



NIH Research Festival

60 Years Onward: The Double Helix in the Clinical Center

Scientific Directors Poster Session



A note from the NIH Research Festival co-chairs

The NIH Research Festival, the annual showcase of intramural research, is the perfect setting to come together and share the joy of doing research at the NIH. Each year we have much to highlight. Consider this year's dizzying and diverse offering of more than 120 talks and 500 scientific posters.

Often overlooked each year, however, is something that we find to be a very unique characteristic of the NIH compared to other research organizations: Many of those involved in upper management—the scientific directors, the institute and center directors, and the NIH director himself—also maintain active intramural labs. And so, we wanted to host a special poster session this year to highlight this fact.

We are delighted that our fellow scientific directors agreed to participate in this poster session to showcase their scientific work...and (gulp) baking abilities! How will this work? In the spirit of putting more *festival* in the Research Festival, the SDs have been instructed to explain one of their research projects via a poster yet also have a generous amount of homemade food on hand. A group of brave postdoctoral fellows then will serve as judges, evaluating the quality of both the posters and food offerings (via some metric currently unbeknownst to us) with the intent of crowning a scientific/culinary champion at the end of the session.

Our real desire, of course, is to attract our largest Festival crowd yet to see and to participate in all the scientific sessions. Our work constitutes less than 2% of the amazing science on display this week. Is this a tradition in the making? We hope so. Can we lasso in the institute directors next year? We'll try.

Thank you to all the scientific directors for their participation, and a warm, sweet welcome to the visiting audience.

Luigi Ferrucci, M.D., Ph.D.
Scientific Director, NIA

Daniel Kastner, M.D., Ph.D.
Scientific Director, NHGRI

Direct Activation of Intracellular Signaling Pathways by Amphetamines: More about DAT

Susan Amara, NIMH • [Poster SD-1](#)



Neurotransmitter transporters are the primary targets for psychostimulant drugs of abuse and for drugs such as methylphenidate and amphetamines. In recent studies we have observed that once amphetamine-like drugs enter dopamine neurons they activate multiple intracellular signaling pathways to trigger changes in the cellular trafficking of the dopamine transporter and other neuronal membrane proteins. Within the cell amphetamines act on G-protein coupled trace amine receptors to increase cAMP and also activate the small GTPases, Rho and Rac1 to trigger endocytosis of the dopamine transporter (DAT) by a RhoA-dependent pathway. This work implies that amphetamine-like drugs not only block monoamine transport and potentiate neurotransmitter action, but also act on specific cytoplasmic targets that regulate protein trafficking and other cellular activities.

Collaborators include members of her former laboratory at University of Pittsburgh and new colleagues in NIMH

The Systems Biology of the Mitochondrion

Robert S. Balaban, NHLBI • [Poster SD-2](#)



It is clear that the domestication of the mitochondrion in the eukaryotic cell has resulted in an extremely complex network regulating the chronic and acute function of this bug. My laboratory has been attempting to study this process in the context of these chronic and acute domestication mechanisms as they occur in different organs, allometric series and disease states. In the realm of chronic regulation, we are examining the positioning and function of mitochondria in the cell using intra-vital multi-photon microscopy and high-resolution EM. These studies have revealed

numerous structural modifications of the mitochondria supporting its function while not interfering with vital differentiated functions of the cell. The mitochondrial protein program, generated by the coordinated translation of the nuclear and mitochondrial DNA, is being examined using a multitude of proteomic approaches. This later step, protein expression, controls the maximum velocity of the mitochondrial reaction sequences. We have found that when a metabolic pathway is up-regulated, the entire enzymatic cascade is up-regulated, no “rate-limiting steps”, suggesting that the entire protein network is required to maintain a properly regulated pathway. This observation alone has implications in the interpretation of knockout and transgenic studies. With regard to acute regulation of function, that is what happens when you run up a flight of stairs, we have developed an optical spectroscopy system, coupled to measures of membrane potential and ATP production rates that permit us to follow most of the oxidative phosphorylation enzymatic cascade with ~ 200 msec time resolution. These studies have shown, in a similar manner to the proteomic examination, that the enzymatic activity of the entire cascade is regulated in a coordinated fashion. That is, increases in activity induced by calcium are seen across the cascade while decrease in activity with ischemic/reperfusion inhibits the entire network. These studies are currently limited to isolated mitochondria; however, a system for the perfused heart is under development to make these studies possible in intact tissues. Finally, what is the signaling mechanism acutely regulating the complexes of oxidative phosphorylation? We have been extensively evaluating the role of matrix post-translational modifications (PTM) and have reached the tentative conclusion that conventional, eukaryotic cell: acetylation, phosphorylation etc., mechanisms cannot explain our observations. We have now turned to evaluating bacterial signaling systems assuming that the retention of these mechanisms, much like matrix DNA coding and transcription mechanisms may have persisted through the domestication process. We will report on our progress on this latter topic in October.

