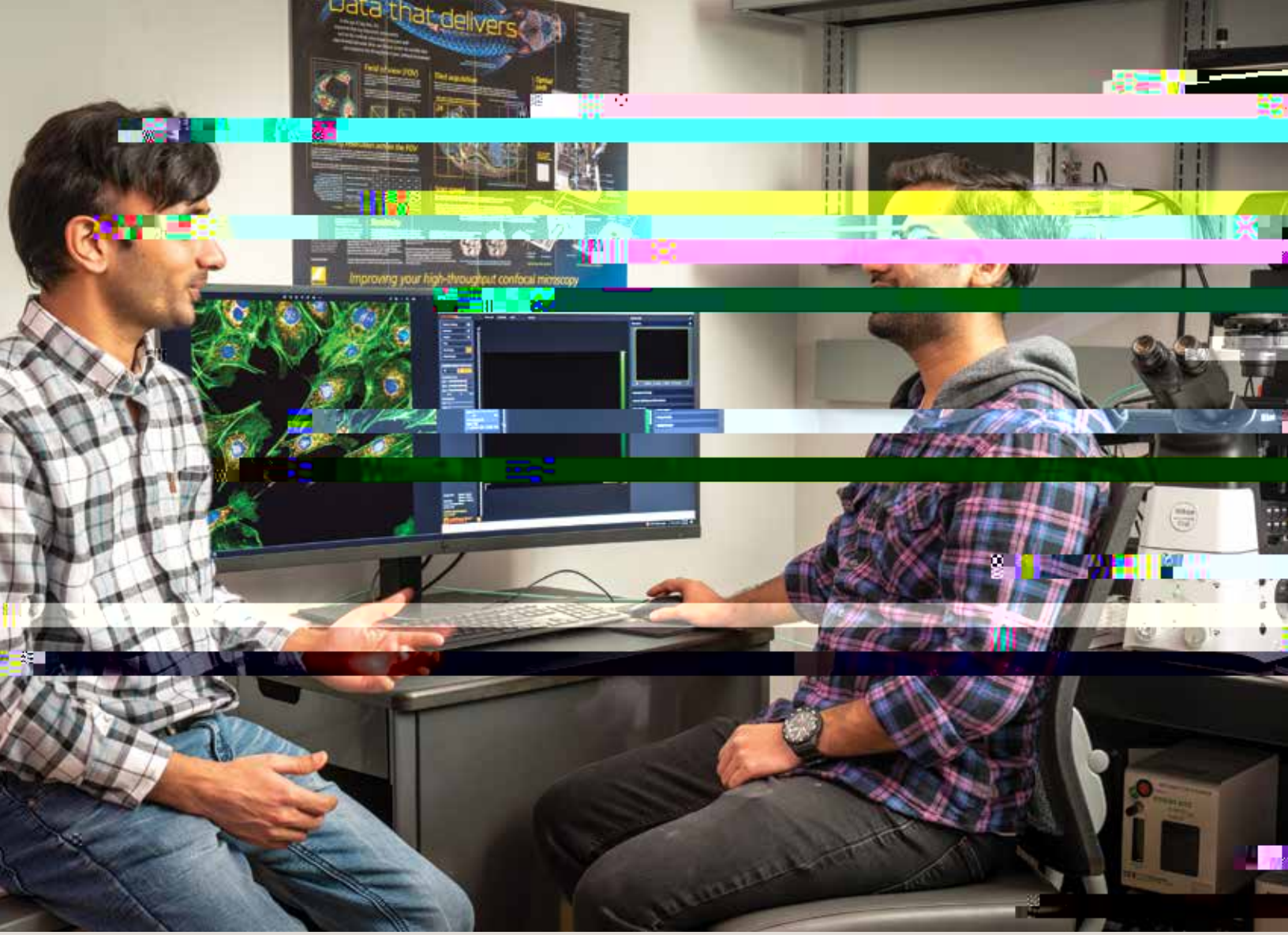
CENTER FOR GENE REGULATION IN HEALTH AND DISEASE

2008-2023



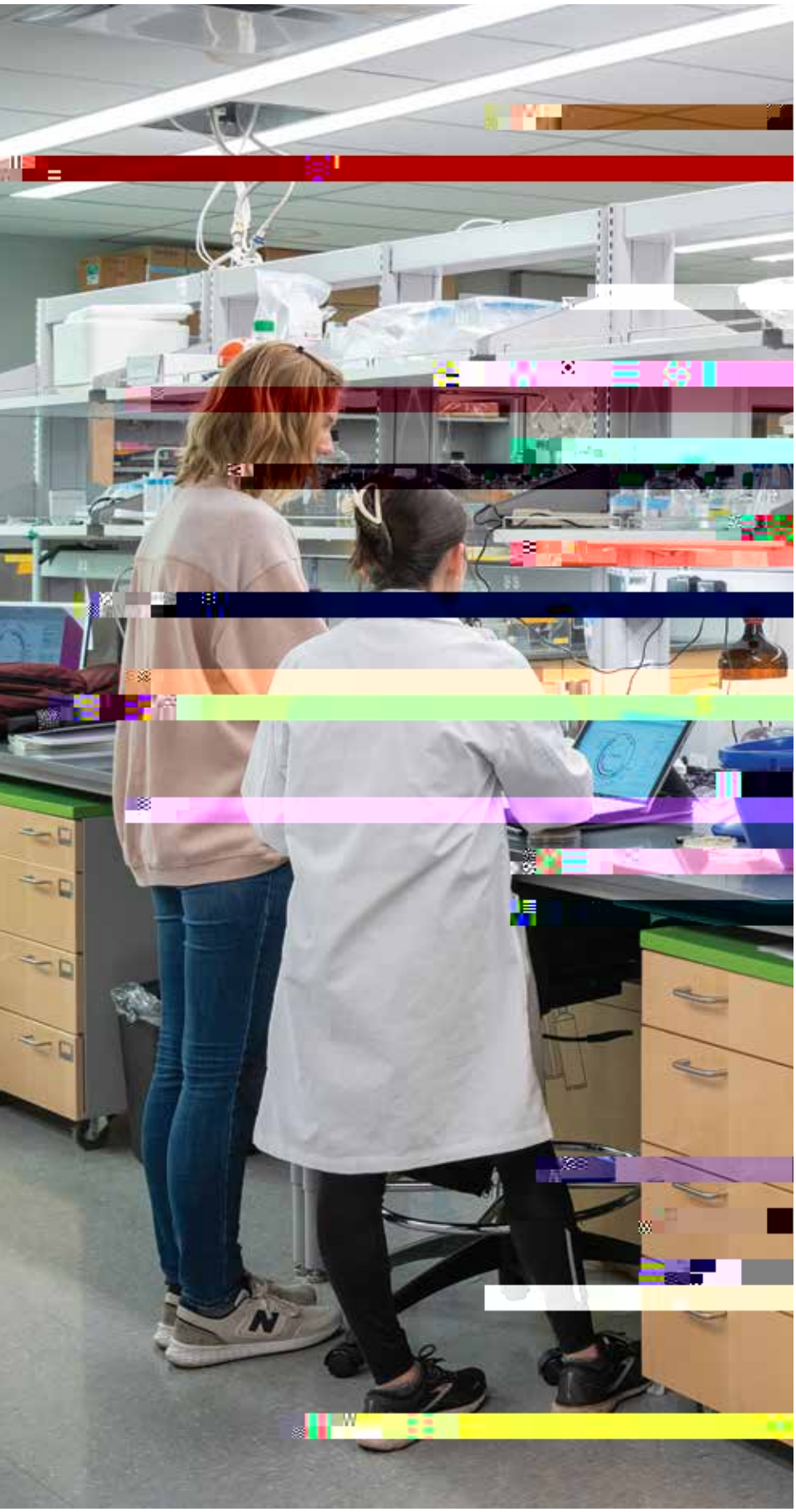
CONTENTS

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.

CENTER FOR GENE REGULATION
IN HEALTH AND DISEASE

VISION STATEMENT

To enhance and integrate



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 Beverly 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's progress and aid advancement.

External Advisory Board Chair

Sta□, 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)

Sta□, Department of Inflammation and Immunity, Cleveland Clinic Lerner Research Institute, Cleveland, OH

Evan Pugh Professor and Eberly Chair in Chemistry, Department of Chemistry
The Pennsylvania State University, University Park, PA

Member, National Academy of Sciences (1985)

The Raymond and Beverly Sackler Chair of Biophysics; Howard Hughes Medical Institute Investigator,
College of Chemistry, University of California, Berkeley, CA

Member, National Academy of Sciences (2002)

Immediate Past Vice President for Research and Sponsored Programs
Kent State University, Kent, OH

