positional, but also vectorial information. Examples of PCP in vertebrates can be very obvious, as in the ordered arrangement of scales on fish or hairs of mammalian skin. Less visible examples are the cilia of the respiratory tract and oviduct as well as the stereocilia of the sensory epithelium of the organ of Corti in the vertebrate inner ear. Aberrant PCP can lead to left/right asymmetry defects, open neural tubes, deafness and kidney disease. PCP signaling is, however, best studied in Drosophila melanogaster, mainly because of the versatility of the fly as model system. Our lab is particularly interested in how Rho kinase (Rock) is required for the migration aspect of PCP establishment which will help to understand tumor cell migration.

A genetic model for Endosomal Microautophagy

Autophagy delivers cytosolic components to lysosomes for degradation and is thus essential for cellular homeostasis and to cope with different stressors. As such, autophagy counteracts various human diseases and its reduction leads to aging like phenotypes. Macroautophagy (MA) can selectively degrade organelles or aggregated proteins, but selective degradation of single proteins has only been described for Chaperone-mediated autophagy (CMA) and endosomal Microautophagy (eMI). These two autophagic pathways, described to date only in mammals, are specific for proteins containing KFERQ-related targeting motifs. In collaboration with the Cuervo lab, we have developed a fluorescent reporter to characterize an eMI or CMA-like process in Drosophila in vivo. Our data provide evidence for a novel, starvation inducible catabolic process resembling endosomal microautophagy in a non-mammalian species. We are thus for the first time able to perform genetic screens for regulatory components of eMI, this only recently identified form of autophagy about which barely anything is known.

It is our goal to use Drosophila as model system to address fundamental questions that are relevant for development and disease in general.

Lab homepage: http://jennylab.aecom.yu.edu/

Selected References:
GANJAM V. KALPANA, Ph.D.

Molecular Genetic Analysis of Tumor Suppressor INI1/hSNF5 in HIV-1 Replication and Cancer

INI1/hSNF5 is a component of the chromatin remodeling SWI/SNF complex. It is an interacting partner for HIV-1 integrase (IN) and also a tumor suppressor biallelically mutated in rhabdoid tumors, a rare but highly aggressive pediatric malignancy. The two major areas of focus in the laboratory are: (i) understanding the role of INI1 in HIV-1 replication and exploring its potential as a drug target for intervention of AIDS; and (ii) understanding the mechanism of tumor suppression by INI1/hSNF5 and developing novel and effective therapeutic strategies for rhabdoid tumors.

INI1 in HIV-1 replication: We have found that INI1/hSNF5 directly binds and recruits components of Sin3a-histone deacetylase (HDAC) complex into the HIV-1 virions and this HDAC1 complex appears to be required for viral infectivity. We are currently isolating and characterizing IN and INI1 mutants defective for binding to HDAC1 complex and testing their effect on HIV-1 replication. We have found that HIV-1 harboring IN mutants defective or binding to INI1 are severely compromised for replication. Furthermore, we have found that: INI1 mutants defective for binding to HDAC1 complex dominant negatively inhibit HIV-1 but not SIV replication. These studies are likely to open up a new paradigm for role of INI1 in HIV-1 replication and may provide novel strategies to inhibit viral replication.

Mechanism of Tumor suppression by INI1/hSNF5: By using a series of genetic systems developed in our laboratory and by isolating cancer-associated mutations of INI1, and a wealth of protein-protein interaction defective mutants of INI1, we are dissecting the exact mechanism of INI1-mediated G0/G1 cell cycle arrest, mitotic arrest, and senescence and tumor suppression. Furthermore, characterizing the INI1-associated HDAC1 complex has revealed an unanticipated role of INI1 in interferon signaling and tumor suppression.

Development of targeted therapies for rhabdoid tumors based on INI1 function: One of the goals of our laboratory is to develop molecularly targeted therapies based on the understanding of genesis of rhabdoid tumors. Majority of rhabdoid tumors have biallelic inactivation of INI1 gene. Our previous studies demonstrated that Cyclin D1 is a direct downstream target of INI1 mediated repression and that rhabdoid tumors are exquisitely dependent on Cyclin D1 for genesis and survival. Our preclinical studies have provided proof of principle for our hypothesis targeting Cyclin/cdk axis is an effective means of inhibiting rhabdoid tumors in vitro and in vivo. The current goal is to develop novel strategies to facilitate clinical translation of laboratory findings to establish an effective therapy for these tumors. For this purpose, we are using non-invasive imaging technology such as microPET to monitor the therapeutic efficacy in primary mouse tumor models, developing novel drugs to target these tumors and investigating the interaction between Cyclin D1, the cdk pathway and INI1 in mouse models.

Identification of downstream pathways regulated by INI1 has been instrumental in novel biomarkers and therapeutic targets for these tumors. Aurora A is repressed by INI1 and it is de-repressed in rhabdoid tumors due to loss of INI1. We have found that Aurora A is a novel therapeutic target as siRNA-mediated depletion of this gene resulted in potent mitotic catastrophe and cell death in rhabdoid tumors.

Recent Selected Publications:
HERB LACHMAN, M.D.