Collaborators include past and current staff of the Laboratory of Cardiac Energetics

Rescuing Cocaine-Induced Prefrontal Cortex Hypoactivity Prevents Compulsive Cocaine Seeking

Antonello Bonci, NIDA • [Poster SD-3](#)



Loss of control over harmful drug seeking is one of the most intractable aspects of addiction, as human substance abusers continue to pursue drugs despite incurring significant negative consequences. Human studies have suggested that deficits in prefrontal cortical function and consequential loss of inhibitory control could be crucial in promoting compulsive drug use. However, it remains unknown whether chronic drug use compromises cortical activity and, equally important, whether this deficit promotes compulsive cocaine seeking. Here we use a rat model of compulsive

drug seeking in which cocaine seeking persists in a subgroup of rats despite delivery of noxious foot shocks. We show that prolonged cocaine self-administration decreases *ex vivo* intrinsic excitability of deep-layer pyramidal neurons in the prelimbic cortex, which was significantly more pronounced in compulsive drug-seeking animals. Furthermore, compensating for hypoactive prelimbic cortex neurons with *in vivo* optogenetic prelimbic cortex stimulation significantly prevented compulsive cocaine seeking, whereas optogenetic prelimbic cortex inhibition significantly increased compulsive cocaine seeking. Our results show a marked reduction in prelimbic cortex excitability in compulsive cocaine-seeking rats, and that *in vivo* optogenetic prelimbic cortex stimulation decreased compulsive drug-seeking behaviours. Thus, targeted stimulation of the prefrontal cortex could serve as a promising therapy for treating compulsive drug use.

*Chen BT, Yau HJ, Hatch C, Kusumoto-Yoshida I, Cho SL, Hopf FW, Bonci A

The Effect of Chronic Pain on the Brain

Catherine Bushnell, NCCAM • [Poster SD-4](#)



This poster will present evidence from anatomical and functional brain imaging studies suggesting that the brains of chronic pain patients are different from those of their healthy counterparts. Further, it will address the question of whether these changes are the cause or effect of pain, as well as the consequences of such changes.

Collaborators include members of her former laboratory at McGill University and new colleagues in NCCAM

Epigenetic Signature of Aging: A Longitudinal Perspective

Luigi Ferrucci, NIA • [Poster SD-5](#)



There is evidence in the recent literature that aging is characterized by a tightly regulated pattern of change in DNA methylation, which is so robust that in healthy individuals it allows the prediction of chronological age with an estimated error of ± 3 years. Limited data suggest that at the tissue level, the “epigenetic age” underestimates chronological age in people who are aging successfully while overestimates chronological aging in people who have severe morbidity. We used data from the INCHIANTI study to test the hypothesis that the same epigenetic signature emerged from cross-sectional studies is also reflected when changes in methylation are observed longitudinally over a 9-year period. We are also exploring whether “epigenetic age” is predictive of mortality and the main aging phenotypes, independent of chronological age. Our finding confirms longitudinally the existence of tightly regulated, age-associated changes in DNA methylation. The biological value of this epigenetic signature is under investigation.

*Ferrucci L, Moore ZA, Hernandez D, Singleton A

Carotid Atherosclerosis Reduction Due to NOX Inhibition in Chronic Granulomatous Disease

John I. Gallin, CC • Poster SD-6



Background: Patients with Chronic granulomatous disease (CGD) suffer immunodeficiency due to defects in the phagocyte NADPH oxidase (NOX2), and concomitant reduction in reactive oxygen intermediates. This may result in a reduction in atherosclerotic injury.

