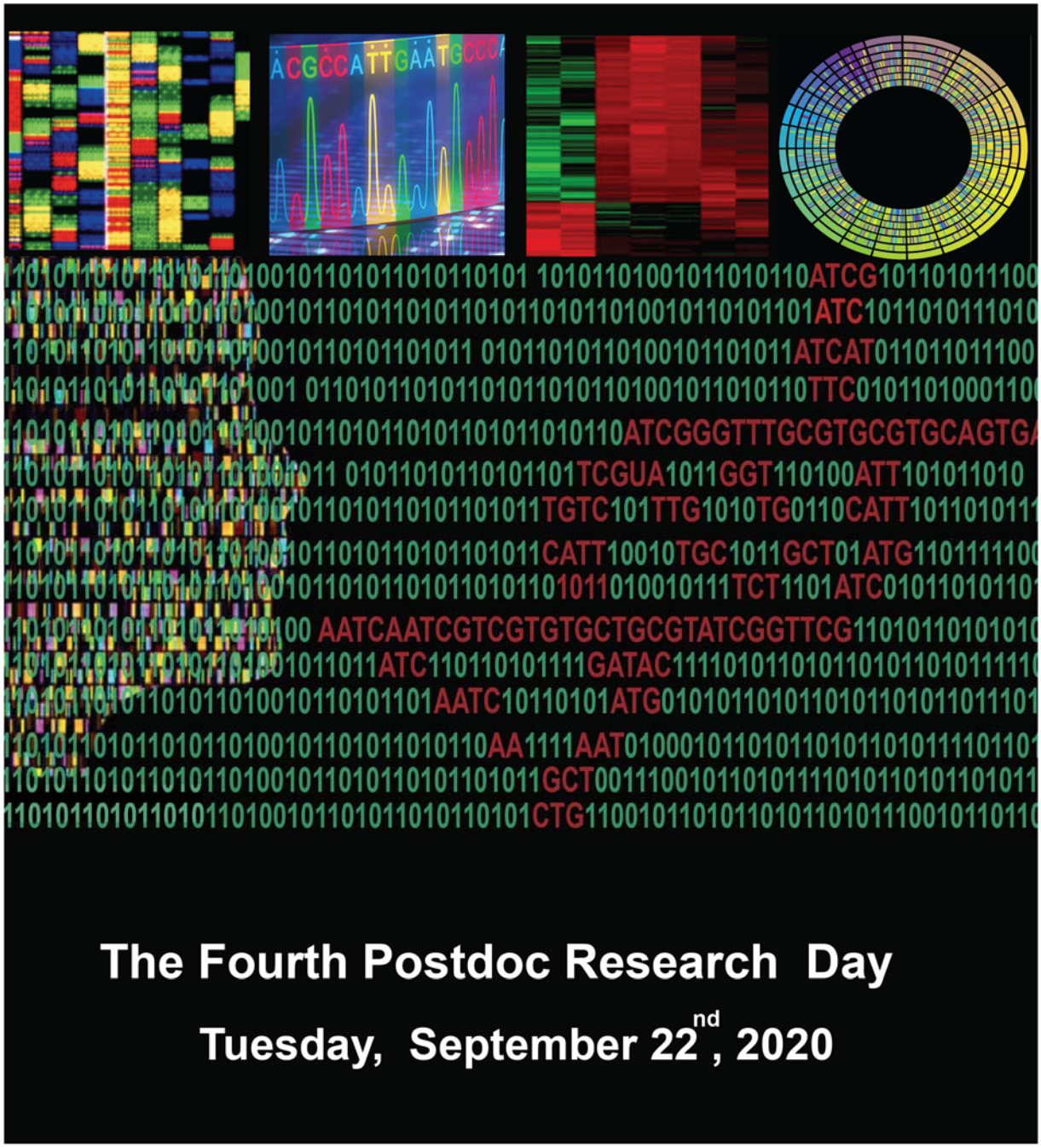

UCONN HEALTH

The Jackson Laboratory
Leading the search for tomorrow's cures

Despite these challenging times, I am so happy to welcome you to our fourth annual UConn Health/Jackson Laboratory Postdoc Research Day. Our event this year will be a little different than usual, starting with having it entirely online. None the less, we have a full schedule of events over the course of the week kicked-off by Dr. Se-Jin Lee who will give a keynote address on Monday, September 21st, in the afternoon. On Tuesday, September 22nd, the main event of the week will continue to be our Speak4Science rapid talks from our postdocs. Immediately following that, a new event this year will be our Virtual Data Chats where each of our speakers will get 20 additional minutes to go more in-depth into their project and interact with all of you. We envision this to be kind of like a poster session, but in virtual format. On page 4 of this book you will find a schedule for the chats including links to their locations. Just like marking down abstracts for posters to visit at a conference, please check out the schedule and plan your afternoon so that you can interact and ask questions of our postdocs.

As in past years, support for this event is provided by Dr. Bruce Liang, Dean of the UConn School of Medicine and the Health Center Research Advisory Council. Special thanks go out to Stephanie Holden, Sarah Wojiksi, the Director of Education at the Jackson Laboratory, Dawn Lindauer and Stuart Duncan, Director of Fellowships, Outreach and Programming at UConn-Storrs. Working with Stuart, we are able to co-host events this year across the Farmington and Storrs' campuses for all of our postdocs. Most importantly, I would like to thank the fantastic team of postdocs who made up this year's PDRD Planning Committee:

Linda Archambault (UConn Health)
Meagan Cauble (UConn Health)
Yuva Kondaveeti (UConn Health)
Sherli Koshy-Chenthittayil (UConn Health)
Amnah Siddiqa (The Jackson Laboratory)
Jennifer VanOudenhove (UConn Health)
Stanley Yang (The Jackson Laboratory)

With all that has been going on in our world over the past year, it is more important than ever that we take these moments to celebrate and be grateful for the wonderful things we do have. Also, moments such as this make us realize how vital it is that as we appreciate and continue to foster the creativity, ingenuity and hard work of young scientists such as the ones you'll hear from today.

Be safe and be well,

Christopher D. Heinen, Ph.D.
Director of Postdoctoral Affairs
UConn Health

*Cover Art created by Amnah Siddiqa

The Fourth

Postdoc Research ~~Day~~ Week

Monday, September 21st, 2020

2:00 – 3:30 **Keynote Address**

Se-Jin Lee, M.D., Ph.D.
Professor, The Jackson Laboratory and Presidential Distinguished Professor, University of Connecticut School of Medicine

Reflections on a 30-year Journey in Biomedical Science

Tuesday, September 22nd, 2020

9:30 – 10:30 **Experiences From the Field: A Panel Session and Q&A on Academia After Your Postdoc Position**

1:00 – 3:00 **Speak4Science**

3:20 – 4:40 **Virtual Data Chats (Group 1-5)**

4:30 – 5:30 **Virtual Data Chats (Groups 6-10)**

Wednesday, September 23rd, 2020

10:00 – 11:00 **Conversations with the Dean**

2:00 – 3:30 **Surviving and Thriving: Resilience-Building in Academia**

Thursday, September 24th, 2020

1:00 – 2:00 **Job Search Overview & Tips – Industry, Government, & Organizations**

Friday, September 25th, 2020

11:00 – Noon **Virtual PostDoc Meet & Greet Social Hour**

Our Speak4Science event will feature a series of 4-minute talks by our postdocs. Each speaker will use one slide to broadly introduce their area of research and why it excites them. To learn more about the details of their research, I encourage you to visit the virtual data chat sessions later in the day. The speaker roster and their corresponding group numbers are listed below.

