GENETICS AND DEVELOPMENT DEPARTMENT NEWSLETTER

MESSAGE FROM THE CHAIR

Welcome to our second issue of the Genetics and Development Department Newsletter.

What can possibly happen in 8 months of the life of an apparently quiet Basic Science Department in a Medical School? Quite a few events in fact, all defined by the pursuit of excellence. The first one, probably the most important one in the long run for the future of the Medical School has been the participation of senior and junior faculty members and of many youthful and hopeful postdoctoral fellows and graduate students in the March for Science, to defend basic science that remains underfunded. The impact of this march on basic science research in this country is not yet known. There may be in the short term future, another march and if there is, we as scientists should consider it as mandatory to participate. Another important event more "private" for members of the Department and bittersweet too (mostly bitter for me) has been the retirement of Dr. Virginia Papaioannou who has symbolized ever since she came to CUMC, unabated research of excellence, integrity and a dedication to educate generations of graduate students that is second to none. I know these words may sound cliché, but I would challenge anyone to think of another person with the genuine and disinterested passion for educating younger generations of scientists as Ginny. The 70th birthday of Dr. Rodney J. Rothstein was the occasion of a remarkable one day symposium on DNA recombination. Two other pillars of the department, Dr. Andrew Tomlinson and Dr. Gary Struhl have started a new phase of their careers, by moving their laboratories to the superb ZMBBI building. They remain however, full-fledged members of the department.

The department has been busy too, recruiting three junior faculty members, one starting this November and the other two will start in January 2018. Importantly one of them is a joint recruit with a clinical department, Pediatrics. Faculty members are raising the visibility of the department by publishing papers and obtaining grants. Students have graduated but our graduate program continues to expand under the new direction of Dr. Michael Shen with a new wave of students coming this Fall. To continue our effort of presentation of the department this issue of the newsletter will highlight the research program of a junior faculty member who arrived a year ago, Dr. Luke E. Berchowitz and of a senior faculty member Dr. Eric Schon.

I hope that everyone from first year graduate students arriving in our program to senior faculty members in basic or clinical departments on campus will find this newsletter informative. We welcome any suggestions to improve it. Academic Year 2017 Issue 2





Gerard Karsenty, MD, PhD Paul A. Marks Professor and Chair of the Department of Genetics and Development Columbia University Medical Center

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HIGHLIGHTS

The Schon Lab



In broad view, the Schon lab is interested in understanding the basic biology and genetics of mammalian mitochondria and of human mitochondrial disease, defined here as disorders of mitochondrial energy production via oxidative phosphorylation (OxPhos). The lab is currently focused on three broad areas:

Basic research: pathogenesis of Alzheimer disease (AD).

The most widely accepted hypothesis to explain the pathogenesis of AD is the "amyloid cascade," in which the accumulation of extraneuritic plaques (containing mainly amyloid β [A β], generated by cleavage of the amyloid precursor protein [APP] by γ -secretase) and intracellular tangles (containing hyperphosphorylated forms of the microtubule-associated protein tau) play a key role in driving the course and progression of the disease. However, there are other biochemical and morphological features of AD, including altered calcium, phospholipid, and cholesterol metabolism, and impaired mitochondrial bioenergetics, that often appear early in the course of the disease, prior to plaque and tangle accumulation. Interestingly, these "other" functions are associated with a subdomain of the endoplasmic reticulum (ER) that is closely apposed to mitochondria, both physically and ER biochemically, called mitochondria-associated membranes (MAM). In the last few years our group, together with that of Dr. Estela Area-Gomez, has generated data in support of a fundamental role for MAM in the development of AD. In particular, we have found that: (1) presenilin-1 and -2 (the active components of γ -secretase), which are mutated in familial AD, are enriched in MAM; (2) ER-mitochondrial communication and MAM function are upregulated in both familial and sporadic AD; (3) the $\varepsilon 4$ allele of apolipoprotein E, the greatest genetic risk factor for developing sporadic AD, also upregulates MAM function; and (4) an APP processing intermediate called C99 (the substrate of γ -secretase and thus the precursor of AB) also localizes to MAM, is elevated in AD, and is likely the pathogenetic culprit in the disease, including the mitochondrial defects. Further work on the MAM hypothesis is ongoing.

Translational research: pathophysiology of mitochondrial diseases.

We are studying three different mitochondrial disorders, from various viewpoints. (i) Ultrastructural analysis of cells expressing mitochondrial disease. We have performed the first application of *in situ* cryo-electron microscopy to the study of a human disease, namely, a form of Leigh syndrome (a fatal infantile encephalopathy) due to a mutation in a subunit of mitochondrial ATP synthase that affects the enzyme's dimerization. As dimerization plays a role in cristae formation, we used cryo-EM coupled with electron cryo-tomography to visualize cristae structure in patient cells in situ, thereby providing insight into the pathogenetic mechanism. (ii) Pathogenesis of Charcot-Marie-Tooth disease type 2A. CMT2A is a peripheral neuropathy due to dominant mutations in mitofusin-2 (MFN2), a protein that promotes inter-mitochondrial fusion and also tethers mitochondria to ER at MAM (see above). We are studying CMT2A cells to try to deduce the pathogenetic mechanism. (iii) Treatment of mtDNA-based diseases. Based on data obtained in vitro, we hypothesized that rapamycin might ameliorate OxPhos deficiency in cells harboring mtDNA mutations. We therefore administered rapamycin to a knock-in mouse model of mtDNA disease, specifically, progressive mtDNA depletion syndrome due to a mutation in a nucleus-encoded enzyme required for mtDNA synthesis, called thymidine kinase 2. Rapamycin extended lifespan in Tk2-mutated mice, even though there was no detectable amelioration of mitochondrial dysfunction. The mechanism is currently unclear, but may involve the utilization of alternative energy reserves to compensate for the reduction in oxidative energy metabolism, and the triggering of indirect signaling events through developmental reprogramming.

