CENTER FOR GENE REGULATION IN HEALTH AND DISEASE

2008-2018

TEN YEARS OF INNOVATIVE RESEARCH AND SUCCESSFUL STUDENT TRAINING

GRHD

CLEVELAND STATE UNIVERSITY

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The Center for Gene Regulation in Health and Disease (GRHD) is the home for modern biomedical research at Cleveland State University (CSU) with a mission to understand the underlying causes of many human diseases and develop treatments based on the molecular mechanisms discovered. The idea of an interdisciplinary Center at Cleveland State University with such a focus came to fruition when CSU received a $900,000 grant from the Ohio Third Frontier Commission's Ohio Research Scholars Program, with help from the Cleveland Clinic Lerner Research Institute.

The Center launched in October, 2008, initially bringing together researchers from the disciplines of biology and chemistry to work on understanding complex molecular mechanisms involved in the regulation of gene expression as well as understanding their relevance to the most devastating diseases, including cardiovascular disease and cancer.

Over the past 10 years, GRHD has doubled the number of investigators and has expanded its disciplines to include physics. GRHD researchers have produced numerous high-quality publications in top peer-reviewed journals. GRHD has nearly tripled its extramural funding and has also received many generous private donations. Today, ranked among the top 10 gene research centers in the country, this highly collaborative environment, brings together faculty and students who are making groundbreaking discoveries and contributing greatly to the local, national, and international scientific community.

We celebrate our 10th anniversary with this special publication. All GRHD faculty were provided the opportunity to submit short pieces describing their research, and members of the community were invited to personally reflect on the evolution of GRHD over the past 10 years. I invite you to read about our history, our major achievements, and our vision for the future.

Anton A. Komar, PhD, Professor
Director, Center for Gene Regulation in Health and Disease
Cleveland State University, Cleveland, OH

Dr. Michael Schwartz, President, Cleveland State University (2002–2009) declaring the official opening of the Center.

Dr. Paul DiCorleto, Chair, Cleveland Clinic Lerner Research Institute (2002-2015) addressing the audience.

Dr. Crystal M. Weyman, founding Director, GRHD (2008-2010) addressing the audience.

Drs. George Stark, Chair, GRHD External Advisory Board, and Michael Schwartz, President, CSU.

CENTER FOR GENE REGULATION IN HEALTH AND DISEASE

VISION STATEMENT

To enhance and integrate research focused on Gene Regulation in Health and Disease leading to better understanding of the molecular mechanisms controlling these processes and the identification of therapeutic targets.

MISSION STATEMENT

The Mission of the Center is:

To develop and support research focused on Gene Regulation in Health and Disease.

To encourage and provide support mechanisms for the acquisition of extramural funding.

To encourage and provide support mechanisms for the dissemination of research results.

To create mechanisms to acquire resources to support research and student training focused on Gene Regulation in Health and Disease.

To develop and expand partnerships with relevant public and private community entities with similar interests.

To develop and promote Cleveland State University's reputation as a local, national and international leader in Gene Regulation in Health and Disease.

From its inception, GRHD has had the great fortune to recruit world-renowned scientists to serve on its external advisory board (EAB). Five of the seven members hold or have held endowed chairs, four are members of the National Academy of Sciences, and all are well recognized in their fields of expertise and have been distinguished with numerous awards.

The original members include Paul DiCorleto, PhD, Sherwin-Page Chair, Cleveland Clinic Lerner Research Institute (2002-2015); Richard W. Hanson, PhD, Leonard and Jean Skeggs Professor of Biochemistry and Chair, Department of Biochemistry, CWRU School of Medicine (1978-1999); Roy L. Silverstein, MD, John and Linda Mellowes Professor and Chair, Department of Medicine, Medical College of Wisconsin (2011-present); and George R. Stark, PhD, Chair, Cleveland Clinic Lerner Research Institute (1992-2002), Distinguished Scientist of the Lerner Research Institute, National Academy of Sciences member (1987) and the Institute of Medicine, Royal Society of London fellow (1990). Sadly, Dr. Richard Hanson passed away in February 2014. This precipitated a reorganization of the EAB and the addition of 4 new members including William M. Baldwin MD, PhD, Cleveland Clinic Lerner Research Institute; Stephen J. Benkovic, PhD, Evan Pugh Professor and Eberly Chair in Chemistry, Pennsylvania State University (1988-present), National Academy of Sciences member (1985), National Medal of Science recipient (2009); Carlos J. Bustamante, PhD, The Raymond and Beverley Sackler Professor in Biophysics and Howard Hughes Medical Institute Investigator, University of California, Berkeley (2000-present), National Academy of Sciences member (2002); and Harry F. Noller, PhD, Director, Center for Molecular Biology of RNA and Robert L. Sinsheimer Professor of Molecular Biology, University of California, Santa Cruz (1992-present), National Academy of Sciences member (1992).

The Advisory Committee has been continuously chaired by Dr. George Stark. The EAB meets yearly to evaluate GRHD progress and aid advancement.

George R. Stark, Ph.D.
External Advisory Board Chair

Staff, Department of Cancer Biology
Cleveland Clinic Lerner Research Institute, Cleveland, OH

Distinguished Scientist of the Lerner Research Institute

Member, National Academy of Sciences (1988)

Fellow, the Royal Society of London (1990)

William M. Baldwin M.D., Ph.D.
Staff, Department of Immunology
Cleveland Clinic Lerner Research Institute, Cleveland, OH

Stephen J. Benkovic, Ph.D.
Evan Pugh Professor and Eberly Chair in Chemistry, Department of Chemistry
The Pennsylvania State University, University Park, PA

Member, National Academy of Sciences (1985)

Carlos J. Bustamante, Ph.D.
The Raymond and Beverley Sackler Chair of Biophysics; Howard Hughes Medical Institute Investigator,
College of Chemistry, University of California, Berkeley, CA

Member, National Academy of Sciences (2002)

Paul E. DiCorleto, Ph.D.
Vice President for Research and Sponsored Programs
Kent State University, Kent, OH

Immediate Past Chair, Cleveland Clinic Lerner Research Institute, Cleveland, OH

Harry F. Noller, Ph.D.
Director, Center for Molecular Biology of RNA; Robert L. Sinsheimer Professor of Molecular Biology; Professor Emeritus of MCD Biology
University of California, Santa Cruz, CA

Member, National Academy of Sciences (1992)

Roy L. Silverstein, M.D.
John and Linda Mellowes Professor and Chair of Medicine,
Medical College of Wisconsin Division of Hematology and Oncology,
Milwaukee, WI

Senior Investigator
Blood Research Institute, Blood Center of Wisconsin, Milwaukee, WI

IN MEMORIAM

Richard W. Hanson, Ph.D. (1935-2014)
Leonard and Jean Skeggs Professor of Biochemistry; Chair, Department of Biochemistry
Case Western Reserve University, Cleveland, OH


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Initially, the Center brought together eight faculty from the departments of Biological, Geological and Environmental Sciences (BGES) and Chemistry (CHM): Drs. G. Valentin Boerner (BGES), Michael Kalafatis, (CHM), Anton A. Komar (BGES), Roman V. Kondratov (BGES), Bibo Li (BGES), Barsanjit Mazumder (BGES), Girish Shukla (BGES) and Crystal M. Weyman (BGES). Dr. Weyman served as founding director (2008-2010) and together with founding members Drs. Kalafatis, Komar, and Mazumder formed the governing body, the GRHD planning committee, which, then and now, oversees the Center's daily operations and budget issues and determines strategies for future development.