Induced pluripotent stem (iPS) cells for disease modeling in schizophrenia

Schizophrenia (SZ) is a common psychiatric disorder affecting ~1% of humanity, leading to a lifetime of disability for a majority of patients. Twin studies show a high level of heritability (between 60-80%). However, lack of complete concordance in monozygotic twins suggests that environmental and epigenetic factors might play a substantial role in disease pathogenesis. A significant obstacle in studying the molecular basis of SZ and other neuropsychiatric disorders is the inaccessibility of the human brain, which has restricted molecular studies, such as gene expression profiling and epigenetic analysis, to autopsy samples. While some interesting findings have been made using postmortem brain, interpreting the data is associated with numerous confounding factors. In addition, since SZ is believed to be a developmental disorder, studying molecular events in postmortem samples is limiting. The discovery of iPS cells, which essentially allows investigators to reprogram somatic cells into pluripotent stem cells capable of differentiating into neurons and other cell types, provides an opportunity to create patient-specific neurons in vitro. The Lachman lab has begun to develop iPS cells from controls and patients with SZ, including a subset that carries a well characterized 22q11.2 del found in ~1% of patients. These cells are being induced to differentiate into glutamatergic neurons and are being subjected to gene expression profiling and epigenetic analysis to identify patient vs control differences. We are using next generation sequencing available through the Einstein Epigenetics Core facility. Gene expression profiling using next generation sequencing (RNA-Seq) carried out on a subset of our samples is providing us with a wealth of molecular data relevant to disease pathogenesis as well as human neurogenesis. Noteworthy so far is discovery of several novel long non-coding RNAs (lncRNAs) that appear to be involved in regulating HOX gene expression and early neurogenesis. In addition, based on disease mapping studies using genome wide association and our preliminary RNA-Seq data, we identified two lncRNAs that we suggest are involved in the development of SZ in a small subgroup of patients.

Epigenetic analysis and knockdown of SZ candidate genes coding for transcription factors and chromatin modifying enzymes followed by gene expression profiling are in the process of being carried out in differentiating human neurons derived from iPS cells.

Selected Recent Publications:


JACK LENTZ, Ph.D.

Molecular Genetics of Retrovirus Induced Cancer and Other Diseases

Retroviruses are associated with a variety of diseases in humans and other vertebrates including cancer and immunodeficiency. The major goals of the laboratory are focused on understanding the molecular basis of retroviral diseases. Mouse retroviruses cause tumors by a mechanism of insertional activation of oncogenes where the viral DNA integrates adjacent to an oncogene, and enhancer elements in the virus activate transcription of the adjacent host gene. We use these viruses as tools for high-throughput identification of cancer-causing genes in the mouse genome. Using sophisticated PCR techniques combined with massively parallel DNA sequencing, the viruses have been used as molecular tags to identify over 60 different genes that cause lymphomas, many of which have not been associated with a cancer-causing role previously, and we are also investigating the molecular mechanisms by which these genes act. Since retrovirus gene therapy vectors cause tumors in human patients by the identical mechanism, we have developed strategies to prevent retroviruses (or any other gene therapy vector that integrates into the human genome) from activating oncogenes and causing cancer. Our newly developed strategies can block most tumors, and are being adapted to human gene therapy use, and we are striving for even greater success.

8% of the human genome is retrovirus DNA. Human endogenous retrovirus K (HERV-K) is the newest of all the retroviruses to enter the germline DNA of humans that is transmitted from parents to children. All humans are born with about 20 distinct HERV-K proviruses (the form of retroviral DNA that is integrated into the host genome) in their germlines. We are investigating whether this retrovirus can infect humans today. We have shown that most HERV-K proviruses in the human formed relatively recently in human evolution, long after the divergence of the human and chimpanzee lineages approximately 6 million years ago. We identified several proviruses that formed so recently that they are not yet fixed in the human genome. We have also identified two HERV-K proviruses that have full length open reading frames for all viral proteins, and are the best candidates to be infectious retroviruses in the human genome today. We are now asking whether HERV-K can indeed replicate in humans today, and whether it might be associated with any diseases.

In collaboration with Drs. Larry Herbst and Robert Burk, we are also studying a herpesvirus and a papillomavirus that are associated with fibropapillomas in endangered and threatened species of marine turtles. We are investigating the evolutionary histories of these viruses, how they are transmitted, the nature of turtle immune responses to them, and the roles of the viruses in causing tumors.

References:
STEVEN K. LIBUTTI, M.D.

Targeting the Tumor Microenvironment to Treat Cancer

The goal of Dr. Libutti's research program is to develop novel cancer therapies through a better understanding of the complex interactions within the tumor microenvironment. In order to better understand the relationship between the tumor and its microenvironment, their research is focused on the interaction between tumor-derived factors and host cells developing in the context of the tumor microenvironment. By understanding this interaction they hope to be able to design novel treatment strategies to inhibit both the growth and the spread of tumors. They are currently studying a variety of tumor-derived factors with effects on tumor-associated vasculature as well as tumor stromal elements. Dr. Libutti's approach to the study of these interactions has been through the utilization of a variety of in vitro and in vivo model systems. His team is using genetic approaches such as gene expression profiling and methylation analysis to understand the changes that occur in cells within the tumor exposed to tumor-derived factors. They have developed techniques, which allow them to isolate endothelial cells, fibroblasts and cancer stem cells from tumor tissue. This has resulted in their ability to study tumor-derived cells directly, and has led to the observation that tumor associated endothelial cells and stromal cells have epigenetic changes compared to normal cells from the same tissue type. This approach has also allowed them to identify specific genes such as FILIP1L (formerly DOC1), which appear to play a role in the ability of cancer cells to invade and migrate through tissues.

The laboratory has also developed mouse models of human cancers that recapitulate the tumors seen in human conditions. The laboratory is particularly interested in endocrine and neuroendocrine tumors and has developed mouse models of MEN1 and vHL. The tumors that result are similar to those seen in patients with these syndromes and serve as a useful tool for studying biomarkers and target genes. A human biospecimen repository for endocrine and neuroendocrine tumors with over 400 samples has also been developed for correlative studies. Endocrine and neuroendocrine tumors are extremely vascular and therefore serve as an ideal model for studies of tumor angiogenesis and the tumor microenvironment.

Various methods of delivering anti-tumor agents, including targeted gene therapy approaches and the use of tumor targeted nanoparticles are being pursued. Dr. Libutti was the first to administer TNF bound colloidal gold nanoparticles as targeted therapy to cancer patients. The overall goal of Dr. Libutti's work is to translate a better understanding of tumor cell-host cell interactions, within the context of the tumor microenvironment, into better therapies for patients with cancer.

Selected Publications:
WEI LIU, Ph.D.