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

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

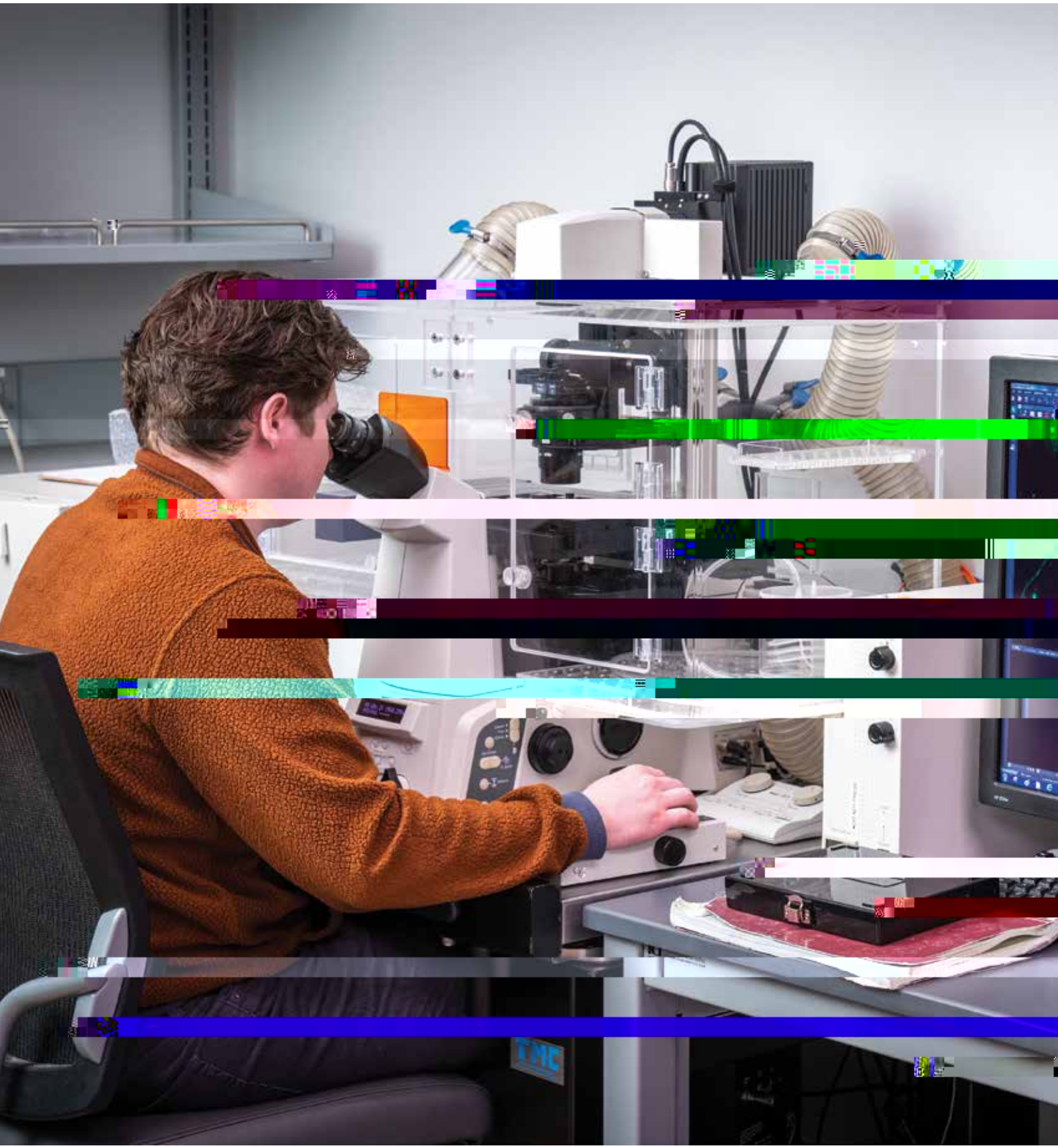
Member, National Academy of Sciences (1992)

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

(1935-2014)
Leonard and Jean Skeggs Professor of Biochemistry; Chair, Department of Biochemistr ased Wniversity,
Cleveland, OH



nitially, the Center brought together these eight faculty members 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.

Throughout the years, additional members joined the Center, 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 Dr. 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. Anton A.

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

Dr. Komar's lab is interested in investigating protein synthesis, co-translational protein folding and translational control of gene expression in eukaryotic cells. Research in the laboratory has two major foci. We are particularly focused on investigating the link between synonymous codon usage 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. These observations provided strong support for the hypothesis that synonymous codon usage serves as a secondary code for protein folding in the cell. The research in the laboratory is further devoted to the study of eukaryotic initiation factor eIF2A that does not function in major steps in the initiation process, but is believed to act at some minor/alternative initiation events such as reinitiation, internal initiation, and/or non-AUG initiation, important for translational control of specific mRNAs. We in particular found that eIF2A is involved in the control of lipid metabolism and that eIF2A-knockout mice reveal decreased life span and metabolic syndrome. Our work deepens the understanding of protein folding, one of the most fundamental mechanisms in the cell and helps elucidate unique features of translational control of gene expression.

Synonymous codon usage a l ers kine ics of ransla ion and direc s co- ransla iona l fo ding owards differen pro ein conforma ions.

1.

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

. The coagulation system leans on a delicate balance between coagulant and anticoagulant factors. Any imbalance/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 and 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.

. Cancer is the primary cause of death worldwide. The traditional way to treat cancer today is "*cu , poison, and urn*" which correlates to surgery, chemotherapy, and radiation respectively with the known devastating side e□ects. Human tumor necrosis factor-related apoptosis-inducing ligand (hTRAIL) is a cytokine that has the capability to induce 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 e□cient 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 a□ected.

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1. (2016) The dual regulatory role of amino acids Leu480 and Gln481 of prothrombin. *J. Biol. Chem.* 291(4), 1565-1581.
2. (2017) The spellbinding e□ects of the acidic COOH-Terminus of factor Va heavy chain on prothrombinase activity and function. *ACS Omega.* 2(9), 5529-5537.
3. (2017) Sensitization of rhTRAIL-resistant triple negative breast carcinoma through silibinin co-treatment. *An icancer Res.* 37(12), 6593-6599,1