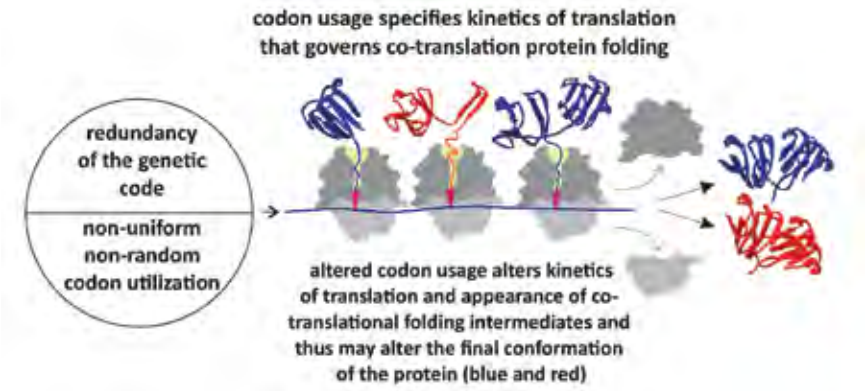
By 2012 membership nearly doubled with the addition of seven members including Drs. Xue-Long Sun (CHM) and Aimin Zhou (CHM) in 2009, Drs. Andrew Resnick (Department of Physics) and Bin Su (CHM) in 2011, and Drs. Anthony Berdis (CHM) and Aaron Severson (BGES) in 2012. In 2010, CSU hired Dr. Sailen Barik from the University of South Alabama, College of Medicine. He served as GRHD director from 2010 to 2013 and retired in 2016. Dr. Hee-Sook Kim, from The Rockefeller University, joined GRHD as Research Assistant Professor in 2017. Dr. Anton A. Komar was appointed in January 2014 and currently serves as director of GRHD. Together the 15 faculty members focus on research to improve the understanding of biological processes and how malfunction of these processes results in various diseases. This research has the significant potential to improve our understanding of the mechanisms and specific molecules that control reproductive health and the aging process as well as implications for the diagnosis and treatment of many of the most common global diseases, including neurological and infectious diseases, heart disease and cancer.

ANTON A. KOMAR, Ph.D., PROFESSOR AND DIRECTOR (GRHD)

RESEARCH INTERESTS: Translational control of gene expression

Dr. Komar's lab is interested in investigating protein synthesis, co-translational protein folding and translational control of gene expression in eukaryotic cells. We are particularly focused on investigating the link between synonymous codon usage, translation, and protein folding. The genetic code is degenerate, hence most amino acids are encoded by multiple, so-called synonymous codons. Synonymous codons were initially presumed to have entirely equivalent functions. However, synonymous codon usage is biased, as abundant and rare codons are distributed non-randomly in whole genomes and along the open reading frames of genes. We found that codon choice has functional implications beyond amino acid coding and that synonymous codons may modulate protein folding by tuning the kinetics of translation. We showed that the presence of rare and/or frequent codons at specific locations in mRNA changes the rate of folding of protein domains after they emerge from the ribosome exit tunnel. These observations provided strong support for the hypothesis that synonymous codon usage serves as a secondary code for protein folding in the cell.

Our work deepens the understanding of protein folding, one of the most fundamental mechanisms in the cell. It also helps to explain how genetic diseases linked to silent mutations develop. Finally, this work gave us a tool to upscale the production of functional active recombinant proteins for medical and biotechnological purposes.



Synonymous codon usage alters kinetics of translation and directs co-translational folding towards different protein conformations.

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1. **Komar AA** (2007) SNPs, Silent But Not Invisible. *Science*. 315, 466-467.
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4. **Buhr F, Jha S, Thommen M, Mittelstaet J, Kutz F, Schwalbe H, Rodnina MV, Komar AA** (2016) Synonymous codons direct cotranslational folding toward different protein conformations. *Mol Cell.* 61, 341-351.
5. **Komar AA** (2018) Unraveling co-translational protein folding: Concepts and methods. *Methods.* 137, 71-81.

MICHAEL KALAFATIS, Ph.D., PROFESSOR AND CHAIR (CHM)

RESEARCH INTERESTS: Blood coagulation and apoptosis (cell death), cancer.

Dr. Kalafatis' lab has two major focus areas. The first is blood coagulation and thrombosis. The coagulation system leans on a delicate balance between coagulant and anticoagulant factors. Any imbalance and/or defects in these systems can result in severe pathological conditions. The prothrombinase complex is the enzymatic complex responsible for timely thrombin formation at the place of vascular injury. It is composed of the enzyme factor Xa (fXa), the non-enzymatic cofactor factor Va (fVa), and the substrate prothrombin assembled on a lipid membrane in the presence of divalent metal ions. fVa contributes to the activation of prothrombin mainly by stabilizing the enzymatic complex and altering the kinetic mechanism of fXa (increased k_{cat}). Our data suggest that amino acids Leu^{480} and Gln^{481} from prothrombin are crucial for proper recognition of the fVa-dependent site(s) for fXa within prothrombinase, thus modulating the enzymatic activity of fXa within the prothrombinase complex. The second area of focus is cancer and apoptosis. Cancer is the primary cause of death worldwide. The traditional way to treat cancer today is *"cut, poison, and burn"* which correlates to surgery, chemotherapy, and radiation respectively with the known devastating side effects. Human tumor necrosis factor-related apoptosis-inducing ligand (hTRAIL) is a cytokine that has the capability of inducing both pathways of apoptosis (first extrinsic and then intrinsic) in cancer cells while it does not harm normal non-transformed cells. We have demonstrated that recombinant hTRAIL together with several natural compounds are efficient in inducing apoptosis in previously described TRAIL-resistant cancer cell lines. Thus, by using natural non-harmful substances and rhTRAIL, under the conditions established, only cancer cells will be specifically destroyed while normal cells will not be affected.