Retinal Development and Stem Cell-based Retinal Repair

The retina is a light-sensitive layer of tissue at the back of the eye. In retina, rod and cone photoreceptors are the cells that detect light and convert it to an electrical signal. This signal is relayed to bipolar cells and then to ganglion cells whose axons transmit this signal to the brain. In this signal processing, horizontal cells and amacrine cells play essential roles. The photoreceptors are metabolically active and are nourished by a layer of support cells - the retinal pigment epithelium (RPE). The retina is fed by both retinal and the choroidal vasculature, which is within and underneath the retina, respectively.

Photoreceptors are vulnerable to progressive dysfunction and death (photoreceptor degeneration) due to inherited and acquired conditions. For example, in the "dry" form age-related macular degeneration (AMD), which is highly prevalent in the elderly and makes up to nearly 90 percent of patients of AMD, RPE and photoreceptors in the macular region growingly become degenerated. Since photoreceptors have no intrinsic capability to regenerate, this cell loss will lead to permanent impairment and loss of central, high-acuity vision, causing substantial burden for affected persons and society.

Stem cell-based retinal repair represents as an emerging strategy in the treatment of the so far incurable photoreceptor degeneration, the convergent end point in variety of retinal diseases. As evidence for its significance, National Eye Institute has initiated an Audacious Goal: "to regenerate the neurons and neural connections in the eye and visual system"..."to save and restore their vision". One of the challenges in this initiative is the efficient generation of healthy and safe donor cells from pluripotent stem cells for cell transplant. Related to this stem cell-based treatment, patient-derived induced pluripotent cells provide an unprecedented tool for disease-modeling and drug discovery.

Molecular dissection of retinal development in model systems provides a foundation for stem cell-based retinal repair. In my lab, we utilize genetic engineered mouse models to investigate the molecular mechanisms of retinal development. We also employ human embryonic stem cells to model retinal development and to generate donor cells for retinal repair. Currently, there are three projects in my lab: 1) To elucidate the regulatory pathways under the control of homeobox genes Six3/Six6 joint functions in retinal cell differentiation; 2) To determine the molecular mechanisms that control Otx2 retinal expression through this Otx2 retinal enhancer; 3) To model retinal development using human embryonic stem cells and to generate donor cells for retinal repair.

The outcomes of our studies are expected to unravel the regulatory pathways for retinal cell differentiation and contribute to stem cell-based retinal repair in the endeavor of saving and restoring vision.

Recent publications
SRIDHAR MANI, M.D.

Phenotyping Orphan Nuclear Receptors

Orphan nuclear receptors (those that lack a well defined physiologic ligand) control nearly every major physiologic and biochemical process in eukaryotes - cell metabolism (e.g., cholesterol, energy, bile acids), xenobiotic detoxification, cell differentiation (e.g., gastrulation, retinal development), circadian rhythm, and cancer cell growth and apoptosis (e.g., NURR77). Of these receptors, the steroid and xenobiotic receptor (SXR or PXR) is a key regulator of genes encoding drug metabolizing and transport proteins. In addition, PXR has been implicated in cancer drug resistance, carcinogenesis and pathophysiologic states like osteomalacia. Our laboratory has provided a first link of how this receptor controls normal intestinal physiology by co-opting bacterial metabolites. These studies have led to investigations into the microbiome, metabolites and PXR related receptor systems in illness and physiology.

Recent Publications:


CRISTINA MONTAGNA, Ph.D.

Genetic, epigenetic and ploidy changes during cell differentiation in development and disease.

Project 1- Role of Septin 9 in Breast Carcinogenesis.  
A comparative cytogenetic approach aimed to identify recurrent DNA copy number variations in a panel of murine models for breast cancer resulted in the identification of Septin 9 (Sept9) as potential novel oncogene. The septin family of genes codes for a highly redundant and conserved family of GTP-binding proteins that assemble into filaments and bind to microfilaments and microtubules. At the locus of genomic amplification deregulation of Sept9 expression occurs by a complex pattern of genetic and epigenetic alterations affecting several Sept9 isoform variants. Our hypothesis is that during malignant transformation, breast epithelial cells undergo genomic amplification of the Sept9 locus and over-express Sept9 mRNA and protein. Additionally, aberrant cytosine methylation occurs at specific alternative promoters within the Sept9 locus resulting in an abnormal pattern of Sept9 isoform variants. We are currently studying how the expression of various Sept9 isoforms is regulated in normal and cancer cells and the functional differences between these isoforms.

Project 2- Stage- and Cell Subtype-Specific Epigenetic Regulation of Mammary Gland Development and breast tumorigenesis.  
We are interested in investigating the DNA methylation changes occurring in the development of the normal mammary gland during puberty, adult age, pregnant, lactating and undergoing mammary gland involution. This approach has the final goal of dissecting the molecular processes that mediate methylation changes in the morphogenesis and differentiation of the normal breast and to identify "hot spot" loci for gene silencing in breast carcinogenesis.

Project 3- Aneuploidy in aging.  
Polyploidy and aneuploidy are the most frequent cytogenetic events observed in mammalian cells. Polyploidization is a widely accepted mechanism for increasing genetic variation in unicellular organisms and for the acquisition of new properties in a variety of cell types (e.g., osteoclast fusion in bone resorption and myoblast fusion in muscle development) and is considered a physiological process. Aneuploidy on the contrary is linked to pathological states. It is a hallmark of spontaneous abortions and birth defects and is observed virtually in every human tumor. While the catastrophic consequence of high levels of aneuploidy observed in abortions is self-explanatory, the role of aneuploidy under physiological conditions is a question waiting for answers. The major goal of this project is to explore a possible correlation between age-associated genome instability in a variety of tissues and functionality of these cells.

Recent Publications:  


BERNICE E. MORROW, Ph.D.

Mammalian Developmental Genetics

Our lab is interested in discovering genes required for human embryonic development to understand the cause of birth defects. Our research begins with collecting DNA samples from affected individuals with genetic disorders having known chromosomal gains or losses, and moves to looking at gene function in vertebrate model organisms. The reason for studying chromosomal disorders is that affected regions in the genome will pinpoint the location of causative genes whose function in organogenesis is sensitive to copy number.