Method development: introduction of exogenous DNA into mitochondria.

It is almost impossible to introduce exogenous DNA into mitochondria via "standard" techniques (e.g. lipofection; electroporation). This problem has been solved in plants and yeast, via biolistic transformation (the "gene gun"), in which DNA-coated gold beads are literally shot into cells. Unfortunately, this approach has not been successful in mammalian cells, thereby precluding our ability to make Targeted mutations in mtDNA to study basic problems in mtDNA genetics, let alone animal models that could be used to develop treatments for mtDNA-based diseases. Our lab has been working on this problem using a variety of approaches, including bacterial conjugation. Most recently, we have taken advantage of reports claiming that adeno-associated virus (AAV) can enter mitochondria, and are using engineered AAV constructs to see if we can bring exogenous DNA into the organelle.

The Berchowitz Lab



fibrous Amyloids are protein assemblies that play an important role in the progression of many severe human diseases including Alzheimer's disease, Parkinson's disease, and ALS. Although amyloids have been predominantly understood in pathological contexts, amyloid-like structures are beginning to be

recognized as having critical physiological functions. My research vision is to discover and understand the pathways and mechanisms by which cells regulate formation, function, and clearance of amyloids. The basis for these studies is our discovery that in order to control protein synthesis, budding yeast regulates assembly of an RNA-binding protein into structures that have many biochemical properties of amyloid. Due to the similarity of these structures to disease-related amyloids they are termed 'amyloid-like.'

What is remarkable about amyloid-like assemblies in yeast is that they are not pathogenic- they are *functional*, *regulated*, and *essential* for sexual reproduction. Assembly is controlled by nutrient availability and clearance occurs rapidly in response to a developmental cue. Yeast's ability to clear these structures is surprising since amyloids are known for being stable and long-lived structures. Through these findings, my lab has developed

a tractable experimental system to investigate the inner workings of amyloid biology in a physiological setting.

Elucidating the regulation and function of amyloid-like assemblies

Our goals are to understand how cells developmentally regulate amyloid-like structures and to determine the mechanisms by which these structures function to control protein synthesis. We are using genetic, biochemical, and cell biological approaches to identify and characterize genes and pathways that cells utilize to developmentally regulate these structures. We are also working to elucidate how environmental factors and protein modifications influence their assembly, reversibility, and clearance. Lastly, we are using a combination of *in vivo* and *in vitro* reconstitution approaches to decipher how cells use amyloid-like assemblies to regulate protein synthesis.

Since their discovery over 150 years ago, the main focus of amyloid research has been on understanding the proteins' disease causing properties. Now, using yeast, we can start to understand some of the physiological roles of these structures. In time, our findings could guide therapeutic strategies aimed at activating clearance and/or preventing accumulation of disease-related amyloids.

DEPARTMENT NEWS

Honors & Awards



Dr. Riccardo Dalla-Favera awarded the Léopold Griffuel Award in Basic Research

Prof. Dalla-Favera, Director of the Institute for Cancer Genetics at Columbia University was awarded the

Léopold Griffuel Award in Basic Research in Paris, on May 20, 2017 by the ARC Foundation for cancer research. This prestigious award honors scientists and physicians that have made major contributions in the understanding, diagnosis, treatment and prevention of cancer.

57th Annual Recipient of the AACR Clowes Memorial Award

In addition to becoming an AACR Fellow, Dr. Dalla-Favera

also received the G.H. Clowes award on Monday, April 3, 2017 after delivering his award lecture titled "The Makings of Human B Cell Lymphoma" at the Washington Convention Center. The award recognizes an individual that has had outstanding recent accomplishments in the field of basic cancer research. Dr. Dalla-Favera is known for his studies on the genetic alterations involved in the pathogenesis of human cancer, in particular, human B-cell lymphoma. His research has significantly contributed to the understanding of normal B-cell function, directly impacting the diagnostics and therapeutic targeting of B-cell malignancies including Burkitt Lymphoma, Diffuse Large B-Cell Lymphoma, and Chronic Lymphocytic Leukemia.



Kelley S. Yan MD, PhD was presented with the Young Physician-Scientist Award from the American Society for Clinical Investigation (ASCI)

Dr. Yan was recently appointed the Dorothy L. and Daniel H. Silberberg Assistant Professor of Medicine. She is the recipient of the 2017 Young

Physician-Scientist Award presented at the Food & Science Evening, on April 22, 2017, as part of the AAP/ASCI/APSA Joint Meeting. The ASCI Council of Young PhysicianScientist Award, initiated in 2013, recognizes young physician-scientists who are supported by NIH or similar significant career-development awards, who are early in their first faculty appointment, and have made notable achievements in their research. The ASCI is an honor society of physician-scientists, those who translate findings in the laboratory to the advancement of clinical practice.