Speakers

Name	Title	Affiliation	Group
1. Martina Capriotti	*How marine suspension feeders capture food*	Avery Point	1
2. Feyza Yilmaz	*The impact of structural variants in canine disease*	JAX	1
3. Lichao Wang	*Cellular senescence and insulin resistance*	UCH	1
4. Hasan Baig	*Biochemical simulation and synthesis tools*	UCH	1
5. Rachael Norris	*Gap junctions transfer organelles*	UCH	2
6. Yang Liu	*Deep learning lung CT images and COVID-19*	JAX	2
7. Ali Foroughi pour	*Deep learning feature interpretation of pathology slides*	JAX	2
8. Nizam Ud Din	*Multiplexed SH2 profiling of phosphoproteome*	UCH	2
9. Jackie Jufen Zhu	*C11orf95-RELA reprograms 3D epigenome*	JAX	3
10. Abhijit Rath	*The challenges in diagnosis of Lynch syndrome*	UCH	3
11. Frederick Varn	*Decoding immune crosstalk in glioma*	JAX	3
12. Binsheng Wang	*Targeting p21^{high} senescent cells*	UCH	4
13. Meagan Cauble	*Intervertebral disc phosphotyrosine signaling patterns*	UCH	4
14. Takayoshi Otsuka	*Towards complex tissue regeneration*	UCH	4
15. Lei Zhang	*Bioengineered ligament*	UCH	5
16. Chinedu Ude	*Chelation therapy for arthroplasty related metallosis*	UCH	5
17. Brittany Knight	*Improving local analgesic injections*	UCH	5
18. Hannah Hamilton	*Alcohol consumption during and after college*	UCH	6
19. Isaac Smith	*Anxiety disorder emergence in youth*	UCH	6
20. Ahmed Abbas	*scATAC-seq data denoising with scRNA-seq data*	JAX	7
21. Aaron Taylor	*Characterizing HOX-deficient ependymoma*	JAX	7
22. Shyam Kishor Sah	*Functional analysis of keloid-associated genetic variants*	UCH	7
23. Puja Kumari	*Hierarchical cell type-specific functions of caspase-11*	UCH	8
24. Ju Chen	*IL-17 signals to Treg cells in colorectal cancer*	UCH	8
25. Xiaowen Chen	*The source of epiallele diversity in AML*	JAX	8
26. Linda Archambault	*Interspecies interactions in oral biofilms*	UCH	9
27. Maria Rocha	*MRSA persisters and polymicrobial niches*	UCH	9
28. Jacquelynn Benjamino	*MA-GenTA: genome-based microbiome profiling*	JAX	9
29. Stanley Yang	*Single-cell sequencing of genetically diverse microglia*	JAX	10
30. Rawan Olayan	*Data alignment to model Alzheimer's disease*	JAX	10

Virtual Data Chats

Group	Name	Time
Group 1	Martina Capriotti	3:20 – 3:40
	Feyza Yilmaz	3:40 – 4:00
	Lichao Wang	4:00 – 4:20
	Hasan Baig	4:20 – 4:40
Group 2	Rachael Norris	3:20 – 3:40
	Yang Liu	3:40 – 4:00
	Ali Foroughi pour	4:00 – 4:20
	Nizam Ud Din	4:20 – 4:40
Group 3	Jackie Jufen Zhu	3:20 – 3:40
	Abhijit Rath	3:40 – 4:00
	Frederick Varn	4:00 – 4:20
Group 4	Binsheng Wang	3:20 – 3:40
	Meagan Cauble	3:40 – 4:00
	Takayoshi Otsuka	4:00 – 4:20
Group 5	Lei Zhang	3:20 – 3:40
	Chinedu Ude	3:40 – 4:00
	Brittany Knight	4:00 – 4:20
Group 6	Hannah Hamilton	4:30 – 4:50
	Isaac Smith	4:50 – 5:10
Group 7	Ahmed Abbas	4:30 – 4:50
	Aaron Taylor	4:50 – 5:10
	Shyam Kishor Sah	5:10 – 5:30
Group 8	Puja Kumari	4:30 – 4:50
	Ju Chen	4:50 – 5:10
	Xiaowen Chen	5:10 – 5:30
Group 9	Linda Archambault	4:30 – 4:50
	Maria Rocha	4:50 – 5:10
	Jacquelynn Benjamino	5:10 – 5:30
Group 10	Stanley Yang	4:30 – 4:50
	Rawan Olayan	4:50 – 5:10

Presenter Abstracts

1. Martina Capriotti– UConn Avery Point

Can marine suspension feeders selectively capture their food?
Martina Capriotti[1], Bridget Holohan[1], Sandra Shumway[1], Evan Ward[1]

[1]Department of Marine Sciences, University of Connecticut

Suspension feeders are aquatic animals that feed by filtering planktonic cells from the water column. Mussels and ascidians are two groups of suspension feeders that are abundant in near-shore waters, and are being studied in my research. The goal of my work is to understand if selective particle capture is mediated by physiological changes in the animal, or is based solely on the size and surface properties of the particles. For example, does the presence of specific biomolecules, like carbohydrates or surface glycoproteins, play a key role in determining which cells are captured and ingested, and which are not?

2. Feyza Yilmaz – The Jackson Laboratory

The Impact of Structural Variants in Canine Disease Models
Feyza Yilmaz[1], Wonyeong Kang[1], Gang Ning[1], Leigh Maher[1], Qihui Zhu[1], Charles Lee[1]

[1]The Jackson Laboratory for Genomic Medicine

The canine genome exhibits greater homology to the human genome compared to other mammalian genomes, and there is a high level of genetic homogeneity within most breeds. Canines are susceptible to many of the human diseases, including Osteosarcoma (OS). OS is a rare tumor with poor prognosis, and the overall survival hasn't improved because of recurrent challenges associated with a lower frequency of clinical samples, genomic complexity, and lack of preclinical models. The naturally occurring canine OS is used as a preclinical model of human OS due to similar clinical manifestations and a significantly greater incidence rate. More interestingly, significant differences between the frequency of OS in canine breeds suggest that some of them are predisposed to OS compared to others, which might be due to underlying genomic variants. Recent comparative genomic studies have identified OS mutational profiles and genomic variants that are common between canine and humans. Although studies showed that genomic variants, including structural variants (SVs), overlap with a disease or candidate disease genes, array CGH platform, and traditional short-read (SR) whole-genome sequencing (WGS) has limitations. Recent studies showed that LRS help to overcome these limitations and reported a seven-fold increase in SV detection compared to traditional SR WGS studies. In this study, we identified SVs from OS-predisposed and OS-nonpredisposed pure breeds to identify genomic variants that overlap with genes by using the LRS platform. We seek to identify genes and underlying pathways that might play a role in OS-genesis. Our study will be one of the few studies which identify SVs in canine genomes by using LRS, which will remarkably improve the number of variants in canines and help gain more understanding in disease etiology of OS and other.