Selected references:

1. **Wiencek JR Hirbawi J, Yee, VC, Kalafatis, M** (2016) The dual regulatory role of amino acids Leu480 and Gln481 of prothrombin. *J Biol Chem.* 291, 1565-1581.
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3. **Manouchehri, JM, Kalafatis, M** (2017) Sensitization of rhTRAIL-Resistant Triple Negative Breast Carcinoma through Silibinin Co-Treatment. *Anticancer Research.* 37(12), 6593-6599.
4. **Manouchehri, JM, Turner, KA, Kalafatis, M** (2018) TRAIL-induced apoptosis in TRAIL-resistant breast carcinoma through Quercetin co-treatment. *Breast Cancer: Basic and Clinical Research.* 12, 1-12.
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BARSANJIT MAZUMDER, Ph.D., PROFESSOR

RESEARCH INTERESTS: Regulation of inflammation

Inflammation is a critical process in the development and progression of a wide range of human diseases. Dr. Mazumder and his team have identified ribosomal protein L13a as a molecular switch to turn off inflammation.

We have shown that in response to inflammatory stimuli, ribosomal protein L13a can be released from the ribosomes of immune cells and form a large regulatory complex with other proteins in the cytoplasm of these cells. This complex binds the messenger RNA (mRNA) of many inflammatory genes and shuts down their expression. However, this only happens at a late stage of inflammatory response, thus allowing the protection against foreign agents/infection at the initial stage and avoiding uncontrolled inflammation at the later stage. Taking the research one step further Dr. Mazumder and his team developed a genetically engineered mouse model where the expression of L13a in macrophages (major immune cells) was abrogated. As a result, these animals failed to control inflammation and showed high susceptibility to many diseases, such as high-fat diet induced heart disease, sepsis and colitis. This newly discovered cellular target to block inflammation and this animal model show tremendous potential to facilitate the discovery of a new generation of anti-inflammatory drugs that could effectively control the progression of these fatal diseases.

Selected references:

1. **Kapasi P, Chaudhuri S, Vyas K, Baus D, Komar AA, Fox PL, Merrick WC, Mazumder B** (2007) L13a Blocks 48S Assembly: Role of a General Initiation Factor in mRNA-specific Translational Control. *Mol Cell.* 25, 113-126.
2. **Vyas K, Chaudhuri S, Leaman DW, Komar AA, Musiyenko A, Barik S, Mazumder B** (2009) Genome-wide polysome profiling reveals an inflammation-responsive post-transcriptional operon in IFN-γ activated monocytes. *Mol Cell Biol.* 29, 458-470.
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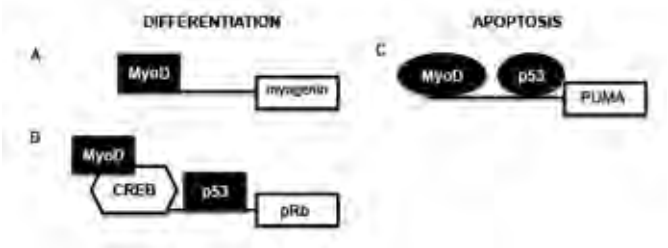
5. **Basu A, Jain N., Tolbert BS, Komar AA, Mazumder B** (2017) Conserved structures formed by heterogeneous RNA sequences drive silencing of an inflammation responsive post-transcriptional operon. *Nucleic Acids Res.* 45, 12987-13003.

CRYSTAL M. WEYMAN, Ph.D., PROFESSOR AND CHAIR (BGES)

RESEARCH INTERESTS: Coordinate regulation of differentiation and apoptosis

Differentiation (cell type specialization) and apoptosis (programmed cell death) are coordinately regulated in most, if not all, cells. Dr. Weyman's lab utilizes the model system of skeletal myogenesis to investigate this coordinated regulation. Treatment options relevant to the amelioration of muscle trauma or disease states include maximizing the regenerative potential of adult muscle stem cells as well as improving the efficacy of protocols utilizing skeletal myoblast transfer or skeletal muscle tissue engineering. For each option, a better understanding of the molecular events controlling skeletal myogenesis could identify targets for better therapeutic manipulation. To this end, we have determined that MyoD, the pioneer transcription factor long known to control muscle differentiation through both direct and indirect binding to DNA (A and B), is also responsible for controlling the coordinated apoptosis via the direct transcriptional regulation of the pro-apoptotic protein PUMA (C). Moreover, we have determined that MyoD works with the transcription factor p53 to drive PUMA expression. p53 is well known for its role in tumor suppression as a pivotal transcription factor responsible for interpreting the extent of DNA damage into either cell cycle arrest or apoptosis. p53 is less well known for its role in skeletal myoblast differentiation. We propose that post-translational modification(s), portrayed in the figure below as shape changes, could explain the mutually exclusive, dual, biological roles in differentiation or apoptosis for both of these key transcription factors. Moreover, we are gathering data that suggests that cell cycle position plays a role in these respective post-translational modifications.



Proposed model for the coordinated regulation of differentiation and apoptosis by MyoD and p53.

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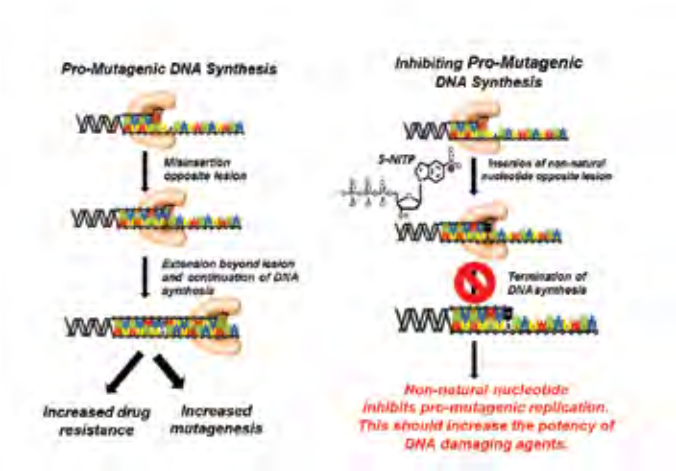
2. **Freer M, Ross J, O'Flaherty J, Weyman CM** (2009) Noncanonical role for the TRAIL receptor DR5/FADD/caspase pathway in the maintenance of MyoD expression and the differentiation of skeletal myoblasts. *Differentiation.* 4, 205-212.
3. **Harford T, Shaltouki A, Weyman CM** (2010) Increased expression of the pro-apoptotic Bcl_2 family member PUMA and apoptosis by the muscle regulatory transcription factor MyoD in response to a variety of stimuli. *Apoptosis.* 15, 71-82.
4. **Shaltouki A, Harford TJ, Komar AA, Weyman CM** (2013) IRES-mediated translation of the pro-apoptotic Bcl_2 family member PUMA. *Translation.* 1, 1-11.
5. **Harford T, Nair D, Kliment G, Shukla G, Weyman CM** (2017) The muscle regulatory transcription factor MyoD participates with p53 to directly increase the expression of the pro-apoptotic Bcl_2 family member PUMA. *Apoptosis.* 22, 1532-1542.