Professor Laura A. Johnston elected to serve as President of the US National Drosophila Research Board of Directors 2017.

Laura A. Johnston is a Professor of Genetics & Development. Her lab at Columbia University Medical Center uses *Drosophila* to study the dynamics of

tissue growth and size control in development, during regeneration and in models of cancer. As elected President of The US National Drosophila Research Board which consists of 13 regional representatives: 8 from the U.S. and one each from Canada, Latin America, Europe, Asia, and Australia/Oceania, and one representative for primarily undergraduate institutions, all of whom serve 3-year terms, she plays an important role in the *Drosophila* research community. Dr. Johnston serves on the Editorial Advisory Board for the journal *Development*, and is a representative of the *Drosophila* community on the Genetics Society of America (GSA) Board of Directors.



Dr. Gerard Karsenty was recently elected Associate Member of EMBO, joining a group of more than 1700 of the best researchers in Europe and around the world.

Dr. Karsenty is one of the nine EMBO Associate Members elected from the US and Japan. This organization supports talented researchers at all stages of their careers, they help with the exchange of scientific information, and most important EMBO provides scientists a research environment to achieve their best work. New EMBO Members are elected annually in recognition of their contributions to scientific excellence. Associate Membership is reserved for a small number of leading scientists outside Europe and is intended to highlight the importance of interacting with scientists on a global scale. New EMBO Members and Associate Members were formally welcomed at the EMBO Members' Meeting in Heidelberg, Germany last month.

Recipient of the Frontiers in Science Award

Dr. Karsenty received the Frontiers in Science Award from the American Association of Clinical Endocrinologists (AACE) in recognition of exemplary contributions to his incredible career. He opened with the lecture titled "But Why Bone?" during the 26th AACE Annual Congress in Houston, Texas.

Research Grants

Luke E. Berchowitz, PhD

National Institute of General Medical Science "Elucidation of regulation and function of amyloid-like assemblies"

Amyloidosis Foundation Donald C. Brockman Memorial Research Grant Research Grant (2018)

Timothy Bestor, PhD

National Human Genome Research Institute "Comprehensive single-molecule enhanced detection of modified cytosines in mammalian genomes."

Riccardo Dalla-Favera, MD

National Cancer Institute "From pathogenesis to new therapeutic targets in diffuse large B cell lymphoma"

Gerard Karsenty, MD, PhD

2018 HICCC Inter-Programmatic Pilot Projects "Systemic regulation of cachexia in metastatic cancers"

Emmanuelle Passegué, PhD

National Heart, Lung and Blood Institute "Emergency myelopoiesis pathways in the control of blood production"

Eric Schon, PhD

IP University Holdings "Approaches to Diagnosis and Treatment of Alzheimer Disease"

Cathy Lee Mendelsohn, PhD

National Institute of Diabetes and Digestive and Kidney Diseases "Retinoic Acid Signaling Controls Urothelial Development and

Regeneration" in a competitive renewal.

Debra Wolgemuth, PhD

Eunice Kennedy Shriver National Institute of Child "Contraceptive Discovery, Development and Behavioral Research Center"

Kelley S. Yan, MD, PhD

National Institute of Diabetes and Digestive and Kidney Disease

"Enteroendocrine cell subsets with reserve stem cell function" Louis V. Gerstener, Jr. Scholar Award (Columbia) "Age-related changes in intestinal stem cell function" Provost's Grant for Junior Faculty (Columbia) "Directed differentiation of enteroendocrine cells"

Zhiguo Zhang, MD, PhD

National Cancer Institute

"The epigenetic mechanism of high grade pediatric glioma"

MEET OUR NEW FACULTY



Vincenzo A. Gennarino (who goes by Alessandro) earned his Ph.D. at the Telethon Institute of Genetics and Medicine (TIGEM) in Italy, where he developed the HOCTAR and CoMeTa tools for identifying mRNA targets. He then did postdoctoral work with Huda Zoghbi at Baylor College of

Medicine, where he applied his knowledge of RNA biology to studying neurological disease. He began by examining post-transcriptional regulation of MeCP2, the protein whose hypofunction causes Rett Syndrome, a devastating neurodevelopmental disorder that strikes little girls between the ages of one and two years. Duplications of the X-linked MECP2 locus cause a different but equally severe disorder in boys, which prompted the question of whether more modest changes in MeCP2 levels might cause disease. The answer was a resounding yes: NUDT21 MeCP2 duplications over-suppress expression, phenocopying Rett syndrome in human children. Alessandro next investigated the post-transcriptional

regulation of a protein involved in a polyglutamine neurodegenerative disease, Spinocerebellar ataxia type 1 (SCA1). Ataxin-1 contains a polyglutamine tract whose expansion causes the protein to misfold and resist clearance. But too much of the wild-type protein can also cause disease, as Alessandro showed when he removed one allele of Pumilio1, which encodes the RNA-binding protein that regulates ataxin1 levels. Pum1-deficient mice have about 30% too much ataxin-1, enough to cause ataxia-along with other symptoms, via misregulation of other Pum1 targets. Alessandro has since identified patients with mutations in PUM1 who manifest a range of symptoms, depending on the severity of the mutation. Alessandro joins the Department of Genetics and Development at Columbia University Medical Center as an Assistant Professor on January 1, 2018. He aims to understand the mechanisms underlying neurological diseases in order to develop viable therapies, while creating a strong training environment for the next generation of scientists.