3. Lichao Wang– UConn Health

Transplanted Senescent Cells Induce Insulin resistance in Mice

Lichao Wang[1], Ming Xu[1]

[1]Center on Aging, University of Connecticut School of Medicine

Insulin resistance (IR) is a pathological state strongly associated with both obesity and aging in which cells become irresponsive to the effects of insulin. IR is the hallmark and earliest detectable abnormality for prediabetes. It also represents a major risk factor for metabolic dysfunction, type 2 diabetes mellitus (T2DM), heart disease, stroke and dementia. Due to its complexity, mechanisms by which IR develops are not fully understood. Cellular senescence refers to the essentially irreversible proliferation arrest that occurs when cells experience a range of stresses. The accumulation of senescent cells has been shown in various tissues in both obesity and aging. Recently, we found that clearance of *p16*^{INK4a}–highly-expressing (*p16*^{high}) senescent cells alleviates IR in obese mice, indicating a causal role of cellular senescence in metabolic dysfunction in obesity. Thus we will test the hypothesis that increased senescent cell burden results in insulin resistance by transplanting human senescent cells or fat explants in mice, and we hope to dissect the role of cellular senescence in the genesis and progression of IR.

4. Hasan Baig – UConn Health

Biochemical simulation and synthesis tools

Hasan Baig[1], Pedro Mendes [1]

[1]UConn Health, Farmington, CT

The development of simulation, analysis and synthesis algorithms and tools for biological models is a well-explored area of research. Many software tools have been developed to aid biologists and scientists to simulate and validate their design models. These tools provide different functionalities including model creation; variety of different simulation and optimization algorithms; user-friendly interfaces; high-speed computing, etc. In this short presentation, I will talk about few of the software tools that I have been working upon which include features like cloud-based high-speed computation, virtual laboratory experimentation, and high-level genetic circuit synthesis.

5. Rachael Norris – UConn Health

Gap junctions transfer organelles

Rachael Norris[1], Mark Terasaki [1]

[1] Dept. of Cell Biology, UConn Health, Farmington, CT

Organelle transfer occurs between various types of cells, and is thought to involve different types of cellular structures. The gap junction protein, connexin 43 (Cx43), has been implicated in organelle transfer between stem cells and injured cells, but its mode of action is not clear. Here, using serial section electron microscopy to localize Cx43 in 3D, we find that gap junctions may form deep protrusions from one cell into another. Some protrusions surround whole organelles. If these protrusions become internalized, they form double membrane vesicles that contain membranes and cytosol from the previously connected neighboring cell. We find mitochondria, multivesicular endosomes, and other vesicles within fully internalized gap junctions. These findings offer an explanation for how gap junctions may mechanistically mediate the transfer of larger cargo between cells, and should broaden the perspective for how gap junctions participate in cell-cell communication.

6. Yang Liu– The Jackson Laboratory

Deep learning of lung lesions detection and quantification from CT images uncover clinical relevance for COVID-19

Yang Liu[1], Abhishek Agarwal[1], Yue Zhao[1], Ziwei Pan[1], Haitham Ashoor[1], Sheng Li[1,2,3]

[1]The Jackson Laboratory for Genomic Medicine
[2]Department of Genetics and Genome Sciences, UConn Health
[3]Department of Computer Science and Engineering, UConn Storrs

The COVID-19 pandemic is straining the diagnostic and treatment capacities of countries around the world. In recent, the vigorous development of deep learning models has greatly improved the accuracy in lesion location prediction on lung CT images. However, there are few artificial intelligent methods for identifying overlapped COVID-19 lesions and classifying lesions on lung CT images. To remedy this situation, we build a deep learning segmentation model on medical images that obtains high accuracy in identifying COVID-19 lesions with average precision at 0.63. Meanwhile, we propose a 3D reconstruction of CT scans for COVID-19 lesion volume quantification and evaluated lesion features related with clinical features, then employ a classification model for predicting ventilator usage on test data. Experimental results on lung lesion quantification found that clinical features *Elderly, Overweight, Gender* and chronical disease condition *Diabetes* influence the lesion volumes significantly. Moreover, the ventilator usage classifier on test dataset achieves F1 score at 0.86 and ROC AUC at 0.92. We are showing the first evidence that CT image can be used to predict if a patient will be more likely to use ventilator, which cannot be predicted using RT-PCR. Our model can be used for patient triage at admission to identify patients at risk of severe illness, ensuring that patients at greatest risk of severe illness receive appropriate care as early as possible and allow for effective allocation of health resources. It can also provide valuable resources for the clinical research community to better understand the impact of SAR-Cov-19 infection on lung lesions.

7. Ali Foroughi pour – The Jackson Laboratory

Interpreting deep learning features via integrative analysis with gene expressions

Ali Foroughi pour[1] and Jeffrey H. Chuang[1]

[1]The Jackson Laboratory for Genomic Medicine

Deep learning has become a popular tool for analyzing hematoxylin and eosin stained whole slide images (WSIs), and has been utilized to study conserved spatial behaviors across cancers [1]. While deep learning models have drastically improved prediction accuracies, they are black-boxes and difficult to interpret. Integrative analysis of deep learning features and gene expressions is an interesting approach to identify the morphological features deep learning models encode, and further investigate their biological relevance. To that end, we propose the concept of an abstract morphological gene, hereafter called mone, defined as the deep learning features encoding the morphology at each region of a WSI. From a modeling perspective, mone values averaged over the WSI share distributional similarities with bulk-seq expression data. In particular, differential mone analysis identifies mones differentiating tumor and normal WSIs, and integrative cross-correlation analysis with bulk-level expressions indicates the potential underlying biology a mone encodes. Pan-cancer analysis of the TCGA data identifies the potential morphologies the inception V3 network encodes. Large value of mone 893 is an indicator of dense cellular regions in breast cancer, which also extends to several other cancer types such as ovarian cancer and lung adenocarcinoma. Mone 869 correlates with expression of COL8A1 in ovarian cancer. Expression of collagen genes is associated with poor prognosis and drug resistance in ovarian cancer [2,3,4]. Further evaluation suggests mone 869 is predictive of collagen content in ovarian cancer. These findings indicate the significant associations between individual deep learning-defined features and both genetic and prognostic quantifications.