Methods: We prospectively assessed the prevalence of cardiovascular risk factors, biomarkers of inflammation and neutrophil activation, and the presence of MRI and CT quantified subclinical atherosclerosis in the carotid and coronary arteries of 41 CGD patients and 17 age-matched healthy controls.

Uni- and multivariate associations between risk factors, inflammatory markers and atherosclerosis burden were assessed.

Results: CGD patients had significant elevations in traditional risk factors and inflammatory markers compared with controls, including; hypertension, hs-CRP, oxidized LDL, triglycerides and low HDL. Despite this, CGD patients had a 26% lower internal carotid artery wall volume compared with controls ($361.3 \pm 12.7 \text{ mm}^3$ vs. $488.6 \pm 28.0 \text{ mm}^3$, $p < 0.001$). This difference was independent of risk factors in multivariate analysis. In contrast, coronary arterial calcification was similar between CGD patients and controls (5.9%, CGD, and 14.6%, controls, $p = 0.35$).

Conclusion: Patients with CGD have evidence of reduced subclinical atherosclerosis. This effect occurs in spite of an overall adverse cardiovascular risk profile. NOX2 inhibition may present an additive target of therapy in the treatment or prevention of atherosclerosis.

*Sibley CT, Estwick T, Zavodni A, Huang C, Kwan A, Soule B, Long Priel D, Remaley AT, Kuhns D, Holland SM, Malech H, Zarembler KA, Bluemke DA, and Gallin JI

The Complexity of Molecular Mechanisms Conferring Drug Resistance in Cancer

Michael M. Gottesman, DDIR • [Poster SD-7](#)



For the past 40 years, our laboratory has been studying the molecular basis of multidrug resistance in cancer. The use of new, specifically targeted anti-cancer drugs offers the promise of revolutionizing cancer treatment, but the development of drug resistance continues to be an important clinical problem. Most studies of drug resistance have been conducted in cultured cancer cell lines, which are a poor model for the more complex mechanisms of resistance that occur in vivo. By interrogating the expression of 380 known drug resistance genes in clinical samples from patients with ovarian cancer, hepatocellular carcinoma, and acute myelogenous leukemia, whose clinical response to chemotherapy is known, we have shown that alterations in expression of many different established drug resistance genes correlates with clinical response (or lack thereof). These studies indicate that precise molecular knowledge for each cancer type, and for each person's tumor, will be needed to make predictions about tumor response, and to design alternative treatment regimens.

*Gottesman, M, Hall M, Madigan J, and Gillet JP

Identification of the Mechanoelectrical Transduction Channel of Inner Ear Sensory Hair Cells

Andrew Griffith, NIDCD • [Poster SD-8](#)



Inner ear sensory hair cells transduce mechanical stimuli elicited by sound or linear or angular acceleration into electrical signals that are transmitted to the central nervous system. Mechanoelectrical transduction occurs at the tips of modified microvilli, called stereocilia, by mechanically gated ion transduction channels whose molecular identity is unknown. We will present genetic, physiologic, and cell biologic data addressing the hypothesis that transmembrane channel-like 1 protein (TMC1, encoded by the deafness gene TMC1) and the closely related TMC2 protein are components of the elusive mechanoelectrical transduction channel of auditory and vestibular hair cells

Collaborators include past and current staff of the Molecular Biology and Genetics Section

Combined Targeted Therapy Against the IGFIR Pathway in Pediatric Sarcomas: Pathways to Success

Lee J. Helman, NCI-CCR • [Poster SD-9](#)



Our laboratory, along with many others, has documented a crucial role for IGFIR signaling in several pediatric sarcomas. However, single-agent Phase 2 studies using human IGFIR antibodies showed objective response rates below 20%. Furthermore, patients typically had relatively short-lived duration of response. We have begun to dissect the mechanisms of acquired resistance in our preclinical models. We found that Akt is rapidly re-activated in the setting of persistent IGFIR down-regulation, and this can be somewhat abrogated by mTOR inhibition. Furthermore, in both rhabdomyosarcoma and Ewing's sarcoma, the Src-family kinase (SFK),

YES, is rapidly activated upon IGFIR blockade, suggesting a bypass resistance mechanism, and combination SFK inhibitors plus IGFIR blockade leads to more durable responses in both rhabdomyosarcoma and Ewing's sarcoma xenografts.