Chao Lu received his PhD degree in 2013 from the University of Pennsylvania under the mentorship of Dr. Craig Thompson. He then joined Dr. David Allis' laboratory at the Rockefeller University as a postdoctoral fellow. Collectively, Chao's work has identified the molecular mechanisms by which

cancer-associated mutations in chromatin regulators reprogram genome-wide chemical modifications of DNA and histones to promote tumor initiation and progression. Eukaryotic cells develop sophisticated mechanisms to package and access their genetic information. Recent studies uncover that proteins involved in genome regulation are frequently altered in human cancers. These findings agree with laboratory observations that cancer cells often display abnormal nuclear architecture, and raise the questions of whether and how aberrant chromatin organization facilitates tumor development. Funded by the Damon Runyon Fellowship Award and the NIH Pathway to Independence award, Chao demonstrated that chromatin mutations, such as mutations in IDH1/2 and histone H3, are pro-oncogenic through blockade of cellular differentiation. These studies provide compelling evidence for a causal role of chromatin dysregulation in oncogenesis, and propose a novel pathway of cancer initiation through accumulation of hyper-proliferative and differentiation-refractory tissue progenitor cells driven by epigenome abnormality. Chao will join the Department of Genetics and Development as an assistant professor in Jan 2018. His goal is to develop novel molecular and genetic tools to understand the dynamic chromatin regulatory process during tissue development, homeostasis and tumorigenesis.



Christine I. Chio is a new junior faculty in the Department of Genetics and Development at the Institute of Cancer Genetics. Dr. Chio received her PhD from the University of Toronto under the mentorship of Dr. Tak Wah Mak, studying the interplay between inflammation and cancer development. Subsequently, she

joined the lab of Dr. David Tuveson at Cold Spring Harbor Laboratory to pursue her postdoctoral training. Since then, her research endeavor has focused on understanding the role of cellular redox regulation, particularly in the development of pancreatic ductal adenocarcinoma (PDA).

A key histopathological feature of PDA that is also associated with its innate clinical and biological aggressiveness is its pronounced desmoplastic (stromal) reaction. Desmoplasia generates a nutrient and oxygendeprived environment in PDA that is unique to the disease. The resultant redox and metabolic adaptations thus create cancer-specific vulnerabilities that could potentially be exploited. The central hypothesis of the Chio lab is that PDA cells harness reactive oxygen species (ROS) as selective secondary messengers to support cancer cell viability and tumor-stroma co-evolution. The goal of her research is to leverage the ability of PDA cells to regulate levels of ROS towards the development of more effective therapies for this highly lethal malignancy. The cytoprotective transcription factor NRF2 is a central regulator of redox homeostasis and is up-regulated in PDA. As transcription factors are difficult to target therapeutically, the Chio laboratory seeks to comprehensively characterize the mechanisms used by NRF2 to promote PDA such that more feasible approaches to counter its effects in PDA may be developed. In pursuit of this goal, genetically engineered mouse models (GEMM), ex-vivo organoid co-culture systems, and patient-derived organoid transplantation models will be used to establish a discovery pipeline and in vivo validation platforms that will facilitate the design of integrated intervention strategies for a disease involving complex interactions between the tumor and the stroma.



Amanda Bergner will build and run the new genetic counseling graduate program being created within P&S. The Columbia Genetic Counseling Graduate Program is being established to train genetic counselors who will be leaders in clinical genetics and genomics, precision medicine, and research. This

will be a two-year (21 month) full-time program with didactic curriculum, clinical practicums, and a scholarly project. Coursework will include medical, scientific, counseling, clinical, laboratory, research, and ethical aspects of human genetics and genomics. The program will also offer a unique focus on new genomic technologies, including whole exome and whole genome sequencing, treatments, and the integration of this information into the management of disease, disease risk assessment and healthcare decision-making. Amanda completed her genetic counseling training at the University of California, Berkeley and internships at the UCSF Medical Center and throughout the Kaiser Hospital System in Northern California. She is a diplomate of the American Board of Genetic Counseling and has been involved in graduatelevel education of genetic counseling, medical and nursing students for the past 17 years, holding core faculty positions in the genetic counseling programs at Johns Hopkins, the NIH/NHGRI and Sarah Lawrence College. Amanda is currently the President of the Accreditation Council for Genetic Counseling which is the organization that provides accreditation for all graduate-level genetic counseling programs in the North America. Additionally, she has maintained a busy clinical practice through the years - first at UCSF in biochemical genetics, and then at Johns Hopkins in general genetics and neurogenetics.

PUBLICATIONS



Taglialatela, A., Alvarez, S., Leuzzi, G., Sannino, V., Ranjha, L., Huang, J.W., Madubata, C., Anand, R., Levy, B., Rabadan, R., Cejka, P., Costanzo, V., and <u>**Ciccia, A**</u>. (2017). Restoration of replication fork stability in BRCA1- and BRCA2-deficient cells by inactivation of SNF2-family fork remodelers.

Molecular Cell 2017 Oct. 68(2):414-430. PMID: 29053959.



Siegmund S, Yang H, Sharma R, Javors M, Skinner O, Mootha V, Hirano M, <u>Schon EA</u>. Low-dose rapamycin extends lifespan in a mouse model of mtDNA depletion syndrome. *Human Molecular Genetics.* 2017 Dec. 26 (23): 4588-4605. PMID: 28973153.