Our main focus is on a disorder termed chromosome 22q11.2 deletion syndrome (22q11DS). Most affected individuals have a similar sized 3 million base pair (Mb) deletion encompassing 60 genes. The deletion occurs by a mistake during meiosis in forming the egg or sperm. Individuals with the syndrome have learning disabilities, psychiatric illness, cleft palate, hearing loss and cardiovascular defects. Many of these defects occur commonly in the general population in non-syndromic forms. This is why molecular genetic studies of this syndrome are particularly relevant to human health and disease.

One key gene in the 22q11.2 region is termed TBX1 and it encodes a transcription factor that is responsible for many of the defects in patients with the syndrome. Using knockout and gain-of-function mutant mice, we have made headway to understand its function. Since it’s a transcription factor, we are interested in genes it can regulate. Part of our mission is to build a genetic pathway downstream of Tbx1 using next-generation sequencing methods such as Chip-seq and RNA-seq from microdissected mouse tissues followed by bioinformatics analysis.

Although most individuals with 22q11DS have the same sized 3 Mb deletion, the severity of malformations varies dramatically. For example, 60% have heart defects, many requiring surgery, while the rest have a normal heart. We hypothesize that the 22q11.2 deletion is the first hit in the genome and it uncovers other mutations that act as second hits to modify the overall phenotype of the disorder. We are taking candidate gene and unbiased whole genome approaches to identify genetic "modifiers" in humans. We have performed a genome wide association study (GWAS) on 1,100 affected individuals using Affymetrix microarrays containing 1.8 million single nucleotide and copy number DNA variations. Whole exome sequencing (WES) was recently done on 186 individuals with 22q11DS to identify exonic mutations. As part of our International 22q11.2 Consortium, we will perform whole genome sequencing (WGS) on 600 individuals to find genes for psychosis. In order to interpret the genomic data, we are taking a systems biology approach. In this way, we will extract biologically important gene networks in a holistic sense. At the same time, genes in the networks will be tested for functional significance in mouse models.

Recent Publications:
ERTUĞRUL M. ÖZBUDAK, Ph.D.

Systems Developmental Biology: Systems-level analysis of developmental timing and pattern formation

The vertebrate segmentation clock is a gene expression oscillator pacing rhythmic segmentation of the vertebral column during embryonic development. The period of the segmentation clock dictates the number and sizes of vertebrae. Fgf, Wnt, Notch and Retinoic Acid (RA) cell-to-cell signaling pathways interact with each other and act upstream the segmentation clock genes to regulate segmentation and differentiation of cells in the tissue. When segmentation goes awry, it results in birth defects (congenital scoliosis).

In our lab, we focus on the following research topics:
Quantitative developmental biology, pattern formation, pacemaker mechanism of the segmentation clock, regulation of gene expression oscillations, morphogen gradients, stochastic gene expression and achieving precision in segmentation, mathematical modeling and computational simulations.

We aim to understand how interlinked signaling pathways and transcription factors govern developmental timing and pattern formation. We utilize real-time imaging tools, single-cell experiments, time-controlled perturbation experiments, mathematical modeling, genome-wide techniques and bioinformatics to achieve these objectives. We use zebrafish as the model organism.

Recent Publications:
SUBJECT: Hepatocyte Transplantation and Liver-Directed Gene Therapy

During the past decade, liver-directed cell therapy and gene therapy for inherited metabolic disorders has progressed to a point where successful clinical application is in sight. Our current preclinical targets are inherited hyperbilirubinemia (Crigler-Najjar syndrome, CN-1) and alpha-1 antitrypsin (AAT) deficiency. We have been pursuing several approaches for liver-directed gene therapy as follows.

**Subproject 1. Hepatocyte-based therapies for genetic liver diseases.** The conventional source for human hepatocytes is livers from deceased or living allogeneic donors. Hurdles to broad clinical application of this promising therapeutic approach include the scarcity of usable donor livers, the limited number of hepatocytes that can engraft in the liver in a single procedure, and the need for prolonged immunosuppression. To overcome these limitations, we are developing strategies to promote repopulation of the host liver with preferentially proliferating transplanted hepatocytes. Initial engraftment of the transplanted hepatocytes is being augmented by transient disruption of the hepatic endothelial barrier with pharmacological agents or low dose hepatic irradiation. Subsequent repopulation of the liver is being achieved by regional X-irradiation of a liver lobe, followed by transplantation of hepatocytes and mitotic stimulation of the engrafted cells using hepatocytes growth factor or drugs that activate the thyroid hormone receptor, TR-beta. Our work has been translated into the first successful hepatocyte allotransplantation in a patient with CN-1. Regiospecific hepatic irradiation is being evaluated in a clinical trial (collaboration with University of Pittsburgh).

Alpha-1 antitrypsin (AAT) deficiency (ATD) is one of the most common potentially lethal inherited disorders in the Western world. The classic form of ATD is caused by mutations that express the misfolded ATZ variant, which is not secreted efficiently by hepatocytes into plasma. The resulting circulatory deficiency results in uninhibited neutrophil elastase activity in the lung, causing severe pulmonary emphysema. ATZ molecules retained in the hepatocyte ER as polymerized globules cause liver disease. We have shown that wildtype hepatocytes transplanted into mice expressing human ATZ proliferate spontaneously, repopulating the liver, correcting the histological abnormality. The mechanism of hepatic repopulation by transplanted normal hepatocytes in AATD, has major implications for therapeutic application of hepatocyte transplantation for the treatment of liver and lung components of the disease, and is a focus of our laboratory.