ANTHONY BERDIS, Ph.D., ASSOCIATE PROFESSOR

RESEARCH INTERESTS: DNA replication, nucleoside analogs, cancer

Dr. Berdis' lab is developing novel therapeutic strategies against brain cancer. Brain cancers are the deadliest of all cancers, having 5-year survival rates of less than 10%. Temozolomide (TMZ) is an FDA-approved chemotherapeutic agent currently used to treat brain cancers. This drug produces DNA lesions such as abasic sites that induce cell death. While TMZ is initially effective in reducing tumor burden, its therapeutic activity rapidly diminishes due to the emergence of resistance. One mechanism for this resistance reflects the ability of DNA polymerases to misreplicate the DNA lesions formed by TMZ (see Figure below). In addition to causing drug resistance, this activity is pro-mutagenic and can create more mutations in a cancer cell which can produce more aggressive cancers.

To combat these problems, we developed an artificial nucleotide analog designated 5-*N*itroIndolyl *T*ri*P*hosphate (5-NITP) that is efficiently and selectively incorporated opposite DNA lesions created by TMZ. Once inserted opposite damaged DNA, this analog inhibits replication beyond the lesion and thus terminates pro-mutagenic DNA synthesis. The analog is not incorporated opposite undamaged DNA and thus does not inhibit "normal" DNA synthesis. We have performed cell-based and animal studies demonstrating that the corresponding nucleoside, 5-NIdR, potentiates the therapeutic activity of TMZ. Combining both drugs produces a synergistic cell-killing effect against brain cancer cells and eliminates brain tumors in animal models without any adverse side effects. Collectively, these data highlight the development of a new and effective therapeutic strategy against brain cancer.



The replication of DNA lesions causes mutagenesis and drives drug resistance. To combat these problems, we developed artificial nucleotides that can selectively inhibit DNA polymerase that replicate DNA lesions produced by anti-cancer agents.

Selected references:

1. **Choi JS, Berdis AJ** (2016) Visualizing nucleic acid metabolism using non-natural nucleosides and nucleotide analogs. *Biochim Biophys Acta.* 1864, 165-176.

2. **Choi JS, Dasari A, Hu P, Benkovic SJ, Berdis AJ** (2016) The use of modified and non-natural nucleotides provide unique insights into pro-mutagenic replication catalyzed by polymerase eta. *Nucleic Acids Res.* 44, 1022-1035.

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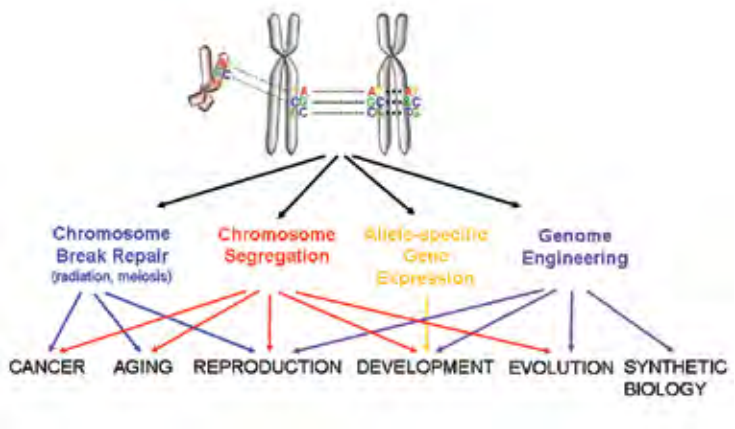
4. **Choi JS, Kim S, Berdis AJ** (2017) Inhibition of translesion DNA synthesis as a novel therapeutic strategy to treat brain cancer. *Cancer Res.* 78, 1083-1096.

G. VALENTIN BÖRNER, Ph.D., PROFESSOR

RESEARCH INTERESTS: Mechanisms of chromosome segregation during meiosis

Chromosomes are the carriers of genetic information in all higher organisms including humans. Each chromosome consists of a single DNA fiber packaged into a sausage-shaped structure. When the DNA fiber breaks, genetic material is frequently lost. Errors in chromosome break repair result in birth defects, premature aging and cancer. Chromosome breaks are induced by radiation treatment and chemotherapy thereby stopping the growth of cancer cells. Cells also induce breaks in their own chromosomes to reshuffle the genetic material for sexual reproduction. The central question of the Börner lab is: How do cells repair chromosome breaks and how do they prevent the loss of genetic information? Our research focuses on DNA repair by homologous chromosome interactions. This type of repair is especially accurate as it uses a highly similar chromosome segment as template. Several surprising discoveries have resulted from our work. We have developed a US-patented approach to identify chromosome segments involved in recognition of homologous stretches of DNA. We are now identifying the machinery that brings homologous chromosome segments together among the myriads of DNA segments within a nucleus. We have also discovered that a cellular protein degradation machinery called the proteasome assists in the DNA break repair process. Unexpectedly, the proteasome relocalizes to chromosomes while break repair is ongoing, thereby ensuring the elimination of proteins that block access to DNA damage. Ultimately, our research will contribute to a better understanding of the machinery that keeps the molecule of inheritance stable.



Chromosome break repair and segregation impacts many cellular processes and affects human health at multiple levels.

Selected references:

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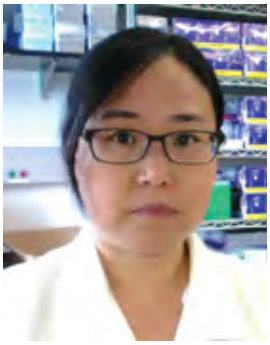
3. **Ahuja JS, Sandhu R, Mainpal R, Lawson C, Henley H, Hunt PA, Yanowitz JL, Börner GV** (2017) Control of meiotic pairing and recombination by chromosomally tethered 26S proteasome. *Science.* 355, 408-411.
4. **Sandhu R, Börner GV** (2017) Stopping chromosomes from breaking bad. *eLife.* 6:e27292.

HEE-SOOK KIM, Ph.D., RESEARCH ASSISTANT PROFESSOR



RESEARCH INTERESTS: *Trypanosoma brucei* host-pathogen interactions

Trypanosoma brucei is a protozoan parasite that causes African sleeping sickness in humans and a similar disease in livestock, mainly in sub-Saharan Africa. *T. brucei* cycles between the insect vector (tsetse fly) and mammalian hosts. In the mammalian host, the parasite expresses a single species of surface coat protein (VSG, variant surface glycoprotein) at any given time, while having over 2000 VSG genes in the genome – a process known as 'VSG silencing' (all VSGs are transcriptionally repressed, except one). To clear the parasite, the host immune system recognizes the expressed VSG and kills the parasite. However small populations of parasites escape the host immune elimination response by expressing a different subset of VSG genes – a process known as 'VSG switching'. Therefore, *T. brucei's* immune evasion via antigenic variation requires precisely controlled VSG silencing and switching mechanisms. Genome integrity factors play important roles in *T. brucei* antigenic variation, and my lab is interested in how DNA replication, transcription and chromatin structure factors talk to each other to control antigen gene diversification and maintain genome integrity.