Pera M, Larrea D, Guardia-Laguarta C, Velasco KR, Chan RB, Di Paolo G, Mehler MF, Perumal GS, Macaluso FP, Freyberg ZZ, Acin-Perez R, Enriquez JA, <u>Schon EA</u>, Area-Gomez E. Increased localization of APP-C99 in mitochondria-

associated ER membranes causes mitochondrial dysfunction in Alzheimer disease. *EMBO Journal*, 2017 November 36(22):3356-3371. PMID: 29018038



Khrimian L, Obri A, Ramos-Brossier M, Rousseaud A, Moriceau S, Nicot AS, Mera P, Kosmidis S, Karnavas T, Saudou F, Gao XB, Oury F, Kandel E, <u>Karsenty G</u>. Gpr158 mediates osteocalcin's regulation of cognition. *J Exp Med.* 2017 Oct. 214(10):2859-2873. PMID: 28851741



Khrimian L, Obri A, <u>Karsenty G</u>. Modulation of cognition and anxiety-like behavior by bone remodeling. *Mol Metab*. 2017 Dec. 6(12):1610-1615. PMID: 29157601



H o TT, Warr MR, Adelman E, Lansinger O, Flach J, Verovskaya E, Figueroa ME, <u>Passegué E</u>. Autophagy maintains metabolism and functional activity of a subset of aged hematopoietic stem cells. *Nature* 2017 March 9 543(7644):205-210.

PMID: 28241143

Hérault A, Binnewies M, Leong S, Calero-Nieto FJ, Zhang SY, Kang Y-A, Wang X, Pietras E, Chu SH, Barry-Holson K, Armstrong S, Göttgens B, <u>Passegué E</u>. Myeloid progenitor cluster formation drives emergency and leukemic myelopoiesis. *Nature* 2017 April 6 544(7648):53-58. PMID: 28355185.



Lefrançais E, Ortiz-Muñoz G, Caudrillier A, Mallavia B, Liu F, Sayah DM, Thornton EE, Headley MB, David T, Coughlin SR, Krummel MF, Leavitt AD, <u>Passegué E,</u> Looney MR. The lung is a site of platelet biogenesis and a reservoir for

haematopoietic progenitors. *Nature* 2017 April 544(7648):105-109. PMID: 28329764

Talos, F., Mitrofanova, A., Bergren, S. K., Califano, A., and <u>Shen, M. M.</u> (2017). A computational systems approach identifies synergistic specification genes that facilitate lineage conversion to prostate tissue. *Nat. Commun.* 2017 April 21, 8:14662. PMID: 28429718



 Toivanen, R., and <u>Shen, M. M.</u> Prostate organogenesis: tissue induction, hormonal regulation and cell type specification. *Development* 2017 April 144(8):1382-1398. PMID: 28400434



Zou, M., Toivanen, R., Mitrofanova, A., Floc'h, N., Hayati, S., Sun, Y., Le Magnen, C., Chester, D., Mostaghel, E. A., Califano, A., Rubin, M. A., <u>Shen,</u> <u>M. M.*</u>, and Abate-Shen. Transdifferentiation as a mechanism of treatment resistance in a mouse model of castration-resistant prostate cancer.

Cancer Discovery 2017 July 7 (7): 736-749. PMID: 28411207 (*co-corresponding author)



Smith, **M.** and <u>Rothstein, R.</u> Poetry in motion: Increased chromosomal mobility after DNA damage. *DNA Repair* 2017 August Volume 56: 102-108.



Pierre Billon, Eric E. Bryant, Sarah A. Joseph, Tarun S. Nambiar, Samuel B. Hayward<u>, Rothstein</u> <u>R., Ciccia A</u>. (2017) CRISPR-Mediated Base Editing Enables Efficient Disruption of Eukaryotic Genes through Induction of STOP Codons. *Molecular Cell*

2017 September 67(6): 1068-1079. PMID: 28890334

PUBLICATIONS



Coleman RT, <u>Struhl G</u>. Causal role for inheritance of H3K27me3 in maintaining the OFF state of a Drosophila HOX gene. *Science* 2017 April 356(6333): PMID: 28302795



Langridge PD, <u>Struhl G</u>. Epsin-Dependent Ligand Endocytosis Activates Notch by Force. *Cell* 2017 November 30 171(6):1383-1396. PMID: 29195077

Janda CY, Dang LT, You C, Chang J, de Lau W, Zhong ZA, <u>Yan</u> <u>KS</u>, Marecic O, Siepe D, Li X, Moody JD, Williams BO, Clevers H, Piehler J, Baker D, Kuo CJ, & Garcia KC. Surrogate Wnt ligands that phenocopy canonical Wnt and β -catenin signalling. *Nature* 2017 May 11 545(7653):234-237. PMID: 28467818.



Yan KS, Janda CY, Chang J, Zheng GXY, Larkin KA, Luca VC, Chia LA, Mah AT, Han A, Terry JM, Ootani A, Roelf K, Lee M, Yuan J, Li X, Bolen CR, Wilhelmy J, Davies PS, Ueno H, von Furstenberg RJ, Belgrader P, Ziraldo SB, Ordonez H, Henning SJ, Wong MH, Snyder MP, Weissman IL, Hsueh AJ, Mikkelsen TS, Garcia KC, & Kuo CJ. Non-

equivalence of Wnt and R-spondin ligands during Lgr5⁺ intestinal stem-cell self-renewal. *Nature* 2017 May 11 545(7653):238-242. PMID: 28467820.