*Yeung C, Wan X, and Helman LJ

In Search of Our Inner Zebras: Exome Sequencing Unveils DADA2, a New Autoinflammatory Disease

Daniel Kastner, NHGRI • [Poster SD-10](#)



The systemic autoinflammatory diseases are a group of disorders in which there are seemingly unprovoked episodes of inflammation, often with unexplained fevers, without the high titer autoantibodies or antigen-specific T cells seen in the autoimmune diseases. The Mendelian autoinflammatory diseases have provided important insights into the workings of the innate immune system; targeted therapies with cytokine inhibitors have shown remarkable efficacy in these illnesses. Herein we describe a new autoinflammatory disease that we first observed among 5 patients referred to the NIH with fevers, increased acute phase reactants, livedoid rash, and very early-onset recurrent ischemic strokes. Utilizing whole-exome sequencing in 3 parent-child trios, and candidate-gene sequencing in the remaining 2 patients, we identified a total of 6 compound heterozygous loss-of-function mutations in *CECR1*, encoding adenosine deaminase 2 (ADA2). All mutations are either novel or present at very low frequency in several large databases, consistent with the recessive mode of inheritance. One of the mutations was present in two affected siblings with late-onset ischemic stroke in an NHLBI database, suggesting that heterozygous mutations in ADA2 may be associated with susceptibility to adult stroke. Patients had at least a 10-fold reduction of serum and plasma concentrations of ADA2, and reduced enzymatic activity. In contrast to ADA1, which is mutated in some patients with severe combined immunodeficiency disease, ADA2 is expressed predominantly in myeloid cells (but not endothelial cells) and is a secreted protein, and its affinity to adenosine is much less than ADA1. There was no accumulation of deoxyadenosine nucleotides in patients' erythrocytes, and there was only a very modest impairment of adaptive immunity. Skin, liver, and brain biopsies demonstrated vasculopathic changes characterized by impaired endothelial integrity and endothelial cellular activation, and in one case necrotizing vasculitis. Knockdown of the zebrafish ADA2 ortholog caused intracranial hemorrhages and neutropenia, phenotypes that were rescued by wild type but not mutant human *CECR1*. We also observed impairment of M2 macrophage differentiation in cultured patients' monocytes. Since our observation of the initial 5 NIH patients, we have received samples from 4 other patients, 3 of whom have polyarteritis nodosum, and all 4 are homozygous or compound heterozygous for *CECR1* mutations. We propose the term "deficiency of ADA2" (DADA2) to denote this illness. Our working hypothesis is that ADA2 acts as a growth factor for both endothelial cells and some subsets of macrophages, and that the deficiency of this protein leads to a spectrum of vascular disease and systemic inflammation. We are currently exploring replacement therapy with fresh frozen plasma. Cellular and gene therapies may also have a role in the treatment of this potentially devastating illness.

*Zhou Q, Yang D, Ombrello AK, Toro C, Stone D, Chae JJ, Rosenzweig SD, Bishop K, Barron K, Kuehn H, Hoffmann P, Tsai W, Cowen EW, Pei W, Milner JD, Silvin C, Heller T, Chin DT, Patronas NJ, Barber JS, Lee C-CR, Wood GM, Ling A, Mullikin J, Kelly SJ, Kleiner DE, Kong HH, Candotti F, Quezado MM, Clavo C, Alao H, Barham BK, Jones A, Goldbach-Mansky R, Fleisher TA, Remmers EF, Burgess SM, Moir SL, Gadina M, Sood R, Boehm M, Aksentijevich I, and Kastner DL

MRI Detection of Laminar Sites of Synaptic Plasticity in the Rodent Brain

Alan Koretsky, NINDS • [Poster SD-11](#)



Developments in both MRI and optical imaging have made it possible to image neural activity throughout an entire circuit and within a local circuit. It remains a challenge to image the strength of synaptic connections within a circuit or to delineate where synaptic weights are changing during learning or plasticity. A combination of manganese enhanced MRI and fMRI is enabling the delineation of potential sites of synaptic weight changes in the adult brain after injury induced plasticity or simple learning. In one case, the predictions from MRI have been confirmed using slice electrophysiology techniques. Slice electrophysiology is further used to understand the detailed synaptic mechanisms underlying the changes detected in MRI.