BARSANJIT MAZUMDER, PH.D., PROFESSOR

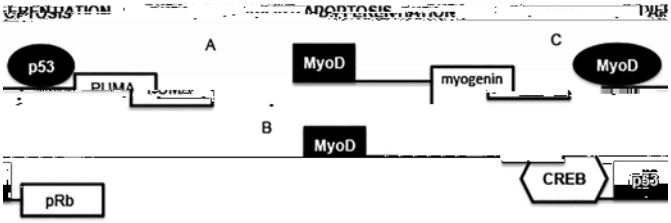
My laboratory at Cleveland State University discovered a novel translational silencing-dependent mechanism for controlling inflammation in myeloid cells. This involves the assembly of the ribosomal protein L13a-dependent multi-protein RNA-binding complex (IFN-gamma-activated-inhibitor of translation) or “GAIT” complex in the 3’ untranslated region (UTR) of target mRNAs. We have generated myeloid-specific L13a-knockout (KO) mice. Induced endotoxemia, colitis, and high-fat diet-induced atherosclerosis in these mice were more severe than control, thus, showing the role of this mechanism in the endogenous resolution of inflammation. However, the role of this mechanism in normal macrophage development from bone marrow and their plasticity is not known. Using an ex-vivo bone marrow-derived macrophage development model, our recent results strongly support the role of the L13a-dependent post-transcriptional mechanism in macrophage development and plasticity. Recently our laboratory also identified an extra-ribosomal function of ribosomal protein L13a in the embryonic development of the preimplantation morula stage to implanted blastocyst. In addition, our laboratory recently discovered a novel and structurally conserved RNA element in the genomic RNA of SARS-CoV-2 and respiratory syncytial virus. This study showed that these RNA elements regulate the translation of viral proteins mediated by L13a-dependent RNA-binding complex formation in response to viral protein-induced signaling. Detailed studies on these novel roles of this protein are ongoing in our laboratory.

1. (2017) Conserved structures formed by heterogeneous RNA sequences drive silencing of an inflammation responsive post-transcriptional operon. *Nucleic Acids Res.* 45(22), 12987-13003.
2. (2018) GAITing the GUT. *Cell Mol Immunol.* 15(12), 1082-1084.
3. (2019) Mutually exclusive amino acid residues of L13a are responsible for its ribosomal incorporation and translational silencing leading to resolution of inflammation. *RNA.* 25, 1377-1392.
4.

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

[illegible]

Di□erentiation (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 e□cacy 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 di□erentiation 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 di□erentiation. We propose that post-translational modification(s), portrayed in the figure as shape changes, could explain the mutually exclusive, dual, biological roles in di□erentiation 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.



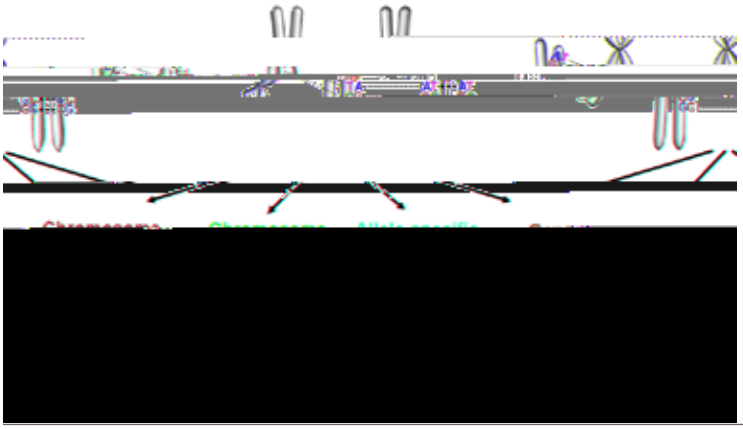
Proposed model for [illegible]e coordina ed regu ia ion of differen ia ion and apop osis y MyoD and p53.

[illegible]:

1. [illegible] (2007) Increased expression of the pro-apoptotic Bcl2 family member PUMA is required for the mitochondrial release of cytochrome C and the apoptosis associated with skeletal myoblast di□erentiation. *Apop osis.* 12(12), 2143-2154.
2.

G. VALENTIN BÖRNER, PH.D, PROFESSOR

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 reshu□e the genetic material for sexual reproduction. The central questions of the Börner lab are: how do cells repair chromosome antreatmiatemplticumans.. antreabreavolvackag, Tcogniradiaa7,hr clo(2014)aHeleaBe a7,thosmaks: a ca



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

MERLIN NITHYA GNANAPRAGASAM, PH.D., ASSISTANT PROFESSOR

The overarching goal of our laboratory is to delineate the processes that regulate tissue proliferation and di□erentiation, and how dysregulation of these pathways contributes to human diseases. Our studies utilize erythroid cells as a model system.

Our current research goals are to understand how transcriptional regulation in erythroid cells ensures that the cell cycle machinery is able to accommodate the rapid pace of the erythroid terminal cell divisions and enucleation, and to investigate the molecular pathogenesis of Congenital Dyserythropoietic Anemia IV. This severe anemia is caused by a hypomorphic mutation in EKLF/KLF1 (a master regulator of erythropoiesis) that arises due to a failure in terminal cell divisions and results in binucleate erythroblasts and erythroblasts with DNA bridges. Additionally, we are interested in understanding the mechanisms of hemoglobin switching to ameliorate and potentially cure Sickle Cell Anemia and β-thalassemia. Here, our goal is to identify factors that induce fetal hemoglobin in adult erythroid cells due to its ameliorating e□ects in these anemias.