**Subproject 2. Human embryonic and pluripotent stem cells as sources of hepatocytes:** A renewable source of hepatocytes from individual subjects would be of great value in developing cell-based models of inherited liver diseases and in hepatocyte-transplantation. Such cells could potentially alleviate the shortage of liver donors and provide autologous cells that would not need immunosuppression after transplantation. Toward this goal, we have differentiated human embryonic stem cells into hepatocytes-like cells (iHep) by manipulating human embryonic stem cells in culture. We have also generated induced pluripotent cells (iPSCs) from skin fibroblasts or urinary epithelial cells of normal subjects and patients with inherited metabolic diseases, and differentiated the iPSCs into iHeps. By transplanting iHeps derived from normal human iPSCs in the jaundiced Gunn rat model of human CN-1, we have shown that the iHep cells express some mature (postnatal) functions of human hepatocytes, engraft in the liver and proliferate under appropriate stimuli. Partial repopulation of the Gunn rat liver with normal human iHep cells ameliorated hyperbilirubinemia. This was the first demonstration of the effective therapy of an inherited metabolic liver disorder by transplanting stem cell-derived hepatocytes.

In ongoing studies we are generating disease-specific iPSCs without integration of any exogenous DNA. Genetic lesions in the patient-derived cells will be corrected by CRISPR-cas or zinc finger nuclelease enhanced homologous recombination. The genetically corrected cells will be differentiated into hepatocytes and tested in preclinical studies by transplantation into animal models of the respective diseases.

**Recent Publications:**


I. Inherited Disorders of Bilirubin Glucuronidation

UGT1A1 is a member of UDP-glucuronosyltransferases (UGT) family of enzymes, which is concentrated in the hepatic endoplasmic reticulum (ER). UGT1A1 mediates the glucuronidation of bilirubin and estrogens. UGT1A1-mediated glucuronidation is required for excretion of bilirubin in bile. We showed that the genetic lesions in any one of the five exons encoding UGT1A1 can abolish or reduce bilirubin glucuronidation, causing potentially lethal Crigler-Najjar syndrome type I (CN-I), or it's less severe variant, Crigler-Najjar syndrome type II (CN-II). We also showed that Gilbert syndrome, a milder form of inherited hyperbilirubinemia, is caused by a promoter variation. We have been studying the regulation of UGT1A1 gene expression. Our objective is to develop novel therapies (gene and cell-based therapies) to cure this disease. Fibroblasts or renal tubular epithelial cells present in urine of CN1 patients will be reprogrammed to IPS cells, genetically corrected, differentiated into hepatocytes and transplanted into jaundice Gunn rat model of CN1.

II. Primary Hyperoxaluria Type 1 (PH1)

PH1 is an autosomal recessive disease caused by mutations in the alanine:glyoxylate aminotransferase gene (AGXT). In humans, insufficient AGXT activity in liver peroxisomes leads to increased oxalate production that causes calcium oxalate stones in the kidney and then in blood, heart, bones, etc. It is a lethal disease unless combined liver and kidney transplantation is performed. We have developed a mouse model of PH1. Our plan is to cure this disease by (a) gene therapy (b) transplantation of adult primary hepatocytes or (c) hepatocytes derived from human embryonic (hESC) or induced pluripotent stem cell (iPSC). For the latter, fibroblasts from the skin of normal volunteers or patients with PH1 are used to generate IPS. Initially we used viral vectors to generate induced pluripotent stem cells. Our current focus is to use non-integrating factors to generate PS cells.

Publications:


NICOLE SCHREIBER-AGUS, Ph.D.

Program for Jewish Genetic Health

The overarching mission of the **Program for Jewish Genetic Health** (PJGH) is to serve as a centralized resource for the Jewish community and its future generations, addressing Jewish genetic health needs from before birth to old age. This mission is accomplished by spreading education/awareness, providing accessible and affordable genetic testing, and offering supportive services.

Over the past few decades, the realm of Jewish genetic health has expanded beyond Tay-Sachs disease carrier testing. In addition to pre-conception screening for many more conditions that can affect offspring, we now are expanding the focus towards diseases such as cancer and adult-onset disorders as well. Significant progress has been made in the realms of diagnosis, prevention, and management of these conditions, with the ultimate goal of identifying treatments and cures.

Our "core" Program team is multidisciplinary and comprises physicians, scientists and genetic counselors, many of whom are faculty at Einstein and/or Montefiore Medical Center. By partnering with local and distant Rabbis, other physicians, bioethicists, Jewish organizations, philanthropists, and even past patients, we have established a network of connections with the Jewish community that expands out the Program's core team and magnifies its reach well beyond the New York area.

Please see [http://einstein.yu.edu/centers/jewish-genetic-health/](http://einstein.yu.edu/centers/jewish-genetic-health/) for additional information and resources, including our online education program called **MyJewishGeneticHealth.com**.

Recent Publications:


JULIE SECOMBE, Ph.D.

Transcriptional Regulation of Cell Growth and Development

In my lab, research focuses on dissecting the mechanisms by which the transcriptional regulators Myc and KDM5 (aka Lid) function. By understanding the genes and processes regulated by these two genes during normal development, we aim to shed light into how dysregulation of Myc and KDM5 family proteins cause human disease, specifically cancer and intellectual disability. To do this, we take advantage of the many genetic tools available by using the model organism Drosophila melanogaster.

There are currently three main projects in the lab:

(1) **Defining the role of KDM5 in Myc-induced cell growth.** Myc is a well-established transcription factor that is overexpressed in many human cancers. We have shown that KDM5 interacts with Myc to regulate the expression of specific subset of genes required to induce cell growth, but precisely how this occurs remains unknown. Importantly, while the most well characterized function of KDM5 is to demethylate histones, it functions with Myc independently of this activity. Instead it requires a motif that binds to specific methylated forms of histone H3 (histone H3 that is di- or trimethylated at lysine 4; H3K4me2/3). Because Myc binding has been previously shown to correlate with promoters enriched for H3K4me2/3, we hypothesize that KDM5 recruits Myc to cell growth-regulatory genes through the ability of its PHD3 motif to recognize H3K4me2/3-containing nucleosomes.