*Yu X, Chen DY, Chung S, Isaac J, and Koretsky A

Genome-Wide Promoter O-GlcNAcylation Impacts RNA Pol II Behavior: A Link Between Metabolism and Polymerase Dynamics

Michael Krause, NIDDK • [Poster SD-12](#)



Nutrient-driven O-GlcNAcylation has been linked to the epigenetic regulation of gene expression in metazoans. In *C. elegans*, O-GlcNAcylated proteins preferentially associate with the promoters of over 800 developmental, metabolic, and stress-related genes. We show that these O-GlcNAc marked genes have an unusual 5' bias in the distribution of both Ser-2 and Ser-5 phosphorylated RNA Polymerase II (Pol II) isoforms. Blocking O-GlcNAc cycling leads to elevated GlcNAcylation of Pol II, whose highly repetitive C-terminal domain (CTD) domain is a known target of O-GlcNAcylation. Blocked O-GlcNAc cycling also leads to a dramatic

5'-biased redistribution of Pol II in response to starvation and feeding that is normally masked by dynamic O-GlcNAc cycling in wild type animals. As expected, the viable O-GlcNAc cycling mutants exhibit significantly altered gene expression in response to nutrient flux. Our findings suggest a complex interplay between the O-GlcNAc modification at promoters Pol II dynamics. We argue that nutrient-responsive O-GlcNAc cycling could buffer the transcriptional apparatus from dramatic swings in nutrient availability by integrating nutrient levels with transcriptional regulation, possibly through direct interactions with Pol II.

*Krause M, Love DC, Ghosh SK, Wang P, Bentley DL, Fukushima T, and Hanover JA

Endocannabinoid-Activated Nlrp3 Inflammasome in Infiltrating Macrophages Mediates β -Cell Loss in Type-2 Diabetes (T2DM)

George Kunos, NIAAA • [Poster SD-13](#)



T2DM progresses from compensated insulin resistance to β -cell failure resulting in uncompensated hyperglycemia, a process replicated in the Zucker diabetic fatty (ZDF) rat. The Nlrp3-ASC inflammasome has been implicated in obesity-induced insulin resistance and β -cell failure. Endocannabinoids contribute to insulin resistance via activation of peripheral CB1 receptors (CB1R), and also promote β -cell failure. Here we show that β -cell failure in adult ZDF rats is associated with CB1R-activation of the Nlrp3-ASC inflammasome in M1 macrophages infiltrating pancreatic islets, but not in β -cells. These effects are replicated in vitro by incubating human or rodent macrophages but not macrophages from CB1R-deficient (Cnr1^{-/-}) or Nlrp3^{-/-} mice with the endocannabinoid anandamide. Peripheral CB1R blockade, in vivo depletion of macrophages or macrophage-specific knockdown of Cnr1 reverses or prevents these changes, and restores normoglycemia and glucose-induced insulin secretion. These findings implicate macrophage-derived endocannabinoids in inflammasome activation and β -cell failure, and identify macrophage CB1R as a therapeutic target in T2DM.

Collaborators include past and current members of the Section on Neuroendocrinology

Three-Dimensional Cellular Ultrastructure by STEM Tomography

Richard Leapman, NIBIB • [Poster SD-14](#)



We show how the development of electron tomography in the scanning transmission electron microscope (STEM) can be used to determine three-dimensional ultrastructure of embedded cells that are sectioned to a thickness of 1 to 2 micrometers. Such specimens are considerably thicker than can be analyzed by conventional TEM tomography, for which resolution is limited by chromatic aberration due to multiply inelastic scattering. STEM tomography is ideally suited to visualizing whole neuronal synapses, and for making quantitative measurements on the numbers, sizes and shapes of synaptic components.