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1. (2011) p66Alpha-MBD2 coiled-coil interaction and recruitment of Mi-2 are critical for globin gene silencing by the MBD2-NuRD complex. *Proc Na l Acad Sci* 108(18), 7487-92.
2. (2013) Erythroid transcription factor EKLF/KLF1 mutation causing congenital dyserythropoietic anemia type IV in a patient of Taiwanese origin: review of all reported cases and development of a clinical diagnostic paradigm. *Blood Cells Mol Dis.* 51(2), 71-5.
3. (2016) EKLF/KLF1-regulated cell cycle exit is essential for erythroblast enucleation. *Blood.* 128(12), 1631-41. (Highlighted in *Hema opoiesis News*).
4. (2018) Survey and evaluation of mutations in the human KLF1 transcription unit. *Sci Rep.* 8(1), 6587.
5. (2023) Identification of a genomic DNA sequence that quantitatively modulates KLF1 expression in di□erentiating human hematopoietic cells. *Sci Rep.* 13(1), 7589. (Highlighted in *Hema opoiesis News*)
6. (2022) PUM1 mediates the post-transcriptional regulation of human fetal hemoglobin. *Blood Adv.* 6(23), 6016-6022. (Highlighted in *Hema opoiesis News*; Highlighted as a featured publication on NIDDK Sponsored Cooperative Centers of Excellence in Hematology website)

JUNIOR GONZALES, PH

KAILASH GULSHAN PH.D., ASSISTANT PROFESSOR

The overall research focus of the Gulshan lab revolves around the role of PIP2 metabolism/ tra□cking and Gasdermin D (GsdmD) mediated IL-1β release in inflammation, cardiovascular disease (CVD), and lung cancer. Our lab uses a wide variety of mouse models to study inflammasome activity, progression of atherosclerosis, and metastasis of lung cancer. We employ a variety of cutting edge techniques such as unbiased lipidomics, RNAseq, Crispr-Cas9 mediated genome engineering, bone marrow transplants (BMTs), 16s rDNA sequencing

PENG JIANG, PH.D., ASSISTANT PROFESSOR

The Jiang Lab is focused on developing computational methods and software to investigate multi-source high-dimensional omics data. We have developed several statistical methods and software, such as – a dynamic time warping (DTW) algorithm-based statistical method and R package to assess temporal gene expression similarity and identify differentially progressing genes, – a Meta-motif-based statistical framework and pipeline to predict the binding potential of SELEX-derived aptamers, and – a comparative RNA-seq pipeline for species lacking both sequenced genomes and reference transcripts. One unique aspect of our research is that we integrate a variety of statistical/ bioinformatic methods, such as network modeling, machine learning, and genomic and transcriptomic data analysis, to leverage complex/large-scale omics datasets. These integrative computational approaches allow us to maximize the knowledge learned from the data to gain novel insights into the fundamental and translational aspects of human diseases.

One special focus of our research is that we are particularly interested in leveraging omics data to investigate tissue regeneration processes. A key and broad question we want to address is whether regeneration in adult mammals can be activated with appropriate treatment or a series of treatments. We are closely collaborating with scientists from basic science and surgeons in a clinical setting to (a) identify key regulators for tissue regeneration; (b) compare the regenerative response to endogenous versus exogenous expression of transcriptional factors; (c) develop and evaluate different strategies (e.g., ECM, exosome and electric stimulation) for intervention.

1. (2014) MPBind: a Meta-motif-based statistical framework and pipeline to k4ss e1.25 Td[x/large-scale omics datasets)Tj/Span<</ActualText<ion

ROMAN V. KONDRATOV, PH.D.

BIBO LI, PH.D., PROFESSOR

Similar to aglets that prevent ends of a shoelace from fraying, telomeres, the nucleoprotein complex at linear chromosome ends, prevent the natural chromosome ends from being recognized as DNA breaks. Telomeres protect chromosome ends from illegitimate degradation, repair, and rearrangement. Hence, telomeres are essential for genome integrity and chromosome stability. Telomere shortening in human somatic cells has been implicated in organismal aging, and genome instability often leads to tumorigenesis. Therefore, studies on telomere biology in the Li lab has a great impact on improving human health and life quality. Telomeres are also important for eukaryotic parasites. *Trypanosoma rucei* is a protozoan parasite that causes debilitating sleeping sickness in humans. It sequentially expresses distinct VSGs, its major surface antigen, to evade the host's immune response, which is essential for a long-term infection. Although *T. rucei* has a large VSG gene pool, VSGs are expressed exclusively from telomere-adjacent regions one at a time (in a monoallelic fashion). The Li lab has shown that loss of telomere proteins in *T. rucei* is detrimental to parasite survival, making telomere proteins potentially good drug targets, since parasite telomere proteins are distinctive from their human homologs. Additionally, the Li lab has shown that *T. rucei* telomere proteins are essential for monoallelic VSG expression and regulate VSG switching frequencies. Therefore, targeting parasite telomere proteins can also paralyze the key immune-evading mechanism of these human pathogens.