8. Nizam Ud Din – UConn Health

Multiplexed SH2 profiling of Phosphoproteome using microscopy

Nizam Ud Din[1], Meagan Cauble[1], Prem Shrestha[1], Kazuya Machida[1], Bruce Mayer[1], Ji Yu[1], Richard D[1]

[1]Berlin Center for Cell Analysis & Modeling, UConn Health

The normal functioning of all organisms depend on the behavior of individual cells which take signals from its environment in the form of ligands and cytokines. These ligands activate a complex signaling network by phosphorylating Receptor Tyrosine Kinases (RTKs). These phosphorylated Tyrosine residues serves as docking sites for molecules which contain a specific domain called Src Homology (SH2) domain, which has been identified in over a 100 types of molecules. As RTK signaling cascade is misregulated in several diseases, such as cancer, it is ideal to visualize its activity via its downstream molecules in order to recognize the signaling state of a cell. Although methods like far-western blotting are helpful to analyze phosphoproteome of a cell, these methods fail to give complete spatial information of molecules in a cell. To get the complete picture, immunofluorescence imaging is the best way. But due to spectral overlap and host-antibody limitation, it is not possible to visualize more than 5 targets at one time.

To overcome these limitations, here we are using SH2 probes, which are engineered and purified proteins containing only the SH2 domain of the proteins. These SH2 probes are designed by introducing specific amino acid sequence between SH2 domain and GST which can be cleaved by PreScission protease hence reversing the affinity of SH2 probes and undocking them from their target phosphotyroine binding sites. We used these probes for multicolor immunostaining, and after imaging probes were removed by cleaving the GST off by PreScission protease. This allowed us to re-stain the cells with another set of multicolor SH2 probes. By repeating these rounds, we hope to image the cells with up to 25 SH2 probes, hence overcoming the spectral overlap limitation of immunofluorescence microscopy.

9. Jacqueline Jufen Zhu – The Jackson Laboratory

C11orf95-RELA reprograms 3D epigenome in supratentorial ependymoma

Jacqueline Jufen Zhu[1], Nathaniel Jillette[1], Xiao-Nan Li[2,3], Albert Wu Cheng[1,4,5,6], Ching C Lau[1,4,7,8]

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[3]Department of Pediatrics, Northwestern University, Chicago, IL
[4] The Jackson Laboratory Cancer Center, Bar Harbor, ME
[5]Department of Genetics and Genome Sciences, UConn Health
[6]Institute for Systems Genomics, UConn Health
[7]Division of Hematology-Oncology, Connecticut Children's Medical Center, Hartford, CT
[8]Department of Pediatrics, UConn Health

Ependymoma is the third most common malignant brain tumor in children. However, there is no effective chemotherapy identified and treatment is limited to surgery with or without adjuvant radiation therapy currently. Thus, to develop targeted therapy based on the underlying biology is an urgent need. Since 2014, C11orf95-RELA fusion was found to be the most recurrent structural variation in approximately 70% of supratentorial ependymomas (ST-EPN), but the molecular mechanisms of oncogenesis are unclear. Here we utilized HEK293T transgene models and a ST-EPN cell line to investigate the epigenomic changes and transcriptional regulations by C11orf95-RELA fusion. By applying ChIP-seq and HiChIP approaches, we found C11orf95-RELA is a novel transcription factor that recognizes a specific DNA motif dictated by the C11orf95 component while the RELA component is required for driving the expression of ependymoma-associated genes. Moreover, C11orf95-RELA modulates chromatin states and mediates chromatin interactions, leading to transcriptional reprogramming in ST-EPN cells. Multiple signaling pathways such as Notch signaling and G-protein signaling are identified to be involved in ST-EPN development. Our findings provide important characterization of the molecular underpinning of C11orf95-RELA fusion and shed light on potential therapeutic targets for C11orf95-RELA subtype ependymoma.

10. Abhijit Rath – UConn Health

Functional assessment of Lynch Syndrome-associated MSH2 missense variants via CRISPR-Cas9 gene editing

Abhijit Rath[1], Akriti Mishra[2], Victoria Duque-Ferreira[3], Chaoran Hu[4, 5], Gregory Omerza[6], Kevin Kelly[6], Andrew Hesse[6], Honey V. Reddi[6], James P. Grady[4, 5], Christopher D. Heinen[1]

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[2]UConn Storrs
[3]University of Saint Joseph, West Hartford, CT
[4]Department of Statistics, UConn Storrs,
[5]Community Medicine and Health Care, UConn Health
[6]Clinical Genomics Laboratory, The Jackson Laboratory for Genomic Medicine

Lynch syndrome (LS) predisposes patients to cancer and is caused by germline mutations in the DNA mismatch repair (MMR) genes. Identification of a frameshift or nonsense mutation resulting in impairment of MMR function is confirmatory for LS diagnosis. However, discovery of a missense variant is often inconclusive, as the effects of these variants of uncertain significance (VUS) on disease pathogenesis are unclear. Unbiased assessment of the impact of VUS on the protein's function can help determine their significance and thus plays a critical role in the therapeutic management of LS patients. Laboratory based

functional studies performed to date have been limited by their artificial nature. To this end, we developed an *in cellulo* functional assay in which we engineered site-specific *MSH2* VUS using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 gene editing in human embryonic stem cells. This approach introduces the variant into the endogenous *MSH2* loci, while simultaneously eliminating the wild-type gene. We characterized the impact of the variants on cellular MMR functions including DNA damage response signaling and the repair of DNA microsatellites. We determined that four VUS clearly disrupted MMR function, four VUS did not impact function and two had intermediate effects, providing valuable information for determining their likelihood of being *bona fide* pathogenic LS variants. This human cell-based assay system for functional testing of MMR gene VUS will facilitate the identification of high-risk LS patients.

11. Frederick S. Varn – The Jackson Laboratory

Tumor-immune interactions are dynamic and influence the evolutionary trajectory of adult diffuse glioma

Frederick S. Varn[1], Kevin C. Johnson[1], Floris P. Barthel[1], Hoon Kim[1], Taylor Wade[1], Disha Lodha[2], Shoaib Ajaib[2], Nazia Ahmed[2], Luciano Garofano[3], Fulvio D'Angelo[3], Lucy Stead[2], Houtan Noushmehr[4], Antonio Iavarone[3,5,6], Roel Verhaak[1], and The GLASS Consortium*

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[4] Department of Neurosurgery, Henry Ford Health System, Henry Ford Cancer Institute, Detroit, MI, USA
[5] Department of Neurology, Columbia University Medical Center, New York, NY, USA
[6] Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY, USA

Diffuse glioma is the most common primary brain tumor in adults and is characterized by a poor prognosis and near universal recurrence following therapy. Given the poor response rate to the current standard-of-care, there is an active interest in applying immunotherapy to treat this disease. However, progress on this front has been limited, due in part to a lack of knowledge of how the immune system interacts with glioma to influence the tumor's development. To understand this process, we collected DNA and RNA sequencing data on initial and recurrent tumor pairs from over 150 glioma patients. By integrating genetic information with *in silico* deconvolution analyses of transcriptomic data, we identify specific mutations and copy number alterations that associate with changes in immune infiltrate levels over time. We additionally find that the abundance of a specific glioma cell type associates with distinct macrophage and microglia activities that have implications for immunotherapy resistance. Collectively, our results indicate that there is an active crosstalk between tumor and immune cells in glioma. Targeting this crosstalk has the potential improve immunotherapy response rates and lead to better patient outcomes.