*Leapman RD, Zhang J, Diamond JS, Chen X, Reese TS, Sousa AA

Applying Genomics for Dealing with Foodborne Outbreaks and More Generally for Bacterial Pathogens

David Lipman, NCBI • [Poster SD-15](#)



The Centers for Disease Control and Prevention (CDC) estimates that each year in the United States, approximately 48 million people get some form of foodborne illness, 128,000 are hospitalized, and 3,000 die of foodborne diseases. Continued globalization of our food supply and distribution system make it more challenging for the public health system to ensure food safety and the CDC's FoodNet surveillance network shows a lack of recent progress in the reduction of foodborne infections. Thus there is growing interest in new approaches for improving detection and prevention of disease outbreaks. Detecting an outbreak (two or more cases of foodborne illness occurring during a limited period of time that are associated with the same organism and the same food service operation or same food product) involves the use of a range of pathogen typing methods as well as coordination among local, state, and federal public health organizations. To detect outbreaks at an earlier stage we need more efficient and specific methods to determine that separate cases originate from the same contaminated source.

DNA fingerprinting has become one of the most powerful and specific forensic methods to connect a suspect to the scene of a crime. With the dramatic improvements in DNA sequencing technologies, whole genome sequencing of pathogens is becoming a feasible approach to have a similarly specific and informative genomic fingerprint to connect separate cases of foodborne illness to a clonal source. Working with state and regional laboratories, the Food and Drug Administration (FDA) and CDC have begun pilot projects to apply whole genome sequencing for real-time monitoring and investigation of outbreaks. I will present on NCBI's work with these organizations and others to develop the computational tools and infrastructure to use sequencing data to monitor foodborne illness. These procedures will be useful not only for tracking infections in the food chain, but also for other applications in infectious disease and basic research.

Collaborators include past and current staff of his NCBI laboratory

miR-155 Regulates Human Retinal Pigment Epithelial (RPE) Inflammation and Physiology

Sheldon Miller, NEI • [Poster SD-16](#)



The inflammatory responses of the retinal pigment epithelium are critical for maintaining the health and integrity of neural retina, RPE, and choroidal blood supply. These three tissues form a homeostatic unit in the back of the eye that respond to the cellular changes produced by aging and disease. In human RPE, out of approximately 13,000 confirmed and putative miRNAs, only two human miRNAs (miR-155 and miR-146a) were significantly up-regulated by an inflammatory cytokine mixture (FDR<0.01; 4 samples). These results help establish a physiological role for miR-155 as a sentinel for danger signals in and around the RPE. This sentinel

works to support self-tolerance and at the same time it acts against danger associated molecular patterns. For example, TLR4 mediated increases in miR-155 can have very different downstream outcomes depending on the input signal (eg, photoreceptor outer segments or LPS). How this occurs is currently unknown. There is a duality in the action of miR-155. Over short periods of time, it can act in close conjunction with other signals to prevent inflammation and over longer periods of time, it can actively sustain the immune response.

Collaborators include past and current staff of the Section on Epithelial and Retinal Physiology and Disease

Recent Advances in the Genetics of Cushing Disease and other Forms of Cushing Syndrome

Constantine Stratakis, NICHD • [Poster SD-17](#)



The majority of benign lesions of the adrenal cortex (AC) leading to Cushing syndrome (CS) are linked to one or another abnormality of the cyclic (c) AMP signaling pathway. Benign adrenocortical causes of CS include the common and sporadic cortisol-producing adenoma (CPA) and a spectrum of corticotropin (ACTH)-independent, and almost always bilateral, hyperplasias.

Macro-hyperplasias are more common among older patients, whereas micro-hyperplasias are frequent among children and young adults. Massive macronodular adrenocortical disease (MMAD) or ACTH-independent macronodular adrenocortical hyperplasia (AIMAH)