1. (2009) Rap1 is essential for silencing telomeric variant surface glycoprotein genes in Trypanosoma brucei. *Cell.* 137, 99-109. Featured as the cover story.
2. (2014) Trypanosoma brucei TIF2 suppresses VSG switching by maintaining subtelomere integrity. *Cell Res.* 24(7), 870-885.
3. (2020) TbRAP1 has an unusual duplex DNA binding activity required for its telomere localization and VSG silencing. *Science Adv.* 6(38), eabc4065.
4. (2021) TbTRF suppresses the TERRA level and regulates the cell cycle-dependent TERRA foci number with a TERRA binding activity in its C-terminal Myb domain. *Nucleic Acids Res.* 49(10), 5637-5653.
5. (2022) POLIE suppresses telomerase-mediated telomere G-strand extension and ensures proper telomere C-strand synthesis in trypanosomes. *Nucleic Acids Res.* 50(4), 2036-2050.
6. (2023) The RRM-mediated RNA binding activity in T. brucei RAP1 is essential for VSG monoallelic expression. *Nature Commun.* 14, 1576.

ANDREW RESNICK, PH.D., PROFESSOR

My lab has developed several innovative new approaches to probe ciliary function by assaying single living cilia. We have developed optical trapping and perfused tissue culture methods as quantitative probes of ciliary mechanics and physiology. Our current work draws upon my prior expertise. I have been applying optical techniques to the study of soft matter systems for nearly 20 years. I began by studying fluid flow in microgravity and developed 'spaceflight' versions of confocal microscopes and optical traps. The Light Microscopy Module (LMM) has been performing world-class research onboard the International Space Station from 2009 to 2021 (https://www.youtube.com/watch?v=SdhmXRHFprs). I now use optical traps and fluid dynamics to better understand how the kidney regulates salt and water balance, maintaining homeostatic function in the presence of normal cell turnover. I seek to understand how changes in flow through a 'healthy' tubule can promote disease progression by aberrant stimulation of the primary cilium. Along with my collaborators Y-N Young (NJIT), Z. Peng (Notre Dame) and J. Garvin (CWRU), we now study how mechanical properties of the primary cilium relate to flow sensitivity and how the cilium base could mechanistically act as a gate to distinguish between mechanical and chemical stimulation. *My long term goal is to bridge the gap between Biology and Physics* to better understand how: 1) solute and water absorption along the nephron is regulated by fluid flow; 2) stimulation of the primary cilium connects with intact tissue response; and 3) these processes contribute to homeostatic kidney function and injury recovery.

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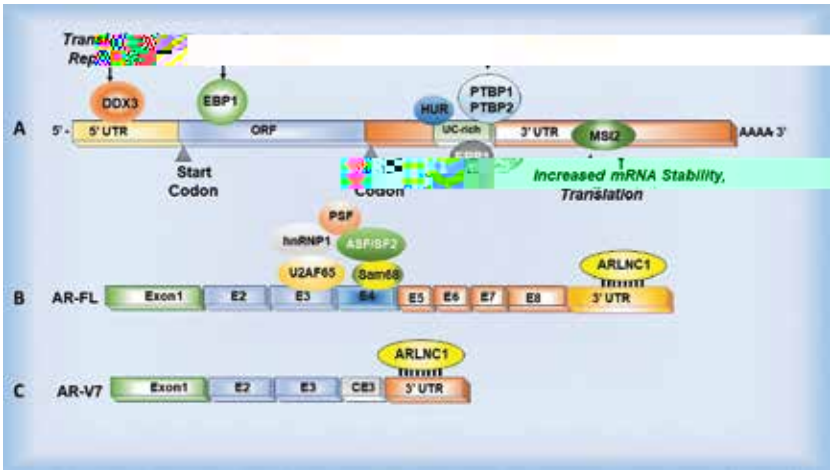
1. (2019) Pulsatile flow through idealized renal tubules: fluid-structure interaction and dynamic pathologies. *Math Biosci Eng.* 17(2), 1787–1807.
2. (2020) Primary cilia have a length-dependent persistence length. *Biomech Model Mechanobiol.* 19(2), 445-460.
3. (2021) Primary cilium: a paradigm for integrating mathematical modeling with experiments and numerical simulations in mechanobiology. *Math Biosci Eng.* 18(2), 1215-1237.
4. (2021) Examining the temperature dependence of louche formation in absinthe. *ACS Omega.* 6(27), 17674-17679.
5. (2021) Physics of martial arts: incorporation of angular momentum to model body motion and strikes. *Plos one.* 16(8), e0255670.
6. (2023) Fluid-structure interaction modelling of neighboring tubes with primary cilium analysis. *Math Biosci Eng.* 20(2), 3677-3699.

GIRISH C. SHUKLA, PH.D., PROFESSOR

Cancer remains the second leading cause of mortality in the United States. The dysregulation of molecular and cellular processes modulates the malignant transformation of a normal to a cancer cell. Cancer cells exhibit altered RNA metabolism, which promotes intrinsic carcinogenic pathways. Our research has functionally linked the dysregulated RNA metabolism to prostate tumorigenesis. My lab studies post-transcriptional regulation of androgen signaling, lipid biosynthesis, and steroid metabolism. We have established links between the androgen receptor mRNA metabolism, long noncoding RNA ARLNC1, and microRNA dynamics in normal and cancer cells. We are studying the link between WT and AR-V7 spliced isoforms and their interplay mediated by ARLNC1 in chromosomal remodeling and global gene expression.



AR mRNA Me a olism: (A) Various RNA inding pro eins ind AR mRNA and con ro i s s a ii y and ransla ion. (B) Splicing fac ors can ind e WT-FL AR mRNA. (C) AR-V7 varian and possi le in erac ion wi e ARLNC1.