(2) **Defining the transcriptional and cellular defects caused by KDM5 mutations that result in intellectual disability.** While many mutations in human KDM5 family genes have been found in intellectual disability patients, the link between KDM5 dysfunction and cognitive impairment remains unknown. Based on the hypothesis that intellectual disability-associated mutations in KDM5 are caused by aberrant transcription, we are generating fly strains harboring disease alleles. We will then examine the transcriptional defects and neuronal phenotypes of these fly strains.

(3) **Determining the mechanism by which Myc induces genomic instability.** Human cancer cells exhibit many chromosomal abnormalities (deletions, inversions, translocations etc) that are generated through genomic instability. Myc overexpression can lead to double-stranded DNA breaks and ultimately genomic instability, although the mechanism by which this occurs has remained elusive. We are investigating this question using lacZ mutation reporter transgenes. Using Drosophila, we aim to define precisely how Myc acts to promote genomic instability, a process that is key to understanding how Myc acts during tumor formation and subsequent metastasis. Genomic instability is also a key feature of cells from old animals, and we are investigating a potential role for Myc as a pro-aging gene.

**Recent Publications:**


The goal of the Spivack laboratory is to understand differences in gene regulation among individuals, using genetic and epigenetic techniques. The mechanistic goal is to understand the subtleties of how specific high-resolution patterns of DNA methylation and microRNA expression regulate gene expression. We have developed several new functional genetic technologies to examine epigenetic function. We have recently completed initial genome-wide searches of the transcriptome, methylome, and microme of lung cancers. The translational goal is to use these functionally sifted epigenetic features, detected non-invasively, to identify individuals at particularly high risk for lung cancer and other lung disorders, to enhance prevention and early detection efforts.

Mechanistically, the role of promoter sequence and epigenetic variation in the regulatory region of carcinogenesis and oxidant pathway genes is being explored in vitro. We develop techniques in the lab, such as human genomic methyl-DNA reporter constructs, patch methylation strategies, in addition to studying native gene regulation models. Unique technologies include the laboratory’s new microRNA:mRNA binding assay, and modelling the functional consequence DNA methylation patterns reproduced in reporter constructs, and now in native chromatin.

Translationally, epigenetic and other biomarkers are being established in laser capture microdissected human lung and several unique, non-invasively collected surrogate specimens developed in the laboratory, such as mRNA expression signatures from brush-exfoliated buccal mucosa cells, and DNA methylation and microRNA analyses from exhaled breath condensate, which are first reports for a new airway biomarker class. These airway derived specimens continue to accrue from a sampling (currently n>1000) of a lung cancer case-control study. The specimens are being studied for quantitative gene expression, and their regulatory substrates listed above, in multiple pathways. These expression, genetic, and epigenetic data are being linked to put a real metric to gene environment interaction.

Selected Publications/Manuscripts:


Our long-term research goal is to investigate the genetic components of aging and aging-related disease using functional genomics approaches. We focus on the identification of gene sequence variation, i.e. single nucleotide polymorphisms (SNPs), in candidate genes and the assessment of their potential functional impact on aging-related phenotypes. Candidate genes include categories of genes implicated in the modulation of common causes of aging, e.g. free radical production, antioxidant defense, genome maintenance, and apoptosis, or more targeted pathways involved in specific aging-related diseases such as breast cancer. Any genetic variation found to be significantly associated with one or more defined aging phenotypes is then further investigated in specific functional tests, utilizing in silico modeling, in vitro cell culture models, and mouse models. We consider the assessment of the functional impact of SNP haplotypes, i.e., allelic variation caused by multiple SNPs in the same gene, in vitro and animal models as essential to confirm the link between genotype and phenotype in aging studies. This should ultimately result in an integrated approach to study the genetics of aging at different levels ranging from genetic determinants in the form of DNA sequence variations, through cell type- and tissue-specific gene expression profiles, to molecular and cellular endpoints in tissues, to impacts on quality and duration of life span. The results are expected to lead to the identification of functional pathways that control basic aging processes and the onset of age-related diseases. Insight into the functional impact of individual genetic variation on the aging process will lead to a better understanding of phenotypic variation in aging human populations, including susceptibility to aging-related diseases and exceptional longevity. Importantly, it will help close the long-held gap between the population genetics and molecular genetics of aging.

Four systematic multidisciplinary studies are currently underway. First, we have initiated a population-based association study to test genotype-phenotype correlations of genome maintenance genes in a breast cancer cohort. We currently focus on the tumor suppressor BRCA1, which is involved in double strand break repair with broad effects on cellular physiology and genomic stability. We have established a high-throughput mouse embryonic stem cell transgenesis and TALEN-mediated cell engineering to knock-in human BRCA1 haplotype variants for functional analysis in vivo. Second, in a cohort of longitudinal study of aging, we are testing the hypothesis that genetic variation at loci involved in genome maintenance mechanisms (e.g., DNA repair, antioxidant defense, cell cycle control, and apoptosis) can be related to individual differences in the rate and severity of aging-related phenotypes. Third, we are focusing on identification of functional SNP haplotypes of genes involved in the Growth Hormone/Insulin-like Growth Factor-1 (GH/IGF-1) pathway. Down-regulation of the GH/IGF-1 pathway is well-known to extend life span in model organisms varying from worms and flies to mice. We are investigating whether this evolutionarily conserved pathway play a role in human longevity using Ashkenazi Jewish centenarian cohorts. Fourth, we are studying mouse models that harbor human gene variations in DNA repair/genome maintenance and as a consequence manifest premature aging phenotypes. Our results from transcriptome analysis delineate a complex genetic network of cellular responses to endogenous DNA damage and suggest it as the cause of the premature aging phenotypes in these mice.

Selected Publications:
JAN VIJG, Ph.D.

Genome Dynamics in Aging

Genome instability has since long been implicated as the main causal factor in aging. Exactly how loss of genome integrity may lead to tissue degeneration, functional decline and increased risk of diseases such as cancer remains unknown. We study genome instability, in relation to age and life span in various organisms, including human, mouse and fruit fly, and its consequences in terms of alterations in tissue-specific patterns of gene regulation.