12. Binsheng Wang– UConn Health

Targeting p21^{high} Senescent Cells to Improve Healthspan and Lifespan

Binsheng Wang[1], Ming Xu[1]

[1]UConn Center on Aging, UConn Health

Aging is the leading risk factor for a variety of chronic diseases. Emerging evidence suggests that modulating fundamental aging processes such as cellular senescence may delay the onset of most chronic conditions as a group and increase healthy lifespan. Cellular senescence refers to the essentially irreversible growth arrest that occurs when cells experience stress. With aging, such cells accumulate in multiple tissues, secreting pro-inflammatory cytokines and chemokines, termed the senescence-associated secretory phenotype (SASP). One common feature of senescent cells is the high expression level of p16^{INK4a} (p16)

and/or $p21^{Cip1}$ (p21). We and others have demonstrated the causal roles of p16-highly-expressed (p16high) senescent cells in various age-related conditions. However, the role of $p21^{high}$ senescent cells in aging remains largely unknown. Moreover, the underlying mechanisms by which senescent cells cause damage *in vivo* are poorly understood. To address these questions, we have generated and validated a novel p21-Cre mouse model (C57BL/6J background) containing p21 promoter driving Cre fused to estrogen receptor (ER). By crossing with floxed mice, we managed to monitor, kill and modulate $p21^{high}$ cells *in vivo*. Preliminary studies in our lab suggest that $p21^{high}$ cells accumulate in various tissues in klotho (kl)-/- progeroid mice, and clearance of $p21^{high}$ cells can improve physical function in kl-/- mice. Additionally, inactivation of NF-κB specifically in $p21^{high}$ cells also can improve tissue function in kl-/- mice. This study will provide invaluable research tools and preliminary data to pinpoint the role of cellular senescence in age-related tissue dysfunction.

13. Meagan Cauble – UConn Health

Phosphotyrosine Signaling Patterns in Intervertebral Disc

Meagan Cauble[1], Nizam Ud Din[1], Prem Shrestha[1], Isaac Moss[2], Kazuya Machida[3], Bruce Mayer[1,3], and Ji Yu[1,3]

[1] Center for Cell Analysis and Modeling, UConn Health
[2] Department of Orthopaedic Surgery, UConn Health
[3] Genetics and Genome Sciences, UConn Health

Low back pain is the leading cause of disability worldwide and is closely linked to degeneration of the intervertebral disc (IVD). An incomplete understanding of the biological mechanisms contributing to the degenerative process has prevented the development of a disease-modifying treatment. The role of mitogenic growth factors (GFs), which rely heavily on tyrosine phosphorylation (pY) for signal transduction, and their associated signaling pathways in the IVD have been studied for the past thirty years in the context of both disease progression and treatment. Results have been contradictory and not led to any available therapeutics. To provide a complete understanding of phosphorylation in disc GF pathways, we have designed a novel SH2-oligo barcoded probe with multiplex imaging capabilities. The core components of these probes are pY-binding SH2 domains of naturally existing proteins, a sequence-specific oligo barcode, and a complimentary fluorescently-labeled imaging oligo. Using a DNA strand invasion strategy, we can efficiently replace old labels with new ones and achieve detection of many targets. This technology will be the basis for future tissue-level work to advance knowledge of disc degeneration mechanisms.

14. Takayoshi Otsuka– UConn Health

Lessons from axolotls towards complex tissue regeneration in mammals

Takayoshi Otsuka [1,2],David M. Gardiner [3], Cato T. Laurencin [1,2,4,5,6,7]

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[2]Raymond and Beverly Sackler Center for Biological, Physical and Engineering Sciences, UConn Health
[3]Department of Developmental and Cell Biology, Natural Sciences II Division, University of California Irvine, Irvine, CA 92697, USA;
[4]Department of Orthopedic Surgery, UConn Health
[5]Department of Biomedical Engineering, UConn Storrs, CT
[6]Department of Materials Science and Engineering, UConn Storrs
[7]Department of Chemical and Biomolecular Engineering, UConn Storrs

Mammals including humans have a limited regeneration capacity for complex tissue regeneration, thus injury or damage usually causes scar formation or fibrosis, resulted in the loss of function. Therefore, improving the regeneration mechanism in humans remains a significant goal. Various technologies have been developed successfully to regenerate single targeted tissues. However, positional information is required to assemble various tissues in the right place to achieve functional complex tissue. On the other hand, salamanders such as axolotls are the only vertebrate that can exhibit robust regeneration potential to regrow complex tissues such as limb throughout their life. Therefore, we utilize them to learn how to regenerate multiple tissues coordinately. A deeper understanding of developmental and regeneration biology will provide clues that can direct new engineering strategies to lead towards coordinated regeneration of tissues. Our major challenge is to identify the signals which enable us to control positional information to regenerate complex tissues, and a limb one day.

15. Lei Zhang – UConn Health

Bioengineered ligament

Lei Zhang[1], Paulos Mengsteab[1], Lakshmi S. Nair[1,2,3,4,5,6,7], Cato T. Laurencin[1,2,3,4,5,6,7,8]

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The aim of this work is to fabricate a kind of bioengineered ligaments and to evaluate it in rabbit ACL reconstruction model. To achieve this goal, two sort of bioengineered ligaments were fabricated, one of them is composed of poly (l-lactic) acid (PLLA) microfibers, and the other is composed of 87%PLLA and 13% polyethylene terephthalate (PET) (termed Tiger graft). Herein, we achieved the fabrication of a bioengineered ligament with a peak load up to 2500 N. Second, we replaced rabbits' ACL with our bioengineered ligament and analyzed their mechanical property and histological characteristics 12 and 24 weeks post- operation. We found that the mechanical properties of the bioengineered ligament were the highest reported in a rabbit ACL model at 12 weeks. It seems that Tiger Graft has a better mechanical property than PLLA graft. Twelve weeks post-operation, the osteointegration of the bioengineered ligament was observed in the bone tunnel. The histological analysis showed the similar microstructure of the bioengineered ligaments as the original ligament structure. The ligament regeneration in bone tunnel underwent a mechanism of endochondral ossification in the bone tunnel. The BMSC therapy promotes the presence of chondrocyte-like cells within the fibers of the ligament. Overall, this work uncovers the mechanism of regeneration for bioengineered ligaments and provides evidence for the potential usage of bioengineered ligament.