Middelhoff M, Westphalen CB, Hayakawa Y, **Yan KS**, Gershon MD, Wang TC, Quante M. Dclk1-expressing tuft cells: Critical modulators of the intestinal niche? *Am J Physiol Gastrointest Liver Physiol*. 2017 October

1 313(4): G285-G299. PMID: 28684459.



Yan KS, Gevaert O, Zheng GXY, Anchang B, Probert CS, Larkin KA, Davies PS, Cheng ZF, Kaddis JS, Han A, Roelf K, Calderon RI, Cynn E, Hu X, Mandleywala K, Wilhelmy J, Grimes SM, Corney DC, Boutet SC, Terry JM, Belgrader P, Ziraldo SB, Mikkelsen TS, Wang F, von

Furstenberg RJ, Smith NR, Chandrakesan P, May R, Chrissy MAS, Jain R, Cartwright CA, Niland JC, Hong YK, Carrington J, Breault DT, Epstein J, Houchen CW, Lynch JP, Martin MG, Plevritis SK, Curtis C, Ji HP, Li L, Henning SJ, Wong MH & Kuo CJ. Intestinal enteroendocrine lineage cells possess homeostatic and injury-inducible stem cell activity. *Cell Stem Cell*. 2017 July 6 21(1):78-90. PMID 28686870.



Zhang H, Gan H, Wang Z, Lee J, Zhou H, Ordog T, Wold M, Ljungman M, **Zhang Z.** RPA Interacts with HIRA and Regulates H3.3 Deposition at Gene Regulatory Elements in Mammalian Cells *Molecular Cell*. 2017 January 19 65(2): 272-284. PMID: 28107649.

G&D in the News

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CUMC Newsroom Bone-Derived Hormone Reverses Age-Related Memory Loss in Mice Study also identified possible

target for novel therapies. August 29, 2017 Posted in: Neurology / Medicine Newsroom Link

Age-related memory loss may be reversed by booking blood levels of osteocalcin, a hormone produced by bone cells, according to mouse studies led by CUMC researchers.



CUMC Newsroom Advanced Prostate Cancer Treatment Failure Due to Cell Reprogramming Response to anti-androgen

therapy decreased in mice that were missing tumor suppressor genes. May 4, 2017

Posted in: <u>Cancer</u>, <u>Prostate Cancer</u> / <u>Medicine</u> Newsroom Link

Researchers discovered a mechanism that reprograms tumor cells in patients with advanced prostate cancer, reducing their response to anti-androgen therapy.



CUMC Newsroom 5 Questions with Prof. Emmanuelle Passegué on Stem Cells April 7, 2017 Posted in: <u>Stem Cells</u> / <u>Medicine</u> <u>Newsroom Link</u>

The new director of Columbia's Stem Cell Initiative talks about stem cells and aging, the hope for stem cell therapies, and her plans for stem cell research at Columbia.



CUMC Newsroom New Technique Searches 'Dark Genome' for Disease Mutations August 10, 2017 Posted in: Medicine, Precision Medicine Newsroom Link

Researchers have found a way to identify disease-causing genetic mutations in the non-coding region of the genome, which has been uninterpretable until now.



CUMC Newsroom Marked for Life: Genes Silenced with Histone Modifications March 27, 2017 Posted in: <u>Genetics</u>

Newsroom Link

Studies answer an old debate in developmental biology: How do cells destined to form a particular tissue or structure remember what they're supposed to be?

TRAINING PROGRAM IN G&D

Michael Shen, PhD

Director of the Training Program in Genetics and Development Columbia University Medical Center

The program in Genetics and Development provides a broad, solid education in genetics and animal development, with rigorous training in critical thinking and experimental design. Genetics is central to all of biology and the training program is guided by the principle that understanding the genetic control of development and physiology is a fundamental goal of biomedical research.



We offer training in a diverse range of research areas that include the regulation of gene expression, cell differentiation, and growth control, the molecular genetics of embryogenesis, cell patterning and organogenesis, the genetics and pathogenesis of inherited disease, the molecular genetics of cancer, molecular physiology, stem cell biology, the genetics of recombination and linkage analysis and human genetics and genomics, biological modeling of human diseases, and the development of targeted therapeutics as part of Columbia's Precision Medicine Initiative. Model organisms from yeast to mouse complement studies of human genetics and development. Thirty one faculty from nine different departments make up the training faculty providing an interdisciplinary yet collegial group of mentors all making use of genetic approaches in their research. This faculty is dedicated to the highest standards of graduate education.

Student Achievements

Celebrating the achievements of the students in our program over the course of this year

Sarah Dugger (year 4) was awarded the TL1 Transform Program Training Fellowship through CUMC's Irving Institute of Clinical and Translational Research. This is a 2-year fellowship funded through the NIH CTSA award and is meant to provide additional research training in clinical and translational science.