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2. **Kim HS, Park S-H, Günzl A, Cross GA** (2013) MCM-BP is required for repression of life-cycle specific genes transcribed by RNA polymerase I in the mammalian infectious form of *Trypanosoma brucei*. *PLoS One.* 8(2): e57001.
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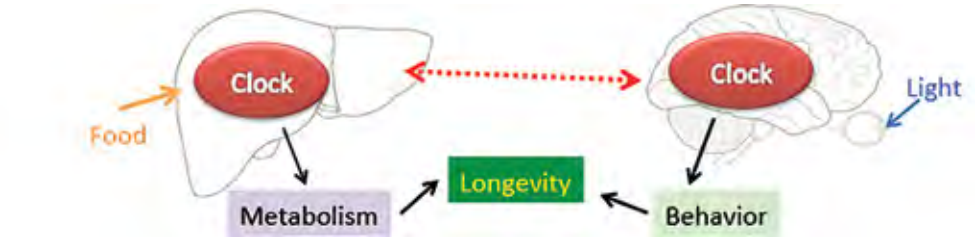
4. **Cross GA, Kim HS, Wickstead B** (2014) Capturing the variant surface glycoprotein repertoire (the VSGnome) of *Trypanosoma brucei* Lister 427. *Mol Biochem Parasitol.* 195, 59-73.
5. **Schulz D, Zaringhalam M, Papavasiliou FN, Kim HS** (2016) Base J and H3.V regulate transcriptional termination in *Trypanosoma brucei*. *PLOS Genetics.* 12 (1): e1005762.

ROMAN V. KONDRATOV, Ph.D., PROFESSOR

RESEARCH INTERESTS: Circadian control of metabolism and aging

Dr. Kondratov's laboratory is interested in how the circadian clock regulates an organism's metabolic response to diet. The circadian clock is an internal time keeping system that generates daily rhythms known as circadian rhythms. The circadian clock controls an organism's metabolism, physiology and behavior. Dr. Kondratov found that circadian clock disruption results in accelerated aging and reduced lifespan. Now we are focused on the role of the circadian clock in health and longevity. It is well known that diet might affect physiology and that wrong diet might significantly compromise health. On the contrary, some good diets, such as calorie restriction, improve health and even extend lifespan in many organisms including primates. We found that the circadian clocks are part of the calorie restriction mechanisms and that functional circadian clocks are necessary for the full benefits of calorie restriction for metabolism and longevity. We continue to work on understanding how the circadian clock and diet can be used to increase longevity.



Circadian clock controls organism metabolism, physiology and behavior. Functional circadian clock is necessary for the full benefits of calorie restriction for metabolism and longevity.

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3. **Khapre RV, Kondratova AA, Patel S, Dubrovsky Y, Wrobel M, Antoch MP, Kondratov RV** (2014) BMAL1-dependent regulation of the mTOR signaling pathway delays aging. *Aging (Albany NY).* 6, 48-57.
4. **Patel SA, Chaudhari A, Gupta R, Velingkaar N, Kondratov RV** (2016) Circadian clocks govern calorie restriction-mediated life span extension through BMAL1- and IGF-1-dependent mechanisms. *FASEB J.* 30, 1634-1642.

BIBO LI, Ph.D., PROFESSOR

RESEARCH INTERESTS: Telomere biology

Research in the Li lab focuses on telomere biology, which has great impact on improving human health and life quality. Telomeres – the nucleoprotein complex at linear chromosome ends – function like the plastic ends of shoe laces and prevent the natural chromosome ends from illegitimate DNA degradation, repair, and rearrangement. Hence, telomeres are essential for genome integrity and chromosome stability. Telomere shortening in human somatic cells is one of the important factors contributing to aging, and genome instability often leads to tumorigenesis. Additionally, targeting telomere proteins in several eukaryotic human pathogens would act as a double-edged sword. First, the Li lab has shown that loss of telomere proteins in the eukaryotic pathogen *Trypanosoma brucei* is detrimental to the parasite survival, making telomere proteins potentially good drug targets, since the parasite telomere proteins are distinctive enough from their human homologues. Second, a number of microbial pathogens, including *T. brucei* (causes human sleeping sickness), *Plasmodium falciparum* (causes malaria), and *Pneumocystis jirovecii* (causes pneumonia in immune-deficient people), regularly switch their major surface antigen, effectively evading the host immune response and successfully establishing long-term infections. These pathogens express their major surface antigens from telomere-adjacent regions. Importantly, the Li lab has shown that *T. brucei* telomere proteins are essential for the proper expression and switching of the parasite surface coat. Therefore, targeting parasite telomere proteins will also paralyze the key immune-evading mechanism of these human pathogens.

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ANDREW RESNICK, Ph.D., ASSOCIATE PROFESSOR

RESEARCH INTERESTS: Fluid flow sensing by the primary cilium

Dr. Resnick's lab is interested in the physiological role of the primary cilium. We are focused on investigating the link between fluid flow, for example flow through a nephron, and biological responses. We are active in three areas of study: quantifying fluid flow in the neighborhood of a cilium, determining and controlling the amount of ciliary bending caused by fluid flow, and determining biological responses that are responsive to fluid flow. Because fluid flow acts over the entire cell surface, locating the site of mechanosensation has been difficult. Our lab uses optical trapping to apply a force to a single cilium. We have shown that optical trapping can both bend the cilium and characterize the ciliary stiffness. We have demonstrated methods to manipulate ciliary stiffness and we have measured the minimum amount of flow required to produce a biological response. We have identified transepithelial sodium current as a flow-sensitive response that also requires an intact cilium. These observations provide strong support to the hypothesis that the primary cilium is a flow sensor and that flow sensing is important to maintain homeostasis.

Our work deepens understanding of biofluiddynamics, one of the most fundamental processes in organisms. Our work helps to explain how certain diseases develop due to faulty flow sensing. Finally, this work provides an opportunity for students who wish to combine Physics and Biology research to produce truly novel science.