16. Chinedu Ude– UConn Health

Chelator Functionalized Glycosaminoglycans for the Treatment of Arthroplasty Related Metallosis

Chinedu Cletus Ude [1,2,3], Shiv Shav [1,2,3,] Samuel. Laurencin [1,2,3,], Mcclinton Aneesah [1,2,3,], Daneshmandi Leila, Lakshmi S. Nair [1,2,3,4,5,6], Cato T. Laurencin [1,2,3,4,5,6,7,8]*

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Metals and metal alloys have been used as medical implants in a variety of applications. Arthroplasty for end-stage hip osteoarthritis is one of such conditions. However, they injure the joints, perturbs homeostasis, and engender metallosis. Current gold standard for metallosis is revision surgeries, which is expensive with numerous risks. Among the propitious alternative is chelation therapy. Our group developed British Anti-Lewisite Functionalized Hyaluronic Acid (BAL-HA), a compound, with the ability to chelate cobalt, chromium, and prevent device-originated metallosis. In this study, chelation effects of higher doses of BAL-HA were explored. Sixteen rats, aged 15 months, (500-600) g, were divided into two groups. Cobalt group received high dose of cobalt chloride ions, while BAL-HA group received cobalt ions and BAL-HA, 5 minutes apart. Blood and urine samples were collected on days 0, 1, 3, 7, 10, and 14 for bio-distribution and elimination evaluations, while organs (hip joints, heart, liver, kidney, and spleen) were harvested at days 7 and 14. It is expected that increased dose of cobalt, would elicit significant metallosis, while the BAL-HA will cause maximum chelation of the cobalt particles. With these results achieved, it would support our claim of possible chelation therapy for arthroplasty metallosis.

17. Brittany Knight– UConn Health

Improving the efficacy of local therapeutic management of musculoskeletal pain using a hind paw model of inflammation

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Knee osteoarthritis is a prevalent joint disease that affects majority of individuals over the age of 65. Over time, increased physical activity and stress on weight bearing joints can cause persistent pain and gait disturbances. Although no current treatments for OA can halt the progression of the disease, the primary reason patients seek medical intervention is for joint-related pain and discomfort. Currently, articular therapeutic injections are employed to decrease symptoms with the intention of improving joint function and mobility. However, due to the current opioid epidemic and the aversive effects of the local therapeutic injections, formulating safer and effective therapies are essential for the well-being of the geriatric population. The goal of our study is to evaluate novel pain-relieving targets using a standardized model of unilateral subcutaneous inflammation. We first assessed the development of spontaneous pain and evoked mechanical sensitivity of the hind limbs following inflammation and later, isolated peripheral neural tissue for transcriptional analysis. Understanding how cutaneous inflammatory pain affects neuronal gene expression will enable us to test novel drug formulations that specifically target peripheral neurons in order to improve the efficacy of localized analgesic treatments. Acknowledgment T90 NIDCR training grant

18. Hannah R. Hamilton – UConn Health

Alcohol consumption during and after college

Hannah R. Hamilton[1], Howard Tennen[2], Stephen Armeli[3],

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The NIAAA has deemed college drinking to be a significant health problem yet drinking remains prevalent among college students and not all students "mature out" of problematic drinking when they graduate. As a postdoctoral research fellow at UConn Health's Alcohol Research Center, I have access to two waves of daily diary data collected from individuals during college and after they have graduated. Using these data, my research examines between-and within person associations between interpersonal interactions, social influences, drinking motives, and alcohol consumption and tests whether these associations are the same for individuals during college and after they leave the college environment. In my virtual chat, I will discuss my findings examining how interactions with and perceived norms of friends and family are related to drinking during and after college, how specific drinking motives are related to drinking alone or with others, and how drinking is related to students' reported enjoyment and self-perceptions.

19. Isaac C. Smith – UConn Health

Risk Factors for Anxiety Disorder Emergence among Offspring of Anxious Parents

Isaac C. Smith[1], Golda Ginsburg[1]

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Children of anxious parents are at increased risk for developing anxiety disorders themselves (Micco et al., 2009). Prevention-based cognitive behavioral interventions offer promise as a means of reducing risk for development of anxiety disorders throughout childhood and adolescence. One such prevention program, the Coping and Promoting Strength program (CAPS; Ginsburg, 2009), resulted in significantly lower incidence of anxiety disorders among 6-12-year-olds at a 12-month follow-up as compared to a control condition (Ginsburg et al., 2015). At a 72 month follow up, the incidence of anxiety disorders was greater than 50% among both intervention and control groups (Ginsburg, Tein, & Riddle, 2020). Thus, additional work is needed to elucidate risk factors for the emergence of anxiety disorders among offspring of anxious parents. The current study used hierarchical binary logistic regression models to predict presence of anxiety diagnoses among a sample of 109 adolescents (49% female, M_{age} = 15.81, SD = 1.90) originally enrolled in the CAPS program between the ages of 6 and 12. The overall model was statistically significant, $\chi^2(5) = 24.37$, $p < .001$, and explained 31% of the variance in anxiety diagnoses (Nagelkerke R-square). After controlling for intervention effects, baseline child-reported anxiety ($\beta = .06$, $p = .03$), sex ($\beta = 1.57$, $p = .001$), and anxiety-specific internal attributions of control ($\beta = -.12$, $p = .03$) significantly predicted anxiety diagnoses such that those with higher baseline anxiety, females, and individuals with lower self-reported internal control were significantly more likely to develop an anxiety disorder. Additional risk factors, such as parental accommodation of anxiety and negative life events, are worth exploring to better understand which high-risk offspring are most likely to develop an anxiety disorder. Implications for the development and implementation of anxiety prevention programs will be discussed.

20. Ahmed Abbas – The Jackson Laboratory

scATAC-seq data denoising through integration with scRNA-seq data

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Single-cell sequencing assay for transposase-accessible chromatin (scATAC-seq) measures chromatin accessibility at the single-cell level. Analyzing scATAC-seq data reveals much knowledge about cell-to-cell variability through variation in genomic sites' accessibility among different cells. However, scATAC-seq data suffers from a large proportion of false zero counts (technical dropout entries). Here, we propose a novel

method for denoising scATAC-seq data (recovering its technical dropout entries) through integration with Single-cell RNA sequencing (scRNA-seq) data. Through matching similar cells from both datasets and exploiting the positive correlation between high gene expression levels and the open chromatin status, we can identify technical dropouts and impute their entries in the scATAC-seq count matrix. Our method outperformed the existing scATAC-seq denoising methods in terms of the quality of integration with scRNA-seq data and the larger number of detected marker genes close to the differentially accessible peaks. Also, it resulted in pseudotime trajectories matching with known hematopoietic lineage tree and functional-relevant co-accessibility.

21. Aaron Taylor– The Jackson Laboratory

Molecular profiling of pediatric ependymoma reveals a HOX-deficient subtype with prognostic implications

Aaron Taylor[1,2,3,4], Matthew D. Burstein[1,2,3,5], Jianhe Shen[1,2], Thomas Chow[1,2], Jack Su[1,2,6], Adekunle Adesina[6,7], Robert Dauser[6,8], William Whitehead[6,8], Andrew Jea[6,8], Daniel Curry[6,8], Murali Chintagumpala[1,2,6], & Ching C. Lau[1,2,3,4,6]

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Ependymomas (EPN) account for ~10% of pediatric brain tumors, often presenting in the first five years of life. Previous studies described prognostically-relevant molecular subtypes of posterior fossa (PF-)EPN. Still, there has been little improvement in survival. We examined the molecular and clinical heterogeneity of sixty-five primary pediatric PF-EPN using mRNA/miRNA array expression to identify prognostic biomarkers and potential therapeutic targets. The known subtypes PFA and PFB showed no prognostic differences, while age remained independently predictive of relapse despite its described association with the PF subtypes. Comparing the youngest PFB cases against older PFB and young PFA revealed robust downregulation of 3' HOX genes, suggesting the observed prognostic influence of age was a surrogate for a pediatric-only molecular subtype within PFB. Substratification using HOX expression revealed this subtype (PFBHOX-) as separate from PFB samples by background-level expression of HOX genes, younger age, and absence of arm-level CN alterations. PFBHOX- cases showed worse prognosis than PFB and restored prognostic separation to published subtypes. While available molecular data is growing each year, PFB subtype heterogeneity may have been obscured by a lack of very young patients in the literature. Reclassification of a published cohort's pediatric samples indicated the presence of the PFBHOX- subtype.