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1. (2021) Regulation of cholesterol biosynthesis and lipid metabolism: a microRNA management perspective. *S eroids.* 173, 108878.
2. (2022) The androgen receptor messenger RNA: what do we know? *RNA Biol.* 19(1), 819-828.
3. (2022) Metabolic pathways, enzymes, and metabolites: opportunities in cancer therapy. *Cancers.* 14(21), 5268.
4. (2023) Di erential expression of non-coding RNAs in stem cell development and therapeutics of bone disorders. *Ce is.* 12(8), 1159.
5. (2023) Survival analysis and prognostic factors of the carcinoma of gallbladder. *World J Surg Oncol.* 20(1), 1-10.

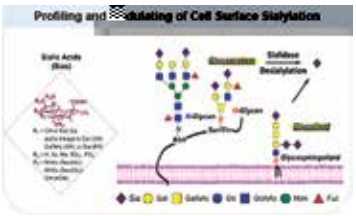
BIN SU, PH.D., PROFESSOR

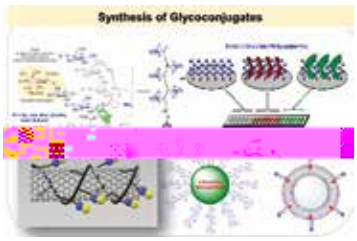
Dr. Su's lab focuses on drug development research. One research direction is anti-cancer drug discovery. We synthesize small molecules to inhibit heat shock proteins that play important roles in tumor progression and drug resistance. The research involves drug design, synthesis, molecular target identification, in vitro and in vivo evaluation, and pharmacokinetic investigation. Currently, our disease model is Androgen Receptor (AR) overexpressed glioblastoma. Another research direction is anti-trypanosomiasis drug discovery. Trypanosomal parasites cause human African sleeping disease, which is an orphan disease. The current treatment is toxic, less e□ective and needs hospitalization, which is di□cult 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. By collaborating with Dr. Bibo Li, the team already identified several lead compounds that showed great selectivity to the parasites.

1. (2021) Small-molecule HSP27 inhibitor abolishes androgen receptors in glioblastoma. *J Med Chem.* 64(3), 1570-1583.
2. (2022) Pharmacokinetic and brain distribution study of an anti-glioblastoma agent in mice by HPLC-MS/MS. *Biomed Chroma togr.* 36(3), e5310.
3. (2022) Synthesis and biological evaluation of imidamide analogs as selective anti-trypanosomal agents. *Bioorg Med Chem.* 61, 116740.
4. (2022) Identification of estrogen receptor down-regulators for endocrine resistant breast cancer. *J Steroid Biochem Mol Biol.* 224, 106162.
5.)40 (.)60.1 ( )

XUE-LONG SUN, PH.D., FAHA, PROFESSOR

Dr. Sun's laboratory is working in the Chemical Biology and Medicinal Chemistry areas. We are interested in cell surface and receptor glycosylation patterns and changes under pathological pathways. One major research project is developing novel chemical probes and enzyme inhibitors to profile and modulate sialylation and desialylation of receptor proteins in immune cells, including monocytes and macrophages related to infection, immune response and inflammation. The long-term goal of this research is to discover the sialylation molecular mechanisms in infection, immune response and inflammation and identify novel targets and lead compounds for antiviral infection and anti-inflammation drug development for flu and coronavirus infection and sepsis. In addition, we are interested in the biomimetic synthesis of native biomolecule thrombomodulin (TM) for the compensation of its loss in the pathological site, as an on-demand anticoagulant and anti-inflammatory therapeutic strategy. Specifically, we are developing TM-liposome conjugates that mimic the native endothelial antithrombotic mechanism of both TM and lipid components and thus will provide a more forceful antithrombotic agent. Also, we are developing TM-glycosaminoglycan (GAG) conjugates and investigating the significance of GAG on the antithrombotic activity and pharmacokinetic properties of TM. Furthermore, we are developing biomimetic glyco-ligands for microarray, carbon nanotube, quantum dot and liposome surface functionalization for biosensor and drug delivery applications.





1. (2019) End-point modification of recombinant thrombomodulin with enhanced stability and anticoagulant activity. *Eur J Pharm Sci.* 139, 105066.
2. (2020) High-throughput multiplex assays with mouse macrophages on pillar plate platforms. *Exp Cell Res.* 396(1), 112243.
3. (2021) The role of cell surface sialic acids for SARS-CoV-2 infection. *Glycobiology.* 31(10), 1245-1253.
4. (2021) Glycopolymer-wrapped carbon nanotubes show distinct interaction of carbohydrates with lectins. *Front Chem.* 10, 852988.
5. (2022) Sialidase inhibitors with different mechanisms. *J Med Chem.* 65 (20), 13574-13593.
6. (2023) Targeting intracellular Neu1 for coronavirus infection treatment. *iScience.* 26(2) 106037.