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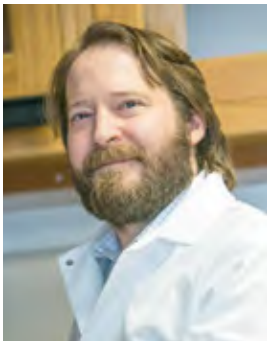
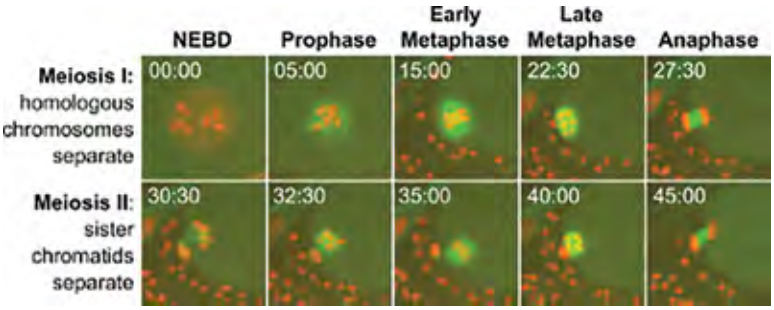
AARON F. SEVERSON, Ph.D., ASSOCIATE PROFESSOR



RESEARCH INTERESTS: Chromosome segregation and reproductive health

As a result of mistakes that occur during the formation of sperm and eggs (also called gametes), approximately one in four human embryos has too many or too few chromosomes. These errors in chromosomal inheritance have a major impact on reproductive health, causing infertility, miscarriage, and congenital birth conditions like Down Syndrome, which occurs when an embryo inherits three copies of chromosome 21 instead of two. The age of the mother at the time of conception is the best predictor of abnormal pregnancy to date, but there are undoubtedly other contributing risk factors.

My lab studies the processes that ensure that every sperm and every egg inherit a single copy of each chromosome to identify where in this chain of events mistakes are likely to occur. We have identified previously unknown factors important for producing healthy gametes, explained apparent differences in the mechanisms that form sperm and eggs in different organisms, and revealed unexpected features of gametogenesis that appear widely conserved in plants and animals. Our research has the potential to lead to tests that predict the likelihood of an abnormal pregnancy and interventions that can improve outcomes for those at risk. Because errors like those that disrupt chromosomal inheritance during the formation of sperm and eggs also occur in many forms of cancer, the importance of our research extends beyond reproductive health.



Chromosome segregation during meiosis. Microtubules (green) mediate the segregation of meiotic chromosomes (red) as chromosome copy number is precisely reduced.

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4. **Severson AF** (2017) Analysis of meiotic sister chromatid cohesion in *Caenorhabditis elegans*. *Methods Mol Biol.* 1515:65-95.
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GIRISH C. SHUKLA, Ph.D., PROFESSOR

RESEARCH INTERESTS: Posttranscriptional control of gene expression

The primary goal of Dr. Shukla's research is to understand molecular mechanisms that control eukaryotic gene expression at the RNA level. With this agenda, the lab is exploring two major topics: (1) mRNA metabolism and microRNA dynamics and (2) miRNA based therapeutic approaches to fine-tune the posttranscriptional gene expression of a multitude of cellular pathways in order to sensitize prostate cancer tumors to current FDA approved drugs. Intratumoral prostate cancer heterogeneity appears to be a consequence of various intrinsic cellular mechanisms including androgen signaling, aerobic glycolysis (Warburg effect), and aberrant activation of multiple transcription factors including androgen receptor (AR) and c-Myc as well as dysregulation of apoptosis. Dr. Shukla's research shows that miRNAs can directly downregulate the expression of diverse tumorigenicity drivers including c-Myc, AR co-regulators, and anti-apoptosis factors. The therapeutic efficacy of miRNAs is achieved by suppression of the Warburg effect by direct targeting of c-Myc, Akt, IGF-1R and GAPDH function. The lab is currently working on miRNA-mediated posttranscriptional regulation of androgen signaling, steroid metabolism, and lipid biosynthesis. In a different project, the laboratory is working on the structure-function of snRNAs including U11, U12, U4atac, and U6atac in nuclear pre-mRNA splicing by using in vitro and in vivo methods.

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1. **Singh S, Zheng Y, Jagadeeswaran G, Ebron JS, Sikand K, Gupta S, Sunker R, Shukla GC** (2016) Deep sequencing of small RNA libraries from human prostate epithelial and stromal cells reveal distinct pattern of microRNAs primarily predicted to target growth factors. *Cancer Lett.* 371, 262-273.

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BIN SU, Ph.D., PROFESSOR

RESEARCH INTERESTS: Anti-trypanosomiasis and anti-cancer drug development

Dr. Su's lab focuses on drug development research. One direction is anti-cancer drug discovery. We synthesize small molecules to target heat shock proteins that play important roles in tumor progression and drug resistance. The research involves drug design, synthesis, molecular target identification, in vitro and in vivo evaluation of the drug's efficacy, and pharmacokinetic investigation. We also use computational chemistry approaches to examine the binding domains of the compounds with their target. The tumor models we use include breast cancer, prostate cancer, and colon cancer. Another research direction is anti-trypanosomiasis drug discovery. Trypanosomal parasites cause human African sleeping sickness, and it is an orphan disease. The current treatment is toxic, less effective and needs hospitalization, which is difficult in most countries in Africa. Dr. Su's team focuses on the development of oral active small molecules that can selectively target the parasites without harming the hosts. This project involves collaboration with Dr. Bibo Li. Our team identified selective tubulin inhibitors that showed great selectivity to the parasites. Currently, we aim to further optimize the compound(s) to improve the druggable characteristics of the candidates.

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1. **Yi X, Zhong B, Smith KM, Geldenhuys WJ, Feng Y, Pink JJ, Dowlati A, Xu Y, Zhou A, Su B** (2012) Identification of a class of novel tubulin inhibitors. *J. Med. Chem.* 55, 3425-3435.
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3. **Zhong B, Vatolin S, Idippily ND, Lama R, Alhadad LA, Reu FJ, Su B** (2016) Structural optimization of non-nucleoside DNA methyltransferase inhibitor as anti-cancer agent. *Bioorg Med Chem Lett.* 26, 1272-1275.
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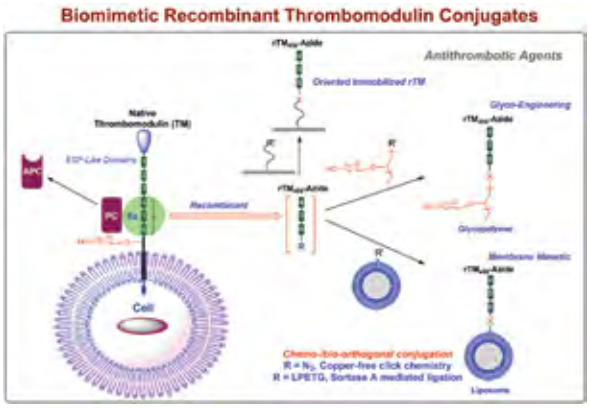
XUE-LONG SUN, Ph.D., PROFESSOR