22. Shyam Kishor Sah – UConn Health

Leu401Pro mutation in ASAH1 and truncated PHLDA3 ^{Q108*} promote keloid-like characteristics of induced pluripotent-derived fibroblasts

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Keloid is a chronic inflammatory skin disorder characterized by aberrant activation of fibroblasts, leading to excessive and prolonged deposition of extracellular matrix components. In addition, there is little high-quality evidences for treatment and management of keloid due to poorly known pathophysiology. Genetic studies have provided evidence for a genetic predisposition to keloid formation. Through linkage analysis and whole-exome sequencing, we have identified mutation in ASAH1 variant and PHLDA3 that are found to be involved in keloid susceptibility. Here, we generated human induced pluripotent stem cells (hiPSCs) from peripheral blood mononuclear cells with Leu401Pro mutation in ASAH1 and truncated PHLDA3^{Q108*} using CRISPR/Cas9 editing technology. Fibroblasts were derived from these hiPSCs to study the role of ASAH1$_{L401P}$ and truncated PHLDA3^{Q108*} in keloid pathogenesis. We found that ASAH1 activity was diminished in ASAH1$_{L401P}$ fibroblasts compared to wild-type fibroblasts. In addition, levels of TGFβ1 and collagen production were highly increased in ASAH1$_{L401P}$ and PHLDA3^{Q108*} fibroblasts. Both ASAH1$_{L401P}$ and PHLDA3^{Q108*} fibroblasts were highly proliferative and shown to express pro-fibrogenic markers likely through modulating TGFB1 signaling as compared to wild-type fibroblasts. These finding will help us understand keloid pathogenesis and may be useful for development of potential therapeutics.

23. Puja Kumari– UConn Health

Hierarchical cell type-specific functions of caspase-11 in LPS shock and antibacterial host defense

Puja Kumari[1], Ashley J. Russo[1], Sureshkumar Muthupalani[2], and Vijay A. Rathinam[1]

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Intracellular sensing of LPS by caspase-11 is a key defense mechanism against bacteria. A remarkable feature of this pathway is its presence in a broad range of immune and nonimmune cells. However, the cell type-specific contributions of cytosolic LPS sensing to antibacterial immunity and sepsis remain poorly defined. By generating several conditional knockouts of caspase-11, we show that caspase-11 intrinsic to LyzM+ myeloid cells greatly contribute to GSDMD and IL-1 activation as well as the pathological manifestations of LPS septic shock. We also found a minor role for CD11c+ dendritic cell (DCs)- and intestinal epithelial cell (IEC)-specific caspase-11 in LPS-induced lethality. In contrast, caspase-11 in MRP8+ neutrophils was slightly protective against LPS shock. Importantly, caspase-11 sensing of cytosolic LPS in LyzM+ myeloid cells and MRP8+ neutrophils, but not DCs and IECs, is necessary for the control of bacterial replication and host survival during infection with an intracellular bacterium, *Burkholderia thailandensis*. Thus, our *in vivo* studies uncovered the hierarchical cell type-specific functions of caspase-11 underlying the protective and detrimental functions of cytosolic LPS sensing during bacterial infections and endotoxin shock, respectively.

24. Ju Chen – UConn Health

IL-17 directly signals to Treg cells for the promotion of early colorectal cancer development

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Regulatory T (Treg) cells are important players in gut homeostasis and tumor development. A high Treg:CD8 ratio in the tumor signifies suppressed tumor immunity and favors immune evasion of cancer. However, Tregs may also play a protective role in cancer by dampening tumor-promoting inflammation. Absence of the Treg-associated cytokines IL-10 and TGF-β increases intestinal tumor burden. A high “Treg signature” in human colorectal cancer (CRC) also indicates better prognosis. We and others have shown that IL-17 signals to transformed colorectal epithelial cells to drive tumor development and inhibits the recruitment of CD8$^+$

cytotoxic T lymphocytes (CTL) and Treg cells. However, the direct IL-17 signaling to Treg cells in CRC still remains unclear. Here, our data demonstrated the ablation of IL-17RA in Tregs resulted in increase in colonic tumor numbers and load. Treg-specific IL-17RA ablation also increased Treg accumulation in tumors. RNAseq data for purified Tregs suggest that the direct IL-17 signaling on Tregs suppresses their proliferation, survival, and migration into colonic tumors. Further, IL-17 co-receptors (IL-17RC and IL-17RE) are upregulated in tumor-infiltrating Tregs. IL-6 and IL-1β abundance in CRC may upregulate the expression of IL-17RC and IL-17RE on Tregs, hence rendering these Tregs susceptible to IL-17-mediated inhibition. Together, these data indicate that IL-17 promotes early stage CRC development by direct inhibiting Tregs in colonic tumors.

25. Xiaowen Chen– – The Jackson Laboratory

Somatic mutations drive specific, but reversible epigenetic heterogeneity states in AML

Xiaowen Chen[1], Sheng Li[1]

[1]The Jackson Laboratory for Genomic Medicine

Abstract

Acute myeloid leukemia (AML) is a highly aggressive cancer that arises from hematopoietic stem and progenitor cells. AML remains challenging to treat mainly due to failure to eradicate residual leukemia stem cells, eventually leading to relapse and disease progression. Epigenetic allele (epiallele) diversity is linked to inferior clinical outcome in AML. However, the source of epiallele heterogeneity in AML is not known. Therefore, we explored the methylation profiles of a cohort of clinically and genetically annotated AML patients and mouse models and investigated whether any somatic mutation in AML might be associated with epigenetic allele diversity. Here, a subset of AMLs carrying driver mutations linked to transcription factors display epigenetic destabilization in a defined set of apparently susceptible loci, an effect that is linked to favorable outcome. In contrast, AML subtypes linking to inferior clinical outcomes manifest a more stochastic patterning and generally higher abundance of epigenetic alleles. Using mouse models of common leukemia alleles affecting *TET2* and *IDH2*, it was shown that epiallele diversity is especially strongly induced by IDH mutations and is enhanced by somatic mutation co-occurrence. Additionally, epiallele diversity was partially reversed by epigenetic therapies in AML driven by *TET2* or *IDH2*. Finally, we built an epiallele classifier to predict AML relapse-free survival, which further confirmed the association between epigenetic diversity and treatment failure. In summary, these findings suggest that epigenetic therapy could be effective in part by reducing the population complexity and fitness of AMLs.