We developed transgenic reporter systems in mouse and fruit fly, which allows us to determine tissue-specific frequencies of various forms of genome instability, e.g., point mutations, deletions, translocations. By crossing the mutational reporter animals with mutants harboring specific defects in various genome maintenance pathways, the relevance of these pathways for the accumulation of specific forms of genome instability is assessed, in relation to the pathophysiology of aging. Similarly, by using knockdown approaches we assess the effect of specific genes, e.g., SOD, FOXO, SIR2, on genome integrity in cultured cells.

To improve our understanding of the possible role of stochastic alterations in genome or epigenome in aging and disease we are now also exploring single-cell approaches to access putative cell-to-cell variation in genome, epigenome or transcriptome during aging. Procedures such as single-cell genomics and single-cell methylomics allow us to uncover the landscape of mutations and epimutations in conjunction with their transcriptional consequences in single cells from organs and tissues during aging.

Finally, as a spin-off from our more basic research we are developing, in collaboration with clinical departments, novel assays for measuring subtle genetic changes in single cells or very small number of cells, such as tumor needle biopsies.

Selected Publications:


DANIEL A. WEISER, MD

Childhood Cancer Translational Research

Our laboratory is focused on childhood cancer research with a goal of elucidating the underlying biology of the most aggressive malignancies. In such patients with typically incurable cancer, we are striving to identify new approaches to and types of treatment. We have multiple ongoing projects:

+ **Identification of biologic drivers of ultra-high-risk neuroblastoma.** Neuroblastoma is one of the most common and deadly childhood cancers. Despite intensive research, there are limited therapeutic strategies for patients with *de novo* chemotherapy resistance that leads to particularly poor outcomes. We have been studying neuroblastoma since 2009 and are identifying additional biologic drivers of highly lethal tumors. We assess features (genetic, transcriptomic, proteomic, histologic) from patients with early death from tumor progression compared with tumor features from those with a maintained complete response. This guides our workup of potential oncogenic targets and discovery of novel therapies for patients.

+ **Characterization of neuroblastoma development from neural crest cells.** We are studying pathways and interactions that result in uncontrolled cell proliferation early in neuroblastoma development with an ultimate goal of identifying new targets and approaches for pharmacologic intervention.

+ **Evaluation of novel combinatorial targeted therapeutic approaches in neuroblastoma.** With expected outcomes lagging behind those of more common childhood cancers, children with neuroblastoma require new approaches to treatment. Our lab works with multiple international clinical and research consortium groups to perform preclinical studies that substantiate human clinical trials.

+ **Detection of circulating tumor DNA in osteosarcoma.** With no reliable non-invasive approach for disease monitoring during and after treatment, we are applying next-generation sequencing approaches to identify solid tumors with blood-based “liquid” biopsies. This will allow clinicians to assess tumor responsiveness to chemotherapy and predict likelihood of recurrence.

+ **Assessment of accelerated aging using miRNA-seq in survivors of childhood cancer.** Chemotherapy has many untoward effects on healthy cells and leads to many signs of accelerated aging in children treated for cancer. Using a known microRNA “aging” signature discovered at Albert Einstein College of Medicine, we are studying what causes this phenotype in childhood cancer, with a goal of offering improved intervention to minimize long-term toxicity of treatment.

Lab website: https://sites.google.com/site/weiserlab/

**Select publications:**


Nearly 20% of all pregnancies end in miscarriage, with the vast majority being due to genomic rearrangements. This is typically sporadic, but 2% of all couples suffer from recurrent miscarriage defined as three or more miscarriages. The primary focus of my laboratory is to better understand how the developing germ cell and embryo protect themselves from genomic damage, to develop methods to diagnose when errors in the defense mechanisms have occurred and to develop novel therapeutic treatments. Studies involve high-throughput genomic assay development, bioinformatic analysis and clinical trials. We utilize in vitro assays, cell culture, mouse models and testing of human samples.

Laboratory Homepage: http://www.einstein.yu.edu/departments/obgyn/miscarriage/research/
Clinical Homepage: http://www.einstein.yu.edu/departments/obgyn/miscarriage/

Selected Publications:
Williams, Z., Litscher, E., Wassarman, P.M. (2003) Conversion of Ser to Thr residues at the sperm combining-site of mZP3 does not affect sperm receptor activity. Biochem Biophys Res Commun. 301:813-8
Review Articles
ZHENGDONG ZHANG, Ph.D.

Computational and Systems Biology of Cancer Metastasis and Human Aging

With recent resource and technology development, biology has entered a new data-driven phase in the 21st century. The research interest of my lab is computational biology and bioinformatics, focusing on algorithm development, data integration, and software implementation. With the advent of new DNA sequencing technologies, it is a particularly challenging and exciting time now to do such computational work, as more and more biological data are being generated at an ever-accelerating speed.

Gene expression in living cells is under strict spatial and temporal control, and its dysregulation is the direct cause of many human diseases. The primary focus of research in my lab is gene expression and its regulation, for which we take an integrated approach to study the following aspects on the whole genome scale:

- Gene expression profiles
- Transcriptional regulation of gene expression
- Epigenetic mechanisms and long range control of gene expression
- Gene copy number variation

The biological systems currently under investigation are breast cancer metastasis and human aging.

- **Breast cancer metastasis** is a complex multi-step process during which tumor cells spread from the primary tumor mass to distant organs. To study the genetic and biochemical determinations of this deadly aspect of cancer progression, we analyze various microarray and sequencing profiles to discover its regulatory sub-networks, DNA binding of key regulators, and copy number variations during the progression. This research project is supported by a grant from NIH/NLM.

- For reasons significant to individuals and the society as a whole, **human aging** is of great interest not only to the academic community but also to medicine and the public in general. However, despite much research progress made over the years, it still remains a poorly understood biological process. To gain novel insights, we use a systems-biology approach to analyze aging-related genes in the context of biological networks. This research project is supported by a New Scholar Award from the Ellison Medical Foundation.