RESEARCH INTERESTS: Developing chemical approaches for cell surface mimicry

The research area in the Sun's group is in Bio-Analytical Chemistry, Chemical Biology and Pharmaceutical Chemistry. The main research interests are developing chemical approaches for cell surface mimicry, analysis and re-engineering, with specific objectives for glycoproteomics, antithrombotics, targeted drug delivery, and cell-based therapy applications. Biomimetic synthesis of native anticoagulant biomolecules, for compensation of their loss in the pathological site, as an on-demand therapeutic strategy is one of the key focuses of our research. Endothelial thrombomodulin (TM) plays a critical role in local haemostasis by binding thrombin and subsequently converting protein C to its active form, which is an anticoagulant protease that selectively inactivates coagulation factors Va and VIIIa. TM expression decreases in perturbed endothelial cells, predisposing them to thrombotic occlusion particularly in response to a variety of inflammatory stimuli and vessel wall injury. TM is a type I membrane protein. The lipid bilayer in which it resides serves as an essential 'cofactor', locally concentrating and coordinating the appropriate alignment of reacting cofactors and substrates for protein C activation. Therefore, we are developing a TM-liposome conjugate that mimics the native endothelial antithrombotic mechanism of both TM and lipid components and thus will provide a more forceful antithrombotic agent. In addition, TM is an endothelial cell membrane proteoglycan. We are developing novel methods to synthesize TM-glycosaminoglycan (GAG) conjugates and investigating the significance of GAG on the antithrombotic activity and pharmacokinetic properties of TM.



Developing chemical approaches for cell surface mimicry.

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2. **Wang L, Jiang R, Sun XL** (2014) Recombinant thrombomodulin of different domains for pharmaceutical, biomedical, and cell transplantation applications. *Med Res Rev.* 34, 479-502.
3. **Jiang R, Wang L, Weingart J, Sun XL** (2014) Chemoenzymatic bio-orthogonal chemistry for site-specific double modification of recombinant thrombomodulin. *Chembiochem.* 15, 42-46.
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AIMIN ZHOU, Ph.D., PROFESSOR

RESEARCH INTERESTS: Interferon, RNase L signaling and cancer

There are two major research projects in Dr. Aimin Zhou's laboratory. The first one is to study RNase L, one of the key enzymes in the interferon function against viral infection and in the control of cell proliferation. Tissue distribution has revealed that RNase L is highly expressed in the spleen, thymus, and all types of immune cells. However, the physiological role of RNase L in immunity is largely unknown. The preliminary results suggest that RNase L may be a potential target for proinflammatory diseases such as diabetes and atherosclerosis. The RNase gene disrupted mouse model and cell lines are used to investigate the effect of RNase L on the function of immune cells. Another project is to elucidate the role of TMCO1, an endoplasmic reticulum (ER)-associated protein. Homozygous frameshift mutation in TMCO1 causes distinctive craniofacial dysmorphism, skeletal anomalies, and mental retardation. TMCO1 also functions as an ER Ca^{2+} load-activated Ca^{2+} channel. Recently, TMCO1 has been found in the laboratory to contribute to cancer progression and metastasis. The project goal is to determine the molecular mechanism by which TMCO1 is involved in cancer biology. The information gained from the studies may suggest TMCO1 as a potential target and a prognostic biomarker for cancer treatment.

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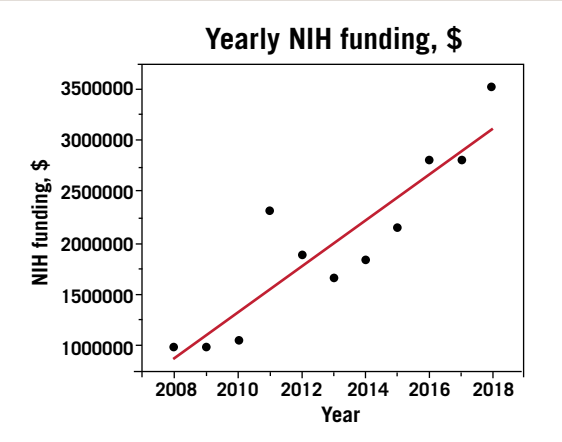
EXTRAMURAL FUNDING

During a time of unprecedented decline in available external funding, GRHD members have been awarded more than $28 million in funding from the National Institutes of Health, the National Science Foundation, the Human Frontiers Science Program, an international program of research support, the American Heart Association, the Department of Defense and the March of Dimes. Significantly, funding from the NIH increased almost 3-fold over the past 10 years, from ~$1 million in 2008 to ~$3 million in 2018.



DONOR SUPPORT

GRHD has also been very successful in attracting nearly $3.6 million in private donor support. A substantial $1 million gift endowed by an anonymous donor has been earmarked to fund graduate scholarships, post-doctoral fellowships, pilot and bridge research projects, and equipment needs.

Additionally, Dr. John C. Vitullo's Pilot and Bridge Funding program was established through the generous gift of Dr. John C. Vitullo, CEO of Omega Laboratories, Inc., Mogadore, Ohio, to support GRHD research. The program seeks to increase the visibility of GRHD as a research center of excellence at CSU, and activities funded will help attract further external support. Many anonymous donors contributed to this fund and we gratefully continue to accept donations.

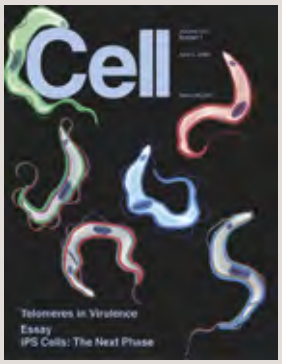
The Endowed John and Patricia Thompson Seminar Series was initiated following the very generous $100,000 gift from CSU alumni John and Patricia Thompson. The series sponsors research seminars by nationally and internationally-recognized scientists in the fields of molecular biology and genetics for GRHD faculty and students. Dr. Stephen J. Benkovic, Ph.D., Evan Pugh Professor and Eberly Chair in Chemistry, The Pennsylvania State University, delivered the inaugural seminar entitled, "The purinosome, an unique metabolon, responsible for cellular de novo purine biosynthesis," on November 2, 2017.