26. Linda S. Archambault – UConn Health

Exploring Interspecies Interactions in Oral Biofilms: A Collaborative Approach

Linda S. Archambault[1,2], Sherli Koshy-Chenthittayil[2], Pedro Mendes[2], Reinhard Laubenbacher[3], and Anna Dongari-Bagtzoglou[1]

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Humans are colonized by diverse microbial communities consisting of bacteria, viruses, and fungi. Increasingly, disease and modern medical treatments lead to an immunocompromised host environment and disrupted microbial communities (dysbiosis) in which normally harmless commensal microbes can interact to become the agents of disease. Many microbes form biofilms on hard (teeth) and soft (mucosal) surfaces of the oral cavity, on oral appliances and on indwelling medical devices. Biofilm structure protects microbes from immune cells and antimicrobials, making them difficult to eradicate. In this study, we are collaborating with

mathematicians to improve our understanding of multispecies biofilms in the oral environment. Through an iterative process using agent-based modeling and laboratory experiments, we have discovered an inhibitory relationship between 2 common oral commensal bacteria, *Streptococcus oralis* and *Lactobacillus casei*. This work forms the basis for further studies into the interactions of these bacterial species with opportunistic fungi within biofilms and will direct discovery of mechanisms to control oral mucosal disease.

27. Maria C. Rocha Granados – UConn Health

Microbial Interactions Modulate Methicillin-Resistant *Staphylococcus aureus* Antibiotic Persistence

Maria C. Rocha Granados[1], Patricia Hare[1,2] & Wendy W. K. Mok[1]

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Antibiotics have changed our quality of life since their discovery. However, bacteria have evolved and developed different mechanisms to survive antibiotic treatment. Among these mechanisms is antibiotic persistence, where bacteria enter into a phenotypic state that enable them to survive antibiotic stress. Bacterial persisters are a subpopulation of cells in a genetically clonal culture that are able to survive doses of antibiotics lethal to their kin without acquiring resistance genes or mutations. Persistence is thought to be a transient adaptive response against intracellular stress, but it can promote adaptive mutations that lead to resistance. Since bacteria respond to environmental cues, it is important to consider bacteria´s niche during antibiotic treatment. At infections sites, other bacteria that are part of the host microbiome can colocalize with the pathogen. These host-colonizing bacteria can secrete metabolites and proteins that affect pathogens physiology, virulence and antibiotic response. The goal of this study is to evaluate the impact of secreted products from commensal bacteria on Methicillin-resistant *Staphylococcus aureus* (MRSA) persistence toward different classes of antibiotics. Additionally, we will identify the persistence-modulating commensal exoproducts using biochemical and analytical techniques. This project will contribute to the understanding of the impact of the molecular interaction and crosstalk between the commensal bacteria and pathogens on bacterial persistence during antibiotic treatment. Our findings can potentially lead to the design of new therapeutic treatments, including antibiotic adjuvants, against antibiotic-refractory microorganisms.

28. Jacquelynn Benjamino – The Jackson Laboratory

MA-GenTA: genome-based microbiome profiling

Jacquelynn Benjamino[1], Benjamin Leopoldo[1], Daniel Phillips[1], Mark D. Adams[1].

[1] The Jackson Laboratory for Genomic Medicine

16S rRNA gene sequencing and metagenome shotgun sequencing (mWGS) are the current standard methods for microbial community profiling. As the field of microbiome research continues to expand, there is growing need for new and improved methods. We present MA-GenTA: Microbial Abundance using Genome Targeted Analysis. MA-GenTA utilizes highly multiplexed probe pools designed from microbial reference genomes to obtain relative abundance data. Probe pools were designed from 830 high quality genome equivalents representing bacteria in mouse stool. The probe pool was tested on a variety of mouse stool specimens with previously acquired 16S and mWGS data. MA-GenTA data was shown to have high correlation to mWGS data down to 0.1% relative MAG abundance as well as detection of a similar number of organisms compared to both 16S and mWGS data. NMDS clustering using the Bray-Curtis dissimilarity metric of experimental groups was consistent among MA-GenTA, 16S, and mWGS derived data. Additionally, functional capability of microbes was inferred by combining relative abundance data from MA-GenTA with

functional pathway data from the reference MAGs used for probe design. MA-GenTA is a newly developed cost-effective, straightforward, quantitative method for microbiome profiling.

29. Stanley Yang – The Jackson Laboratory

Natural genetic variation determines microglia heterogeneity in wild-derived mouse models of Alzheimer's disease

Hongtian Stanley Yang[1], Kristen D. Onos[1*], Kwangbom Choi[1], Kelly J. Keezer[1], Daniel A. Skelly[1], Gregory W. Carter[1, 2, 3] and Gareth R. Howell[1, 2, 3]*

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Microglia are now considered drivers of Alzheimer's disease (AD) pathology. However, single-cell RNA-sequencing (scRNA-seq) of microglia in mice, a key preclinical model organism, have shown mixed results regarding translatability to human studies. To address this, scRNA-seq of microglia from C57BL/6J (B6) and wild-derived strains WSB/EiJ, CAST/EiJ and PWK/PhJ carrying *APP/PS1* was performed and demonstrated that genetic diversity significantly altered features and dynamics of microglia in baseline neuroimmune functions and in response to amyloidosis. There was significant variation in abundance of microglial subpopulations, including numbers of disease-associated microglia and interferon-responding microglia across the strains. Further, for each subpopulation, significant gene expression differences were observed between strains, and relative to B6 that included nineteen genes previously associated with human AD including *Apoe*, *Trem2*, *Bin1* and *Sorl1*. This resource will be critical in the development of appropriately targeted therapeutics for AD and a range of other neurological diseases.

30. Rawan Olayan – The Jackson Laboratory

Transcriptomic profiling of diverse inbred mice identifies sex-specific Alzheimer's-related pathway modifications

Rawan Olayan[1], Asli Uyar[1], Kristen D. Onos[2], Gareth R Howell[2,3], and Gregory W. Carter for the MODEL-AD Consortium[1,2,3]

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Alzheimer's disease (AD) is a heterogeneous disease associated with complex brain changes and major alterations in gene expression. Having a comprehensive atlas of changes in human brain transcriptome, as in the Accelerating Medicine's Partnership for AD, enables the use of animal models to validate, assess, and compare such changes. Identifying the optimal animal model can further advance the discovery of the early disease characteristics and development of potential drugs. Our method identifies sex-specific Alzheimer's-related pathway modifications in specific inbred mouse models that mimic disease effects in human. We perform comprehensive transcriptome profiling of brains from a panel of diverse inbred mice. Then, we perform pathway analysis on the differentially expressed (DE) genes to determine the specific characteristics in each population of samples in mouse and human, separately. Using a set of common pathways between

human and mouse, we identify and measure the overall relationships via the dimension reduction technique canonical correlation analysis. We observe that female mouse models are associated more with Alzheimer's-related pathways compared to male mouse models. We believe that using diverse mouse models to model AD in human can better recapitulate the molecular changes during the origin and progression of late-onset AD.

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