Laura Crowley (year 3) was awarded the NSF Graduate Research Fellowship. The oldest of its kind, the Graduate Research Fellowship Program is a 3-year fellowship that supports graduate students conducting basic science research in science, technology, engineering, and mathematical fields. **Tarun Nambiar (**year 3), Sarah Joseph (year 4), and Sam Hayward (year 2) are authors on a paper titled "CRISPR-Mediated Base Editing Enables Efficient Disruption of Eukaryotic Genes through Induction of STOP Codons" which was recently published in Molecular Cell. The paper was a collaborative effort between the laboratories of Dr. Alberto Ciccia and Dr. Rodney Rothstein

Congratulations to our Thesis Defenders!

Michael Smith

Yelena Zhuravlev

Canman Lab July 14, 2017 *"Molecular interactions at play during Cytokinesis"* Rothstein Lab August 15, 2017 "Rand51 interacts with the DNA Damage Checkpoint to regulate increased global mobility of chromosomes"

Sedef Tinaztepe

Goff Lab September 6, 2017 "Biochemical and genetic investigation of immature murine leukemia virus assembly"

PLEASE WELCOME OUR FIRST YEAR STUDENTS 2017!

Jeffrey Bellah comes to us from Emory University, where he has been researching the development of a drug-induced tumor in zebrafish in the lab of Dr. Andreas Fritz. His application expressed an interest in researching topics concerning organogenesis and pattern formation in development. Jeffrey once raised a lamb and a kid in his kitchen.

Jane Chen is well known to us, as she has been working in

Garv Struhl's lab since 2015. We are excited to welcome Jane to the Graduate Program! Jane comes to us from Shanghai, China, having already received a Master's in Law and Public Health Policy from the University of Minnesota in Minneapolis. She then went back to school and received a BA in Biochemistry from School Columbia's of General Studies in 2016. Her application expressed an interest in stem cell research and microbiology. When not in the lab, Jane studies ballet, salsa, and swing dancing, and fences both foil and saber.



Left to right: Bulat Ziganshin, Jeffrey Bellah, Jane Chen, Lizzie Goldberg, Wanqi Wang, and Grace Herod

minor in Bioethics at the University of Virginia, where she was an Echols Scholar. Grace has been researching the development and behavior of the lymphatic vasculature of the meninges in the Kipnis lab. She is excited about exploring yetuncharted aspects of cell differentiation and tissue regeneration with an ultimate goal of pursuing her own research in a university where she can share knowledge with the next generation of scientists. This summer, Grace explored

Grace Herod has just completed her BS in Biology with a

12 countries in Europe on a backpacking trip.

Wangi Wang is a recent graduate of Smith College, where she has been studying the organization of circadian systems in mice at the Harrington lab. Wangi has already lived around the world, coming originally from China and having studied in Northampton, MA, London, England, and Stanford, CA. While here, Wangi is interested in studying the relationship between circadian rhythms and neurodegenerative diseases and cancer progression.

Lizzie Goldberg has been studying Medicine at the University of Florida, College of Medicine, where her first research rotation was at the Gunel lab at Yale University. This experience led Lizzie to put her MD/PHD program on hold to pursue a PhD with us. Lizzie is interested in bridging the gap between clinical research and improved patient outcomes. While at Columbia she is interested in studying the underlying mechanisms that lead to oncogenic transformation. When she's not in the lab, you can find Lizzie at the gym working out for her next body building competition. **Bulat Ziganshin** holds an MD from Kazan State Medical University in Kazan, Russia. He's been living and working in the US since 2012, where he's been an Associate Research Scientist in Cardiac Surgery at Yale University. As a surgeon, Bulat has been researching the genetics of thoracic aortic disease in collaboration with Professor Allen E. Bale for the past four years. Now, he's looking forward to becoming a part of the future of research and patient care in aortic disease as he acquires his own expertise in Genetics and Development. Bulat is also an accomplished soccer player, having played for the junior team of Arsenal Football Club in London as a child.

Click here to see our Student Friday Seminar Series Fall 2017 Schedule

G&D DEPARTMENTAL TUESDAY SEMINAR SERIES

FALL 2017 SCHEDULE

September 1 st	Philippe Pasero, PhD Institute of Human Genetics National	November 14 th	Diana Laird, PhD UCSE School of Medicine
	Center for Scientific Research, France Hosted by: Dr. Alberto Ciccia		Hosted by: Dr. Laura Johnston
		November 21 st	Shingo Kajimura, PhD
October 10 th	Anthony De Tomaso, PhD		University of California, San Francisco
	University of California, Santa Barbara		Hosted by Dr. Gerard Karsenty
	Hosted by: Dr. Emmanuelle Passegué		
		December 5 th	Heinrich Jasper, PhD
October 24 th	Katherine Lemon, MD, PhD		Buck Institute for Research on Aging
	Harvard Medical School		Hosted by: Dr. Kelley Yan
	Hosted by: Dr. Mimi Shirasu-Hiza		
		December 12 th	Orie Shafer, PhD
October 31 st	Takehiko Kobayashi, PhD		University of Michigan
	IMCB Tokyo University		Hosted by: Dr. Mimi Shirasu-Hiza
	Hosted by: Dr. Rodney J. Rothstein		