The Inaugural John and Patricia Thompson Seminar

Dr. Stephen Benkovic

NATIONAL AND INTERNATIONAL VISIBILITY

Over the past 10 years, GRHD researchers have published more than 225 manuscripts in high-profile, peer-reviewed journals including *Science*, *Nature*, and *Cell*. These publications have been cited more than 3,700 times, and GRHD is now included in the Nature Index which tracks the affiliations of high-quality scientific articles. Based on the amount of funding and the quality and quantity of publications, GRHD ranks in the top 10 gene research centers in the country, among notables, the Plant Gene Expression Center at the University of California at Berkeley and



STUDENT TRAINING

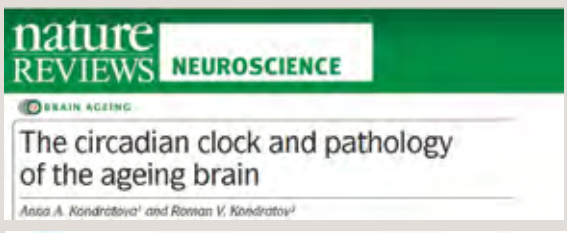
GRHD is home to nearly 100 scientists. Throughout its history, GRHD faculty have mentored more than 80 undergraduate and more than 150 graduate students in their laboratories, and many students have gone on to pursue their careers and/or further their education at top universities and institutions in the country, including Harvard, Stanford, and Columbia Universities as well as the National Institutes of Health (NIH), The Scripps Research Institute, The Cleveland Clinic Lerner Research Institute, and many others.

Opportunities that GRHD researchers provide to their students are very well aligned with the central mission of CSU, to educate those who might not otherwise have the opportunity, teach them to think constructively, critically, and creatively, and graduate them, fully prepared to succeed.

Presently, GRHD labs support more than 50 graduate students pursuing doctoral degrees in Regulatory Biology or Clinical-Bioanalytical Chemistry through programs jointly offered by Cleveland State University and the Cleveland Clinic Lerner Research Institute. Additionally, many students are seeking the Cellular and Molecular Medicine Specialization (CMMS), which offers unique opportunities for doctoral students whose interests lie in the application of modern cellular and molecular approaches to understanding disease causes and mechanisms.

Cleveland Clinic
Lerner Research Institute

CLEVELAND STATE UNIVERSITY



the Center for Eukaryotic Gene Regulation at the Pennsylvania State University. With this recognition, GRHD was selected out of the ~ top 20 Genetic Centers across the globe, and featured in a video produced for the American Society of Human Genetics (ASHG) Annual Meeting 2015, by WebsEdge, a global leader in web-based and conference TV.

GRHD faculty are in high demand as speakers at national and international conferences and workshops.

EXCERPT FROM EAB REPORTS 2014-2017 AND TESTIMONIALS FROM EAB MEMBERS

"It is extraordinary that CSU has put together such a strong research center only a few years after its inception."

"The spirit and collaborative interactions among the GRHD faculty and between the GRHD faculty and scientists elsewhere in Cleveland are remarkable."

"GRHD is well on the way to becoming one of the jewels in the university's crown."

"The GRHD members carry out a wide range of scientific investigations at a very high level. Despite the diversity of their individual projects, they nevertheless interact with each other extraordinarily well, so that the scope of their collective expertise becomes a great cumulative strength. In this setting, trainees participate in superb science, learning how to think critically and how best to take what is valuable and innovative for their own projects from the broad expertise and experience of their colleagues. Thus, GRHD provides a superb environment that produces groundbreaking research, while simultaneously educating students in how best to be productive in their future independent careers."

George Stark, PhD
Chair, GRHD advisory board; Staff, Department of Cancer Biology, Cleveland Clinic Lerner Research Institute, Cleveland, OH; Distinguished Scientist, Lerner Research Institute; Member, National Academy of Sciences; Fellow, Royal Society of London

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"What stands out about this group is their cohesiveness, their enthusiasm. This is a group that will bring a lot of acclaim to the university."

Stephen Benkovic, PhD
Member, GRHD advisory board; Evan Pugh Professor and Eberly Chair in Chemistry, Department of Chemistry, The Pennsylvania State University, University Park, PA; Member, National Academy of Sciences

CLEVELAND SCIENTIFIC COMMUNITY

"The Center for Gene Regulation in Health and Disease (GRHD) at Cleveland State University has become an asset to biomedical science in Cleveland, providing not only cutting edge research and top notch scientists, but access to a pool of uniquely qualified and talented students. At the Lerner Research Institute at Cleveland Clinic, our scientists serve as mentors for outstanding PhD students from GRHD, who bring talent and a strong work ethic to our research laboratories. We are grateful to have the opportunity to interact with both students and faculty from GRHD."

Christine S. Moravec, PhD
Director, Research Education and Training Center, and Staff, Department of Molecular Cardiology, Cleveland Clinic Lerner Research Institute, Cleveland, OH; Assistant Dean for Basic Science Education, and Director of Graduate Education, Cleveland Clinic Lerner College of Medicine, Cleveland, OH

"Congratulations on a decade of developing and sustaining so many innovative and impactful research programs, providing a high caliber education to the next generation of scientists, and putting GRHD on the map as an outstanding place to train. Looking forward to seeing what you accomplish over the next 10 years."

Donna Driscoll, PhD
Tippit Family Chair in Faculty Development and Vitality, Director, Lerner Research Institute Faculty Center, and Staff, Department of Cellular & Molecular Medicine, Cleveland Clinic Lerner Research Institute, Cleveland, OH; Professor, Cleveland Clinic Lerner College of Medicine, Cleveland, OH

"This group has a tradition of attracting excellent graduate students and vigorous faculty who provide a valuable resource for all of northeast Ohio. They have developed notable research programs and provide an excellent model for undergraduate students, many of whom join these research laboratories."

Alan M. Tartakoff, PhD
Professor, Department of Pathology, and Co-director, PhD Program in Cell Biology, Case Western Reserve University School of Medicine, Cleveland, OH

"I have had exciting and productive collaborations with the faculty in GRHD at CSU and I believe the best is still to come. The center has already been very successful - securing highly competitive federal funding for its innovative research while at the same time training and inspiring undergraduate and graduate students at the university."

Maria Hatzoglou, PhD
Professor, Department of Genetics, Case Western Reserve University School of Medicine, Cleveland, OH

ENGAGING IN NEW FRONTIERS OF RESEARCH AND DISCOVERY

Conceptual design of the COSHP/GRHD Science and Research (SR) annex, developed by Eberhard Architects LLC, in collaboration with the Office of University Architects and the Division of Capital Planning.

We are truly looking forward to identifying novel opportunities for research and discovery, particularly in partnership with local and national research institutions. GRHD is especially proud to be part of the growing biomedical research community of the Greater Cleveland area, and committed to providing high quality training to the next generation of students at CSU.

We know that sustained growth of the Center will not be possible without hiring new dynamic, research faculty and expanding appropriate, modern laboratory space. Toward this goal, a plan to develop additional, state-of-the-art laboratory space for the College of Sciences and Health Professions through a combination of public and private support has been proposed and we deeply appreciate the ongoing efforts by CSU.

WE BELIEVE GRHD'S FUTURE IS VERY BRIGHT!

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