describes a heterogeneous group of disorders that are associated with aberrant G-protein-coupled receptor (GPCR) expression (E). Abnormal GPCR-E has been found in CPAs; a small number of both MMADs and CPAs harbor somatic *GNAS* (*Gsa*) mutations. AIMAH can also be found in the context of McCune-Albright syndrome. Micro-hyperplasias are either pigmented (the classic form being that of primary pigmented nodular adrenocortical disease or PPNAD) or non-pigmented (NP-MAH) and isolated (i) or in the context of other syndromes (Carney complex - CNC). Both CNC and iPPNAD are caused by germline *PRKAR1A* mutations; somatic mutations of this gene that regulates cAMP-dependent protein kinase (PKA) are also found in 10-20% of all CPAs and abnormalities of PKA are present in most MMADs. NP-MAH forms of adrenal hyperplasia and some CPAs are associated with phosphodiesterase (PDE)-11A and PDE-8B sequence defects. Other PDEs may be involved, too. From all the above, it is clear that increased cAMP signaling leads to tumors in AC. Mouse models of *PRKAR1A* deficiency also show that increased cAMP signaling leads to tumors in AC and other tissues. Whole-genome transcriptome profiling of tumors from humans and mouse models identified Wnt signaling as the main pathway activated by abnormal cAMP signaling, along with cell cycle abnormalities. Most recently, we further demonstrated that activation of Wnt-signaling is a somewhat generic endpoint of cAMP/PKA activation, even in bone. We conclude that cAMP signaling aberrations are essential in the pathogenesis of benign cortisol-producing lesions of the AC, especially micronodular hyperplasias.

Collaborators include past and current staff of the Section on Genetics and Endocrinology

Asthma and Allergic Sensitization in the U.S. Population: Results from the National Health and Nutrition Examination Survey (NHANES 2005-2006)

Darryl Zeldin, NIEHS • [Poster SD-18](#)



We examined relationships between specific IgEs to a wide variety of indoor, outdoor, and food allergens and asthma-related outcomes in the National Health and Nutrition Examination Survey (NHANES 2005-2006). Study subjects aged 6 years and older (N=8,086) had blood taken for measurement of 19 specific IgEs against common aeroallergens and selected foods using the Pharmacia ImmunoCAP System, and data on asthma-related outcomes were collected by questionnaire. Elevated levels of pet- and mold-specific IgEs contributed independently to asthma-related outcomes; the greatest increases in odds were observed for current asthma and pet-specific IgEs (adjusted OR=3.70, 95% CI 2.53-5.40) and mold-specific IgEs (adjusted OR=2.15, 95% CI 1.43-3.23). In contrast, elevated levels of dust mite, food-, plant-, rodent- and cockroach-specific IgEs were not independently associated with asthma-related outcomes.

*Zeldin DC, Salo PM, Arbes Jr. SJ, Jaramillo R, Weir C, Gergen PJ, Calatroni A, Mitchell HE and Cohn RD

PI3K/AKT/mTORC1-Signaling Pathway Plays a Role in Induction of Autophagy by Type I Interferons

Kathryn Zoon, NIAID • [Poster SD-19](#)



Autophagy is a stress-induced cellular recycling mechanism that occurs at a basal level in all eukaryotic cells. Type I interferons are cytokines that have the ability to induce antiviral, antiproliferative and immunomodulatory activities in cells. Recently, we found that treatment with IFN-alpha2c and IFN-beta induces autophagy in Daudi B cells, starting at 24 h as indicated by an increase of autophagy markers LC3-II, Atg5-Atg12 complexes, and a decrease of p62. Higher levels of LC3-II were also detected 48 h post IFN-alpha2c treatment in HeLa S3, MDA-MB-231, T98G and A549 cell

lines. The increase in expression of autophagy markers correlated with inhibition of mTORC1 activity in Daudi cells. Treatment of Daudi and T98G cells with IFN-alpha2c in combination with either rapamycin (mTORC1 inhibitor) or LY294002 (PI3K inhibitor) increased the level of LC3-II, indicating that PI3K/AKT/mTORC1 signaling pathway may affect IFN-induced autophagy in Daudi and T98G cells. The role of mTOR and factors upstream of mTOR in Type I IFN-induced autophagy was confirmed by siRNA knockdown experiments. The presence of autophagosomes was shown using transmission electron microscopy. In conclusion, our findings demonstrate a novel function of Type I IFN as inducer of autophagy in a variety of cancer cell lines.

*Schmeisser H, Fey SB, Horowitz J, Fischer ER, Balinsky CA, Miyake K, Bekisz J, Snow AL, Zoon KC

<http://researchfestival.nih.gov>



Intramural Research Program