Lab web site: www.zdzlab.org

**Recent Publications:**


DEYOU ZHENG, Ph.D.

Bioinformatics and Computational Genomics

The research field of my group is Computational Genomics and Bioinformatics, with a strong focus of mining large-scale experimental genomic data to decipher the function of the human genome and the genomes of other model organisms. We develop and apply computational techniques for integrating data of comparative genomics and functional genomics (and epigenomics) to decode the structure, function, and evolution of the human genome. More generally, we are interested in bioinformatic and statistical approaches for exploiting novel and biologically significant patterns in big genomic data. Recently, we have become more focused on the expression, regulation, and evolution of human genes (both coding or non-coding) that are involved in the development, specification, maturation, and maintenance of human neural systems. Working extensively with experimentalists and by deep sequencing of the transcriptomes in human neurons, our study has led to many interesting findings and will contribute important information to neuronal development, neurodegenerative diseases and many other brain diseases. Please see our website for more details:
http://dain.einstein.yu.edu/zhenglab

Recent publications:
BIN ZHOU, M.D., Ph.D.

Molecular Mechanisms in Heart Development and Disease

Our research focuses on molecular mechanisms in cardiac development and disease. We apply an integrated approach of mouse genetics, developmental embryology, cell and molecular biology to study specification and lineage development of cardiac cells, transcriptional regulation of cardiac development, and involved signaling pathways.

**Endocardial Cell Lineage Specification and Differentiation:** Our molecular model for studying endocardial cell specification and differentiation is the transcription factor NFATc1 (Nuclear Factors in Activated T-cells-1). It is the only known transcription factor specifically expressed by the endocardial cells during heart development. We have generated several endocardial specific Cre and reporter gene mouse lines to trace the endocardial cell lineage during heart development. Our data indicate that the progenitor cells in the endocardium is the origin of cardiac mesenchyme and coronary vascular endothelium, and that VEGF, NOTCH, and NFATc pathways regulate the endocardial to mesenchymal or endothelial transition and subsequent heart valve or coronary vascular formation.

**Transcriptional Regulation of Cardiac Development:** Our study of NFATc1 regulation has led to the discovery of an important auto-regulatory loop via a transcriptional enhancer during cardiogenesis. We are currently characterizing this enhancer paradigm by identifying its upstream regulators and downstream key components using DNA affinity pull-down, Mass-Spec, and RNA-Seq. We are also using ES cell differentiation, early mouse embryos, and ChIP-Seq to identify the cis-elements for the early endocardial expression of NFATc1 when cardiac cells are specified. These studies will define the transcriptional hierarchy of endocardial specification.

**Modeling of Heart Valve Disease:** Congenital heart valve disease is a major birth defect and aortic valve stenosis is a common disease in the elderly. We are generating and characterizing mouse models for either condition by ablation of endocardial cells or genes in the valve cells to better understand the endocardial involvement in these diseases.

**Epigenetic Regulation of Heart Formation:** We are also interested in and study epigenetic regulation of heart formation, specifically the roles of DNA methyltransferase (Dnmts) and RE1-silencing transcription factor (REST1) in the inactivation of fetal cardiac gene program, cardiomyocyte differentiation and maturation, and heart formation. We are using the cardiac specific gene inactivation models for Dnmts and REST and genome wide sequencing analysis of DNA methylation, transcription, and DNA-binding to determine the potential interaction of Dnmts and REST in cardiac fetal gene silencing and its functional consequences in cardiomyocyte differentiation/maturation and heart formation.

**Recent Publications:**


Lin, CH., Lin, CY., Chen, CH., Zhou, B.,* and Chang, C.P.,* 2012. Partitioning the heart: mechanisms of cardiac septation and valve development. *Development* 139:3277-3299 (*co-corresponding authors)*


1. Patch-ligase DNA methylation functional assay results for the DAPK promoter showing the reporter construct without promoter, the reporter construct with unmethylated DAPK promoter (unM) and reporter constructs with DAPK promoter methylated at different CpG sites (MP1 to MP6; Spivack laboratory).

2. Mouse embryo showing the pattern of gene deletion (dark blue) obtained with a cre allele expressed mainly in the forebrain. (Hébert laboratory).

3. Digital and microPET images of an Ini1+/- mouse bearing primary tumors before and after treatment with flavopiridol. Left two panels digital images and right panels represents MicroPET images of the same mouse. The top two panels are before treatment and the bottom two panels are images of the same mouse after treatment (Kalpana laboratory).

4. Functional roles of genes can be assessed easily in zebrafish by morpholino oligonucleotide mediated gene knockdown and the phenotype can be rescued simply co-injecting mRNA of the targeted gene together with the targeting morpholinos. (Ozbudak laboratory).

5. LAM-PCR to amplify cancer-causing genes in retrovirus induced lymphomas (Lenz laboratory).

6. Hepatic steatosis in mouse infected with a mutant murine leukemia virus (Lenz laboratory).

7. An immuno-histochemical analysis of the heterozygous mucopolysaccharidosis mouse brain showing beta-glucuronidase activity in green, NeuN (a neuronal marker) in red and nucleii (DAPI) in blue (RoyChowdhury Laboratory).

8. Genome-wide sequence coverage and mutation localization in single S2 cells treated with or without ENU. (Vijg laboratory).

9. A genetic assay for cell competition in Drosophila. In the left panel, some pigmented cells have been generated in the eye, which are genetically defective and would normally be lost by ‘cell competition’, which has occurred in the eye shown in the right panel. On the left, however, the unpigmented cells are unable to recognize and eliminate the defective cells, because of a defect in a gene required for cell competition (Baker laboratory).

10. The binding of certain transcription factors can significantly alter the local histone modification profiles. Shown here is the decline of acetylation on histone H3 lysine 9 (H3K9ac) upon binding of a repressor. The profiles near transcription start sites (TSSs) are without (black) and with (colors) the binding of this repressor. (Zheng laboratory).