JACKSON R. TAYLOR, PH.D., ASSISTANT PROFESSOR

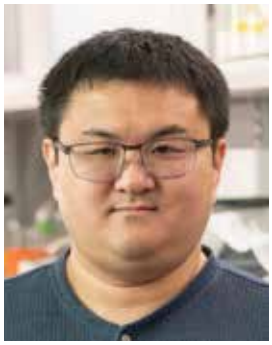
Most of the genes in our genome are activated or silenced by a variety of naturally-occurring chemical modifications to DNA, called “epigenetic modifications.” These modifications change substantially as we grow older, altering gene activity. In the Taylor Lab, we seek to better understand the relationship between epigenetic modifications and the aging process. Our lab uses *Drosophila melanogaster* (fruit flies) to study (i) how epigenetic modifications change with age and disease, and (ii) how experimental manipulation of epigenetic modifications affects health, longevity, and the progression of various human diseases (e.g. Alzheimer’s Disease). By studying these questions, our goal is to develop strategies to help reduce disease and disability in humans as they age. We employ a variety of techniques, including next-generation sequencing and bioinformatic analysis, genetic engineering, and population longevity experiments.

Most recently, we discovered that increasing levels of the epigenetic-modifier gene Sirt6 extends lifespan and preserves physical activity with age in flies. This pro-longevity effect of increased Sirt6 levels is mediated through epigenetic repression of ribosome biogenesis genes. These genes normally promote protein synthesis, and their repression in turn leads to decreased protein synthesis – a phenotype associated with slowed aging. Currently our lab is focused on identifying additional molecular and tissue-specific mechanisms by which Sirt6 regulates aging, and exploring the potential role of Sirt6 in Alzheimer’s Disease. We are also performing screens to identify new epigenetic modifiers of aging.

(Left) Transgenic fruit fly engineered to express GFP when epigenetic perturbations occur. (Right) Summary mechanism for lifespan extension by Sirt6 overexpression. Sirt6 overexpression epigenetically represses Myc target genes involved in ribosome biogenesis, by removing the activating epigenetic mark H3K9ac in the TSS/proximal promoter region, leading to reduced protein synthesis and lifespan extension.

1. (2014) Age-related variations in the methylome associated with gene expression in human monocytes and T cells. *Nature Commun.* 5(1), 5366.
2. (2017) Transcriptomic profiles of aging in naïve and memory CD4+ cells from mice. *Immun Ageing.* 14(1), 1-14.
3. (2021) The role of retrotransposable elements in aging and age-associated diseases. *Nature.* 596(7870), 43-53.
4. (2022) Sirt6 regulates lifespan in Drosophila melanogaster. *Proc Natl Acad Sci.* 119(5), e2111176119.

JINGQI YAN, PH.D., ASSISTANT PROFESSOR



AMIN ZHOU, PH.D., PROFESSOR

[illegible]

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 functions 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 cells are used to investigate the e□ect of RNase L on the function of immune cells such as macrophages. 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.

[illegible]

1. [illegible] (1993) Expression cloning of 2-5A dependent RNase: a uniquely regulated mediator of interferon action. *Cell.* 72, 753-765.
2. [illegible] (2013) Lack of RNase L attenuates macrophage function. *PLoS One.* 8(12), e81269.
3. [illegible] (2014) RNase L contributes to experimentally induced type I diabetes onset in mice. *J Endocrinol.* 223(3), 277-87.
4. [illegible]

Dr. S epjen Benkovic

EXCERPT FROM EAB REPORTS 2014-2022 AND TESTIMONIALS FROM EAB MEMBERS

“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,

STUDENT TRAINING AND OUTCOMES

Throughout its history, GRHD faculty have mentored nearly 300 students, both undergraduate and graduate, in line 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. Following graduation, undergraduate students overwhelmingly enrolled in graduate or medical schools (87.25%), whereas the majority of graduate students remained in academia and/or became employed in the biotech/health industry (85.70%). GRHD laboratories, in partnership with Cleveland Clinic's Lerner Research Institute, support CSU's Ph.D. programs in Regulatory Biology and Clinical-Bioanalytical Chemistry, including a specialization in Cellular and Molecular Medicine. While 66% of GRHD trained undergraduates remained in the state, 43.8% of graduate students pursued careers or further education in prestigious institutions such as Harvard, Stanford, and Columbia Universities, the National Institutes of Health, and The Scripps Research Institute.

ENGAGING IN NEW FRONTIERS OF RESEARCH AND DISCOVERY

GRHD is a time-tested, proven model for both the advancement of biomedical science and the training of a diverse community of graduate and undergraduate students at CSU. GRHD accomplishments continue to be very impressive, and are comparable to similar centers and departments within universities in the US with strong cell and molecular biology programs. The spirit and collaborative interactions among the GRHD faculty and between the faculty and scientists elsewhere in Cleveland and around the country continue to be remarkable. As such, we look forward to identifying novel opportunities for research and discovery particularly in partnership with local and national research institutions.

We are truly aware that with achievements and recognition come risks. Though 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 improvement to the research infrastructure, continued hiring of new dynamic, research active faculty, and expanding appropriate, modern laboratory space. To that end, we deeply appreciate the ongoing e□orts by CSU to help solve these issues and continue the growth of the Center for Gene Regulation Health and Disease into a premiere biomedical research center in the US.

WE BELIEVE THE FUTURE OF GRHD IS VERY BRIGHT!

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