SPRING 2018 SCHEDULE

January 23 rd	David K. Cortez, PhD Vanderbilt University School of Medicine Hosted by: Dr. Alberto Ciccia	April 3 rd	Jimmy L. Holder, Jr. MD, PhD Baylor College of Medicine Hosted by: Dr. V. Alessandro Gennarino
January 30 th	Marcus Smolka, PhD Cornell University Hosted by: Dr. Rodney J. Rothstein	April 10 th	D. Allan Drummond, PhD University of Chicago Hosted by Dr. Luke Berchowitz
February 6 th	Eric Alani, PhD Cornell University Hosted by: Dr. Jean Gautier	April 17 th	Junjie Chen, MD Anderson Cancer Center Hosted by: Dr. Zhiguo Zhang
February 13 th	Saul A. Villeda, PhD UCSF School of Medicine Hosted by Dr. Emmanuelle Passegué	April 24 th	Anne Brunet, PhD Stanford University Hosted by: Dr. Gerard Karsenty
February 20 th	Quaid Morris, PhD University of Toronto Hosted by: Dr. V. Alessandro Gennarino	May 1 st	Victor Ambros, PhD University of Massachusetts (Medical School) Hosted by: Dr. V. Alessandro Gennarino
February 27 th	Don Fox, PhD Duke University School of Medicine Hosted by: Dr. Ben Ohlstein	May 8 th	Fernando Camargo, PhD Boston Children's Hospital Hosted by: Dr. Kelley Yan
March 6 th	Ahmad (Mo) Khalil, PhD Boston University Hosted by: Dr. Luke E. Berchowitz	May 15 th	Greg Cox, PhD Jackson Laboratory Hosted by: Dr. Wayne Frankel
March 13 th	Heidi McBride, PhD Montreal Neurological Institute and Hospital Hosted by: Dr. Eric Schon	May 22 nd	Shankar Srinivas, PhD University of Oxford Hosted by Dr. Frank Costantini
March 20 th	Leanne Jones, PhD UCLA Hosted by Dr. Emmanuelle Passegué	.	
March 27 th	Marcelo Nobrega, MD, PhD University of Chicago Hosted by Dr. V. Alessandro Gennarino	Time:	n: Roy and Diana Vagelos Education Center 104 Haven Avenue - Room 201 4:00pm

Past Events



On April 22nd, more than 1 million people from all over the world joined together to support science in the single largest event in history.

March for Science NYC Dr. Max E. Gottesman and Dr. Gerard Karsenty

The G&D Department also showed their love and support for science and research by joining The March for Science in NYC <u>http://www.marchforscience.nyc/</u>. Dr. Mimi Shirasu-Hiza helped to organized a large group of faculty, postdocs and students and met downtown, proudly wearing our winning retreat T-shirts and lab coats.



G&D Departmental Graduate Program Director Retires

The Department bid farewell to Dr. Virginia Papaioannou with a retirement party held in her honor on July 11th. Dr. Papaioannou received her bachelor's in Biological Science from University of California

Davis in 1967. Dr. Papaioannou then completed her Ph.D. in genetics at University of Cambridge, England under the mentorship of Dr. Michael Ashburner. She then completed two post-doctoral fellowships, one at the Marshall laboratory, University of Cambridge (1972-1974) and one in the Department of Zoology at the Sir William Dunn School of Pathology within the University of Oxford. Over the past 36 years, Dr. Papaioannou has held academic appointment, first in the Department of Pathology at Tufts University School of Medicine and Veterinary Medicine prior to joining Columbia University in 1993. Between 1993 and 2016 she served as director of the graduate program in Genetics and Development and received the training grant in Genetics and Development five consecutive times. In addition to this commitment to Education in the department, she was a member of the Operation and Steering Committees of the Integrated Program in Cellular, Molecular and Biophysical Studies from 1995 to 1998, a member of the Executive Committee of the Graduate School of the Arts and Sciences from 2001-2007, a member of the Presidential Awards for Outstanding Teaching Committee from 2010-2013, and a member of the Columbia University Provost's Review Advisory Committee from 2013-2016. Dr. Papaioannou's Emeritus status is well deserved for her lasting contribution to the Department's mission of research excellence, in her role as Director of the Graduate Program in Genetics and Development and her active participation in many research activities on campus.



Departmental Retreat

The 32nd annual Genetics and Development Departmental Retreat was held at the Wyndham Hamilton Park Hotel & Conference

Center in New Jersey on September 22 & 23. The two day event included research talks by faculty members and a poster session presented by students and postdocs. A very special thank you goes to Dr. Charles Cantor for his continuous and generous support!



Symposium in honor of Dr. Rodney J. Rothstein

The Department of Genetics and Development organized a special symposium in honor of Rodney J. Rothstein at the occasion of his 70th birthday. This symposium was held at Columbia University Medical Center on Friday, November 3, 2017. Guest speakers from all over the world along with researchers, colleagues, stu-

dents and former lab members came to participate in this remarkable one day event.

G & D Newsletter - Issue 2



The Genetics and Development Department joins social media

This September, the Graduate Training Program Committee decided that it is time our department had a social media presence.

Within the day, we had established a presence on Twitter, Facebook, and Instagram, with our Second Year students taking charge of soliciting updates. The Instagram team has been having the most fun, posting everything from views of the George Washington Bridge to in-lab antics.



Congratulations Ginny!

Velocity: Columbia's Ride to End Cancer

Dr. Virginia Papaioannou participated in Columbia's first Velocity Ride to End Cancer which helped raise \$1.4 million for the Columbia Cancer Center (HICCC). She reached her goal of riding 25 miles and raised \$4000.

You can now follow along at the following addresses:

