10.7. 2022

IN-PERSON

5TH ANNUAL ULTIMATE BIOMED RETREAT

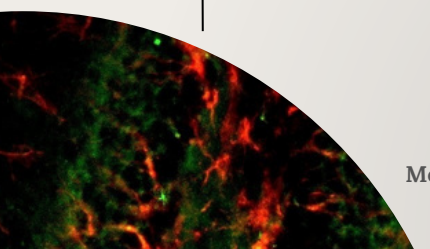
PRESENTED BY THE DIVISION OF BIOMEDICAL SCIENCES

HOSTED BY THE BIOMED GRAD PROGRAM COMMUNITIES

GENOMICS AUDITORIUM
UC RIVERSIDE

Cover Image: **Manolia Ghouli, Binder Lab**

Memories on fire - dentate gyrus stained for mGFAP (red) and NeuN (green)



T A B L E – of – C O N T E N T S

Cover image winner:
" Memories on fire"

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dentate gyrus stained for mGFAP (red) and NeuN (green)

Manolia Ghouli, Graduate Student
University of California, Riverside
–Binder lab, Biomedical Sciences

A special thank you to our retreat committee, volunteers, staff support, and Biomed Faculty for their hard work, time, and effort with coordinating this event.

Without your contributions, this event would not be possible.

Committee Co-Chairs:

Dr. Sean O'Leary

Angelina Lam

Retreat Committee

Carla Urmeneta

JingRong Zhao

Pawrsa Nikzad

Biomed Faculty

Qi Chen

Staff Support

Yael Alonso

Angelica Bazan

Hermila Torres

Maribel Velarde

UC RIVERSIDE
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“Ultimate Biomed Retreat (UBR) “Vision, Mission, and Purpose Statement”

Participants: All Faculty, Fellows, Staff and Students in the Division of Biomedical Sciences and the Graduate Program for Biomedical Sciences

UCR Vision: This forum will engage the diversity of individuals, perspectives and expertise in activities focused on enrichment, evaluation, and creative exploration of synergies to facilitate the Division in attaining its aspirational goals to be a campus, school, and national leader in the practice of innovative high-impact Biomedical Sciences research, teaching and service.

UBR Mission: To provide an annual forum for the Division to:

- Feature and celebrate our achievements and progress
- Foster community amongst all in the Division and its administered programs
- Provide opportunities for leadership and impact for trainees, staff and those not traditionally in leadership positions
- Involve, engage, and enrich the entire Division community
- Identify opportunities & challenges in its 3-part research, teaching, and service missions
- Identify aspirational, strategic, and pragmatic goals with metrics for the upcoming year
- Ensure that the Division’s goals and activities embody the values of the School of Medicine
- Foster and evaluate the Division’s commitment to pursuing an anti-racist agenda in its 3-part mission

UBR Purpose: To foster community and high-impact research involving all cohorts and ranks in the Division and Division-sponsored programs; reveal and examine our community strengths, challenges, and opportunities; deconstruct institutional racism present within academia; and provide a safe interactive forum for team building, introspection, and professional development.

Thank-you all for your active participation in this retreat and we hope to see you again next year for our 5th Annual Ultimate Biomed Retreat which will be held in the fall quarter of 2022!

Sean O’Leary, Angelina Lam, Carla Urmeneta
JingRong Zhao, Pawrsa Nikzad, and Qi Chen
2022-2023 Steering Committee – BMSC – Ultimate Biomed Retreat

UC RIVERSIDE
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DIVISION OF BIOMEDICAL SCIENCES

THE 5TH ANNUAL
ULTIMATE BIOMED RETREAT
OCTOBER 7, 2022
AGENDA

Welcome to the Retreat!

8:15 - 8:45 AM — **Registration, Breakfast, and Poster Set-up**
Registration and Breakfast in Genomics Lobby
Poster set-up at Entomology Courtyard

8:45 - 9:05 AM — **Welcome to the 5th Ultimate Biomed Retreat!**
Honoring Dr. Christian Lytle
Monica Carson, PhD., Chair, Division of Biomedical Sciences

9:05 - 9:30 AM — **BMSC FAO Division Report**
Isaac Owusu-Frimpong, BMSC Financial Administrative Officer

Morning Session: Wellness & Connection

Moderators: Elyza Do and Angelina Lam

9:30 - 10:00 AM — **"Decreasing Tabacco Product Access in Riverside County"**
Eddy Jara, Dr.Ph.D., Program Coordinator, RUHS-Public Health

10:00 - 10:30 AM — **"Cultivating & Understanding the Importance of LGBTQ + Inclusion"**
Toi Thibodeaux, Assistant Director, LGBTQ Center

10:30 - 11:00 AM — **"Addressing Personal Well-being"**
Naveena Rai, SOM Student Support and Wellness

11:00 - 1:30 PM — **Lunch and Poster Viewing**
Community Partner Tables and Resources

Afternoon Session: Professional Development

Moderator: Trevor Biddle

1:30 - 1:40 PM
Afternoon Welcome
Seema Tiwari-Woodruff, Ph.D., BMSC Grad Program Director

1:40 - 1:55 PM
"Careers in the pharma and biotech worlds"
David Pearson, Ph.D., Managing Director, Entrepreneurial Programs, UCR Office of Technology Partnerships

1:55 - 2:10 PM
"From Scientist to Ecosystem Builder"
Rosibel Ochoa, Ph.D., Associate Vice Chancellor, Office of Technology Partnerships

2:10 - 2:25 PM
"Community Engaged Research: Introduction and Opportunities"
Andrew Subica, Ph.D., Associate Professor, Center for Healthy Communities

2:25- 2:40 PM
"Where do you see yourself in 5 years?"
Maricela Covarrubias Argueta, Ph.D., MRB Incubator Laboratory Manager, Office of Technology Partnerships

2:40- 3:10 PM
Professional Development Q&A Panel
30 minute Q&A w/ Professional Development Speakers

Afternoon Session II: Scientific Sessions

Moderator: Angelina Lam

3:10 - 3:15 PM
"Single-cell analysis identifies specific platelet subpopulations in COVID-19, sepsis, and systemic lupus erythematosus drive the disease severity"
Xinru Qiu, GGB Graduate Student, Godzik Lab

3:15 - 3:20 PM
"Targeting Human PTM SUMOylation as a Novel Strategy for Anti-Viruses"
Runrui Dang, Bioengineering Graduate student, Liao Lab

3:20 - 3:25 PM
"Parasympathetic signaling controls biosynthesis of endocannabinoids in the small-intestinal epithelium in diet-induced obesity and drives hyperphagia via local CB1Rs"
Courtney wood, Neuroscience Graduate Student, DiPatrizio Lab

3:25 - 3:30 PM	**"Dissecting Human and Influenza Virus Interaction with qFRET Technology"** Feras Farha , Cell, Molecular and Developmental Biology Undergraduate Student, Liao Lab
3:30 - 3:45 PM	**Q&A First Group**
3:45 - 4:00 PM	**Afternoon break**
4:00 - 4:05 PM	**"Sex-specific effects of inflammation: why we should care about sex in research"** Paula da Silva, Neuroscience Graduate Student, Carson Lab
4:05 - 4:10 PM	**"Cannabis and Fat"** Bryant Avalos, Biomedical Sciences Graduate Student, DiPatrizio Lab
4:10 - 4:15 PM	**"Cortical Circuit Mechanisms of Multimodal Temporal Pattern Discrimination"** Sam Post, Psychology Graduate Student, Goel Lab
4:15 - 4:20 PM	**"Understanding the HVEM Protein Receptor Through It's Structural Clues"** Jacob Sola, CNAS Department of Chemistry Undergraduate Researcher, Godzik Lab
4:20 - 4:35 PM	**Q&A Second Group**

Retreat close and Reception Welcome!

4:35 - 4:45 PM	**Closing remarks and Thank you's!!!**
4:45 - 5:45 PM	**Reception Welcome and Poster Presentations**
5:45 - 6:00 PM	**Presentation Awards and Adjourn**

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See You Next Year!

5TH ANNUAL ULTIMATE BIOMED RETREAT
WELLNESS & CONNECTION SPEAKER BIOS

EDDY JARA, DR.PH.D.

Program Director, RUHS - Public Health

Dr. Eddy Jara is Program Director with the Riverside County Public Health Department. He leads the tobacco use prevention program and the Blue Zones Initiative in Riverside County. His 30+ year trajectory in community-based prevention interventions includes serving as a Technical Health Trainer for Peace Corps-Ecuador, Assistant Professor at Loma Linda University School of Public Health and Health City Coordinator at the City of Riverside. He appreciates his collaboration with UCR entities such as, serving on School of Medicine community advisory boards, preceptoring School of Public Policy students and co-authoring a paper with members of UCR Healthy Campus.

TOI THIBODEAUX

Assistant Director, LGBT Resource Center, UC Riverside

Toi Thibodeaux has served as the Assistant Director for the LGBT Resource Center at UC Riverside since 2008 and is the current co-chair for the Chancellor's Advisory Committee on LGBT Students, Faculty & Staff. In addition, Toi was appointed to serve as a committee member for the University of California Office of the President Task Force & Implementation Team on LGBT Climate & Inclusion from 2012-2014. From 2013-2014, Toi was invited to serve on the Congress of the United States, House of Representatives 41st District LGBT Advisory Committee for Congressman Mark Takano. In 2018, Toi was a recipient of the "Woman of Distinction" award by Jose Medina, California State Assembly Member and Chair of the Higher Education Committee.

NAVEENA RAI

Student Support & Wellness Specialist, School of Medicine, UC Riverside

Naveena Rai is the UCR SOM Support & Wellness Specialist. She is currently an Associate Marriage and Family Therapist as well was an Associate professional clinical counselor. Naveena obtained master's degree in clinical psychology from Antioch University, Santa Barbara. She has experience working with sexual assault and domestic violence survivors, conducting psychoeducational classes, including a child abuse intervention program, and parenting program. Additionally, Naveena has worked as a health and wellness peer educator for three years, aiding incoming first-year and transfer students with different concerns such as transitioning from home, procrastination, and nutritional education.

5TH ANNUAL ULTIMATE BIOMED RETREAT
PROFESSIONAL DEVELOPMENT SPEAKER BIOS

DAVID PEARSON, PH.D.

Managing Director, Entrepreneurial Programs, Technology Partnerships, UC Riverside

Dr. David Pearson earned his PhD at Yale in Molecular Biophysics and subsequently an MBA from the Sloan School at MIT. He has 35 years' senior management experience across technical, operational, and general management roles in the pharmaceutical and biotech industries, including 20 years in Europe. He has been at UCR for 3 1/2 years as the Managing Director for Entrepreneurial Programs with Rosibel Ochoa and is the Director of the UCR EPIC Life Sciences Incubator.

ROSIBEL OCHOA, PH.D.

Associate Vice Chancellor Technology Partnerships, Research and Economic Development, UC Riverside

Dr. Rosibel Ochoa oversees the Office of Technology Partnerships at the University of California Riverside leads programs and initiatives that support strategic regional economic development based on technology entrepreneurship. Her team consisting of 22 associates and more than 15 entrepreneurs in residence focused on accelerating the commercialization of academic research, the training of the entrepreneurial workforce and the access of capital, C-level talent and infrastructure to the region's entrepreneurs so they can build and grow their companies in the Inland Southern California.

Since joining UC Riverside in mid- 2016, she has secured over $20 million in grants and contracts to support the creation of over 10 programs and initiatives that supports technology startup creation, incubation, and industry-university partnerships. She is the recipient of four competitive awards from the US Economic Development Administration, the Small Business Administration and the Principal Investigator of the UC Riverside NSF I corps site.

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5TH ANNUAL ULTIMATE BIOMED RETREAT
PROFESSIONAL DEVELOPMENT SPEAKER BIOS

ANDREW SUBICA, PH.D.

Associate Professor, Social Medicine, Population, and Public Health, UC Riverside

Andrew Subica is an Associate Professor of Social Medicine, Population, and Public Health. He studies mental and physical health disparities in vulnerable populations using community engaged research methods. His work has been funded by the National Institute of Mental Health, National Institute on Drug Abuse, National Institute on Alcohol Abuse and Alcoholism, and Centers for Disease Control and Prevention, and served an NIH-funded mental health scholar at the University of Southern California and clinical fellow at the Central Texas VA Medical Center before joining UCR.

MARICELA COVARRUBIAS ARGUETA.

MRB Incubataor Laboratory Manager

Maricela Argueta is a UCR alum that currently manages the UCR EPIC Life Sciences Incubator Lab at MRB. Maricela received her Bachelor of Science focusing in Biology from UCR in 2000. In the time since graduating, she has had the opportunity to work both within academia and industry in a wide range of life science technologies. Maricela has managed projects in core research facilities, technical support, and provided training to labs across the nation

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Lightning Talks

1. **Single-cell analysis identifies specific platelet subpopulations in COVID-19, sepsis, and systemic lupus erythematosus drive the disease severity**

   XINRU QIU, Godzik Lab

   University of California, Riverside

   Dysregulation of the immune system is a primary mechanism of many diseases from sepsis to autoimmune diseases and, recently, COVID-19. While most of the attention in the analysis of the diseases of the immune system is focused on the professional immune cells, recently abnormal platelets have been implicated in severe outcomes is several of them. Here, we identify and compare the expression signatures of platelets in individuals with COVID-19, sepsis, and SLE using an integrated analysis of single-cell transcriptomes from several publicly available datasets. We identify platelet subtypes specifically over- and under-represented in fatal and less severe disease cases that could be used both as a benchmark to identify patients with negative prognosis and, potentially, provide targets for intervention. Our analysis gives cellular and molecular insights on platelet responses to severe immune system dysregulation and offers potential path to therapeutic intervention aimed for improving outcomes for subsets of patients with severe forms of several diseases.

2. **Targeting Human PTM SUMOylation as a Novel Strategy for Anti-Viruses**

   RUNRUI DANG, Liao Lab

   University of California, Riverside

   Although vaccine plays critical and first-line roles for anti-virus infections, not full protection from vaccination in different populations, such as children or elders, highlights the urgent need for therapeutics. But current anti-virus therapeutics all target virus proteins, which is strain-specific and has potential to induce drug resistance development. Targeting host factors for virus life cycle become an attractive strategy for next generation anti-virus therapeutics development. Recently, various studies uncover the intensive interactions of virus with human post-translational modification (PTM) pathway, SUMOylation. In one hand, numerous viral proteins are SUMO substrates, and SUMO modification affects virus replication through various mechanisms. On the other hand, viruses encode various SUMOylation enzymes that interfere with host SUMOylation pathways. However, the real roles of human SUMOylation for virus life cycle have not been elucidated until recently that, for the first time, we discover that the human SUMOylation pathway is essential for the IAV and IBV viral life cycle. First, these two viruses were completely inhibited by a novel SUMOylation specific inhibitor, STE025, discovered from our FRET-based high-throughput screening, and the inhibition was very high potent with IC50~ 0.1mM in a virus-induced cell death rescue assay; Second, we determined that both IAV and IBV M1, which is essential for viral life cycle, can be SUMOylated and the mutation of IAV and IBV M1 SUMOylation site, K21R, completely abolishes the viral particle generation, strongly suggesting the requirement of SUMOylation for IAV and IBV life cycle. Third, more interestingly, IAV and IBV could not develop drug resistance under the SUMOyaltion inhibitor selection. These results suggest that blockage of the human SUMOylation pathway is very effective for IAV and IBV inhibition. We, therefore, propose that the host SUMOylation pathway is a critical host factor for the IAV and IBV virus life cycle and inhibition of SUMOylation provides a novel strategy for future anti-viral therapeutics development, such as influenza virus and other viruses.

3. **Parasympathetic signaling controls biosynthesis of endocannabinoids in the small-intestinal epithelium in diet-induced obesity and drives hyperphagia via local CB1Rs**

Courtney Wood, DiPatrizio Lab

University of California, Riverside

The endocannabinoid (eCB) system is an endogenous lipid signaling system that controls food intake and energy balance. In diet-induced obese (DIO) mice, overactivation of cannabinoid receptor subtype-1 (CB1R) in the small-intestinal epithelium (SI) inhibits nutrient-induced release of satiation peptides and promotes hyperphagia. We tested the hypothesis that parasympathetic signaling at muscarinic acetylcholine receptors (mAChRs) leads to increased biosynthesis of the eCB 2-arachidonoyl-sn-glycerol (2-AG) in the SI epithelium in DIO, which drives overeating via local CB1Rs. Male mice were maintained on a high-fat/high-sucrose western-style diet (WD) for 60 days to induce DIO. Mice received IP injections of methylhomatropine bromide (ATR, a peripheralized mAChR antagonist), DAU5884 (DAU, a selective m3 mAChR antagonist), or pirenzepine (PIR, a selective m1 mAChR antagonist) 30 minutes prior to tissue harvest. Levels of 2-AG and its precursor, 1-stearoyl-2-arachidonoyl-sn-glycerol (SAG), in the SI were quantitated by UPLC-MS/MS. Ex-vivo activity of the synthetic and degradative enzymes for 2-AG, diacylglycerol lipase (DGL) and monoacylglycerol lipase (MGL), respectively, in the SI were also analyzed. Food intake, water intake, and ambulation were recorded with automated feeding chambers. DIO mice exhibited elevated levels of SAG, 2-AG, and DGL activity in the SI, when compared to lean controls maintained on standard chow. These effects were blocked by ATR, DAU, or PIR. Furthermore, ATR, DAU, or AM6545 (a peripheralized CB1R neutral antagonist) reduced caloric intake in DIO mice to levels found in lean mice during a 24 h test. A second group of male mice conditionally lacking CB1Rs in the SI (IntCB1-/-) and controls (IntCB1+/+) were maintained on WD for 60 days. Mice received single IP injections of ATR or AM6545 and caloric intakes were recorded for 24 h. ATR and AM6545, independently and combined, reduced caloric intake in IntCB1+/+ DIO mice for up to 24 h but had no effect on intake in IntCB1-/- mice. These results suggest that in DIO, hyperactivity at Gq-coupled mAChRs in the periphery increases the PLC-dependent generation of SAG, which is then converted to 2-AG by DGL in the SI and activates local CB1Rs to drive hyperphagia.

4. **Sex-specific effects of inflammation: why we should care about sex in research**

PAULA DA SILVA FROST, Carson Lab

University of California, Riverside

Disparities in the generation of sex-specific data has direct implication in treatment of disorders. Currently, most of research is obtained from male data, but evidence from both human and animal models have shown sex to differentially modulate the inflammatory response. Here, using a model of systemic inflammation to study sex-specific intestinal responses; intraperitoneal lipopolysaccharide (IP-LPS) was administered to male and female mice, and intestine was collected 24 hours later for analysis. Male and female show a different response with a very specific profile. Only in females there is an increase in conductance and permeability in jejunum in response to IP-LPS. The changes are accompanied by alterations in tight-junction claudin-3, that is more internalized in females than male villi. On the other hand, only in males there is an increase in glucose absorption in response to IP-LPS. To directly address the sex-specific inflammatory and metabolic response, gene expression was analyzed in jejunum tissue. Female jejunum is more responsive than male, upregulating chemokines ccl2, ccl8, cxcl9, TLR4 downstream signaling cascade myd88, traf6 and oxidative stress related gene expression nod1. This female specific response was also demonstrated in the expression of metabolic genes, again generating a unique signature marked by a major upregulation of hif1a and mTOR related genes. Males mostly downregulate gene expression in response to inflammation, including nfkb expression, and genes associated with mTOR pathway. Collectively, this data shows LPS elicits a sex-specific response in jejunum, with female mice showing a more robust pro-inflammatory profile than males.

5. Cannabis and Fat

BYRANT AVALOS, DiPatrizio Lab

University of California, Riverside

The endocannabinoid (eCB) system in the brain and peripheral tissue controls food intake and energy homeostasis. In general, activation of the eCB system increases food intake and storage of energy from food for future use as fuel. In contrast, inhibiting eCB system activity reduces food intake and body weight, and increases energy expenditure in diet-induced obesity (DIO). Similar appetite-stimulating effects occur following acute consumption of Cannabis sativa and low doses of its main intoxicating chemical constituent, Δ9-tetrahydrocannabinol (THC). Conversely, studies in humans suggest that chronic cannabis users display paradoxical improvements in a variety of metabolic parameters when compared to non-users, including decreased risk of developing Type-2 Diabetes (T2D); however, the underlying molecular mechanisms involved in these processes are largely unknown. In the current study, we tested the hypothesis that chronic exposure to THC or whole cannabis oil extracts – matched for THC content by ultra-performance liquid chromatography/mass spectrometry (UPLC/MS2) – can mitigate metabolic dysfunction in DIO by reversing dysregulation of the adipose-pancreatic (adipoinsular) axis, which includes fat-derived adipokines that control glucose homeostasis. In addition to decreased adipose tissue mass in DIO mice, drug treatments reversed DIO-associated changes in expression of genes for the adipokines adipsin, leptin, and adiponectin in epididymal fat, with extracts more potently restoring levels of adipsin and leptin to levels found in lean control mice fed a low-fat/no sucrose standard lab chow. Plasma insulin levels were also lower in DIO mice treated with THC or extracts.-- Moreover, chronic exposure to extracts, but not THC, was associated with improved glucose clearance in DIO mice. Insulin sensitivity, as assessed by IP ITT, indicated no differences across groups in glycemic response to insulin, which suggests that extract-induced improvements in glucose homeostasis were not due to changes in tissue sensitivity to insulin. Future work aims to further understand the potential role of CB1R on adipocytes in driving the metabolic improvements that arise from the adipoinsular axis.

6. Cortical Circuit Mechanisms of Multimodal Temporal Pattern Discrimination

Sam Post, Goel Lab

University of California, Riverside

Discriminating between temporal features in sensory stimuli is critical to complex behavior and decision making. However, how sensory cortical circuit mechanisms contribute to discrimination between subsecond temporal components in sensory events is unclear. To elucidate the mechanistic underpinnings of timing in primary visual cortex (V1), we recorded from V1 using 2-photon calcium imaging in awake-behaving mice performing a go/no-go discrimination timing task, which was composed of patterns of subsecond audio-visual stimuli. In both conditions, activity during the early stimulus period was temporally coordinated with the preferred stimulus. However, while network activity increased in the preferred condition, network activity was increasingly suppressed in the nonpreferred condition over the stimulus period. Our results demonstrate that discrimination between subsecond intervals that are contained in rhythmic patterns can be accomplished by local networks and suggest the contribution of neural resonance as a mechanism.

7. Dissecting Human and Influenza Virus Interaction with qFRET Technology

Feras Farha, Liao Lab

University of California, Riverside

Influenza viruses cause seasonal epidemics and occasional pandemics around the world. During each flu season, IAV and IBV viruses are circulated widely in the community, with IAV being the dominant circulating virus and IBV accounting for 25% of all flu cases on average. Förster resonance energy transfer (FRET) is a technique for detecting protein interactions in vitro and in vivo that is widely employed in biological and biomedical research. Our research provides a direct interaction of SUMOylation E3 ligase with influenza A M1 protein and influenza B M1 protein, providing new insights into human-virus interactions for future therapeutics development.

8. Understanding the HVEM Protein Receptor Through It's Structural Clues

Jacob Sola, Godzik Lab

University of California, Riverside

"HVEM (Herpes virus entry mediator) is a cell surface receptor protein from the TNF-receptor superfamily that serves a bi-directional, still minimally understood, role in the regulation of the human immune system. CD160, LIGHT, BTLA, and the IgD glycoprotein each form a unique complex with HVEM. Each ligand binds to a specific interface on HVEM’s surface, differentially regulating a complex network of protein-protein interactions within the cell surface. The bi-directional capability to positively or negatively regulate the immune system suggests HVEM’s potential to serve as a therapeutic target for a wide range of pathological conditions. Computational methods in this study provide insight into the structural-phenotypic relationship in HVEM. Analysis of a structural map produced in the study will allow researchers to predict effects of point mutations on specific residues and to guide the development of specific therapeutic antibodies."

Poster Abstracts

1. AlphaFold Model Analysis of Translocated Effectors in Legionella pneumophila

Abraham Takkouche[1,2], Lukasz Jaroszewski[2,4], Alexei Savchenko et. co.[3,4] and Adam Godzik[2,4]

1. University of California Riverside, 900 University Ave. Riverside, CA 92521, USA
2. Division of Biomedical Sciences, University of California Riverside School of Medicine, 900 University Ave. Riverside, CA 92521, USA
3. Health Research Innovation Centre, Cumming School of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, T2N 4N1, CANADA
4. Center for Structural Biology of Infectious Diseases, NIAID Research Center

Leucine-rich repeats (LRRs) are a protein structural motif found almost exclusively in eukaryotic genomes. Their structure resembles a horseshoe, with parallel β-sheets on the concave side and α-helices on the convex side. One of the most prominent examples of proteins with a LRR motif is the ectodomains of Toll-like receptors, essential in recognizing and responding to pathogens. Bacteria often use proteins with LRRs as virulence factors, interacting and disrupting the cellular machinery of host cells. As part of a project on characterizing virulence factors of pathogenic bacteria, we generated and analyzed AlphaFold models of 360 effectors from L. pneumophila, a pathogenic bacterium responsible for a severe form of pneumonia (Legionnaires' disease). Using Pfam sequence analysis structure comparisons to experimentally determine protein structures, 9 LRR motif-containing proteins were identified among L. pneumophila effectors. This finding contributes to the existing evidence that LRR effector proteins have been acquired through interdomain horizontal gene transfer and are now being used against their former hosts.
All structures in this group follow the general LRR motif with the exception of lpg1933. Lpg1933 effector, while still categorized as a leucine-rich repeat, is both shorter and less uniform than the others. Lpg1933 is also the only effector in this set with no other orthologs. By contrast, orthologs of three of the L. pneumophila LRR receptors (lpg0945, lpg1602, and lpg1958) are found in many other bacteria from the Legionella genus. Detailed analysis of the LRR effectors from L. pneumophila is now ongoing in the collaborating experimental laboratories.

2. Dorsolateral striatum, not motor cortex, is a bottleneck for responding to task-relevant stimuli in a learned whisker detection task in mice

Angelina Lam[1], Behzad Zareian[2], Edward Zagha[2,3]

1. Division of Biomedical Sciences, University of California Riverside School of Medicine, 900 University Ave. Riverside, CA 92521, USA
2. Department of Psychology, University of California Riverside, 900 University Ave. Riverside, CA 92521, USA
3. Neuroscience Graduate Program, University of California Riverside, 900 University Ave. Riverside, CA 92521, USA

A learned sensory-motor behavior engages multiple brain regions, including the neocortex and the basal ganglia. How a target stimulus is selected by these regions remains poorly understood. Here, we performed electrophysiological recordings and pharmacological inactivations of motor cortex and dorsolateral striatum to determine the representations within and functions of each region during performance in a selective whisker detection task in male and female mice. From the recording experiments, peak pre-response activity and significant choice probability emerged in the motor cortex before the dorsolateral striatum, suggesting a sensory-to-motor transformation in which the striatum is downstream of motor cortex. We performed pharmacological inactivation studies to determine the necessity of these brain regions for this task. We found that suppressing the dorsolateral striatum, but not motor cortex, severely disrupts responding to task-relevant stimuli, without disrupting the ability to respond. Together these data support the dorsolateral striatum, and not motor cortex, as an essential node in the sensory-to-motor transformation of this whisker detection task.

3. Bifunctional ligands for targeted degradation of surface receptors

Anne Marie Prentiss, Parima Udompholkul, Carlo Baggio, and Maurizio Pellecchia

1. University of California Riverside, 900 University Ave. Riverside, CA 92521, USA

Agonistic agents targeting the extracellular domain of cell surface receptors can at times induce receptor internalization followed by degradation. We recently derived dimeric EphA2 targeting agents that are effective in inducing receptor internalization and degradation in cancer cell lines. Because receptor dimerization/clustering is a pre-requisite for internalization and degradation, we are exploring possible general avenues to create bi-functional ligands that can simulatively cause targeted degradation of multiple surface receptors.

4. Lysine-covalent PIN1 inhibitors: an exploratory study

Beatrice Balboni, Giulia Alboreggia, Mishael Umejesi, and Maurizio Pellecchia

1. University of California, Riverside, School of Medicine, Riverside, CA 92521

In recent years, covalent inhibitors have been widely reconsidered for optimal drug candidates in many therapies, to overcome drug resistance and side effects. Covalent non-reversible inhibitors can achieve a high target active site occupancy with an optimal and prolonged inhibitory or modulatory effect on the protein target, independently from equilibrium-driven binding kinetics, even when competing with a high affinity substrate. With this idea, we focused our work on the synthesis and characterization of a novel lysine-covalent class of inhibitors, targeting PIN1, a cancer related protein, which malfunctioning and misregulation is reported to be linked to many types of cancers.
In this poster we present the design and preliminary characterization of selective agents that covalently bind to a Lysine residue present near the active site of PIN1 protein.

5. Chronic Exposure to Cannabis sativa Extracts Improves Metabolic Dysfunction and Dysregulation of the Adipoinsular Axis in Diet-Induced Obese Mice

Bryant Avalos Leyva, Courtney P. Wood, Nicholas V. DiPatrizio

1. Division of Biomedical Sciences, School of Medicine, University of California, Riverside;
2. UCR Center for Cannabinoid Research (UCRCCR)

The endocannabinoid (eCB) system in the brain and peripheral tissue controls food intake and energy homeostasis. In general, activation of the eCB system increases food intake and storage of energy from food for future use as fuel. In contrast, inhibiting eCB system activity reduces food intake and body weight, and increases energy expenditure in diet-induced obesity (DIO). Similar appetite-stimulating effects occur following acute consumption of Cannabis sativa and low doses of its main intoxicating chemical constituent, Δ9-tetrahydrocannabinol (THC). Conversely, studies in humans suggest that chronic cannabis users display paradoxical improvements in a variety of metabolic parameters when compared to non-users, including decreased risk of developing Type-2 Diabetes (T2D); however, the underlying molecular mechanisms involved in these processes are largely unknown. In the current study, we tested the hypothesis that chronic exposure to THC or whole cannabis oil extracts – matched for THC content by ultra-performance liquid chromatography/mass spectrometry (UPLC/MS2) – can mitigate metabolic dysfunction in DIO by reversing dysregulation of the adipose-pancreatic (adipoinsular) axis, which includes fat-derived adipokines that control glucose homeostasis. In addition to decreased adipose tissue mass in DIO mice, drug treatments reversed DIO-associated changes in expression of genes for the adipokines adipsin, leptin, and adiponectin in epididymal fat, with extracts more potently restoring levels of adipsin and leptin to levels found in lean control mice fed a low-fat/no sucrose standard lab chow. Plasma insulin levels were also lower in DIO mice treated with THC or extracts. Moreover, chronic exposure to extracts, but not THC, was associated with improved glucose clearance in DIO mice. Insulin sensitivity, as assessed by IP ITT, indicated no differences across groups in glycemic response to insulin, which suggests that extract-induced improvements in glucose homeostasis were not due to changes in tissue sensitivity to insulin. Future work aims to further understand the potential role of CB1R on adipocytes in driving the metabolic improvements that arise from the adipoinsular axis.

6. NMR-Guided Design of Potent and Selective EphA4 Agonistic Ligands

Carlo Baggio[1], Anna Kulinich[1], Cassandra N. Dennys[2], Rochelle Rodrigo[2], Kathrin Meyer[2], Iryna Ethell[1], and Maurizio Pellecchia[1]

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In this work, we applied an innovative nuclear magnetic resonance (NMR)-guided screening and ligand design approach, named focused high-throughput screening by NMR (fHTS by NMR), to derive potent, low-molecular-weight ligands capable of mimicking interactions elicited by ephrin ligands on the receptor tyrosine kinase EphA4. The agents bind with nanomolar affinity, trigger receptor activation in cellular assays with motor neurons, and provide remarkable motor neuron protection from amyotrophic lateral sclerosis (ALS) patient-derived astrocytes. Structural studies on the complex between EphA4 ligand- binding domain and a most active agent provide insights into the mechanism of the agents at a molecular level. Together with preliminary in vivo pharmacology studies, the data form a strong foundation for the translation of these agents for the treatment of ALS and potentially other human diseases.

7. Phylogeographic Analysis of COVID-19 Infectious Cases in Riverside, California

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The rapid transmission and infection rate of the SARS-CoV-2 outbreak limited the development of extensive disease contact tracing during this period.
In this study, an attempt to recreate contact tracing of SARS-CoV-2 in Riverside, California with genomic tracking using a global EpiCoV sequencing database was carried out. This study provides information on the geographic location of the closest-related COVID-19 genome to COVID-19 cases in Riverside. Evolutionary information on COVID-19 genomes help to identify the sources of infections of the COVID-19 cases in Riverside.
The extent of local and distant transmission can be determined based on the location of the closest genome to the genomes of COVID-19 cases in Riverside. We identified and compared the pattern of infections for different variants of concern. These patterns can be associated with the features of the dominant variant and the level of public health measure at the time of infection, therefore data was stratified by time and compared against Riverside County and California State public health guidelines. Our findings indicate that the pattern of infections in Riverside was not due to extensive local infections, but rather from contributions from all around the world. The distribution between different variants of concern also depends on the level of restrictions, especially with Omicron being the least home-grown.

8. LYsine COvalent Degraders (LYCODE): exploring E3-covalent ligands for targeted protein degradation

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A promising therapeutic strategy consists in designing bi-functional molecules that induce the degradation of diseases-associated proteins, through the ubiquitin-proteasome system. Several E3-ligases have been used for this purpose including the Inhibitor of Apoptosis Protein (IAP) family, including XIAP, cIAP1, and cIAP2. In this poster, we present novel degraders that use a potent and selective agent that covalently bind to a Lysine residue present in the BIR3 domain of different IAPs.

9. Dynamics of Ribosome Scanning During Translation Initiation

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Faithful recognition of the mRNA start codon at the initial stage of translation is an essential process during regulation of gene expression. For this purpose, eukaryotes utilize a 43S pre-initiation complex (PIC), which moves along the mRNA 5' untranslated region (UTR) to locate the start codon; this movement is termed "scanning" and is thought to proceed linearly with significantly processive 5'-to-3' directionality. Although the scanning model was proposed many decades ago, the exact molecular mechanism of the motion, and how it may vary between different mRNAs and under various cellular conditions, remain unclear due to the highly dynamic nature of the process. We developed a multi-color single molecule fluorescence method to observe PIC dynamics in real time on the translation initiation timescale. Using this technology, we aim to directly measure the rate of scanning on full-length yeast mRNA, in order to understand the dynamics of PIC movement along different UTR lengths and structural contexts. Furthermore, we seek to parse the roles of key initiation factors and their biochemical activities in the scanning mechanism. Our data provide direct insights into this vital process in translational control.

10. Loss of PTPN2 Activity Alters Iron Handling Gene Expression in IBD Patients and Causes Iron Deficiency in Mice

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Anemia is the most common extraintestinal complication of inflammatory bowel disease (IBD) and is a risk factor for Crohn's disease (CD) onset. Iron deficiency is the most common cause of anemia in IBD; however, the mechanisms involved are poorly understood. Here, we investigated the role of the IBD risk gene, protein tyrosine phosphatase non-receptor type 2 (*PTPN2*), in regulating iron homeostasis.
Proteomic analyses were performed on serum from IBD patients genotyped for the IBD-associated loss-of-function *rs1893217 PTPN2* variant (n=10/genotype). Constitutive *Ptpn2* wild type (WT), heterozygous (Het), and knockout (KO) 3-week-old mice were analyzed for serum iron content, liver non-heme iron and liver expression of the iron regulatory hormone, hepcidin (*Hamp1*). Protein and RNA from duodenal epithelial cells (DECs) were assayed by western blotting and qPCR. Localization of the brush border ferrous iron transporter, DMT1, in duodenal tissue was determined by immunohistochemistry (IHC). Iron homeostasis genes, the iron carrier transferrin (TF) and the transferrin receptor (TFRC), were reduced (-log p-value = 10.7) in CD patients with the *PTPN2* risk variant. *Ptpn2*-KO mice had reduced i) serum iron ($p<0.001$; n=11); ii) serum TF saturation ($p<0.01$; n=9); and iii) liver non-heme iron levels ($p<0.01$; n=10), vs. *Ptpn2*-WT and Het mice. This indicated that *PTPN2* loss decreased serum and liver iron storage. Moreover, *Ptpn2*-KO mice had reduced liver expression of *Hamp1* ($p<0.01$; n=7), likely suppressed by low serum iron. DEC gene expression of ferritin (*Fth1)*, an intracellular iron storage molecule, was reduced ($p=0.048$; n=5) while *Tfrc1*, a mediator of basolateral cellular iron uptake, was significantly increased ($p=0.0048$; n=6) in *Ptpn2*-KO mice. Reduced FTH1 expression ($p=0.007$; n=12) in DECs of *Ptpn2*-KO mice was confirmed by western blot, indicating reduced intracellular iron storage. DMT1 expression was unchanged (n=6), whereas IHC showed reduced apical membrane DMT1 in duodenal epithelium of *Ptpn2*-KO mice (n=6), suggesting a possible mechanism of impaired intestinal non-heme iron uptake.
CD patients with the *PTPN2* loss-of-function *rs1893217* SNP display alterations in serum iron handling proteins. Loss of PTPN2 activity in mice causes features of anemia including iron deficiency associated with mislocalization of the duodenal transporter DMT1.

11. Understanding the HVEM Protein Receptor Through It's Structural Clues

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HVEM is a cell surface receptor protein from the TNF-receptor superfamily that serves a bi-directional, still minimally understood, role in the regulation of the human immune system. It has several ligands including CD160, LIGHT, BTLA, and the IgD glycoprotein that compete for HVEM's surface and differentially regulate a complex network of protein-protein interactions with the ability to positively and negatively regulate the immune system. This gives HVEM the potential to serve as a therapeutic target for a wide range of pathological conditions. Computational methods in this study provide key insight into the structural aspects of HVEM binding to the different ligands. Analysis of the interface interactions of a 3D structural map created with computational methods will allow researchers to predict effects of point mutations on specific residues and to guide the development of specific therapeutic antibodies, providing another tool in the study of HVEM and its potential role in therapeutics.

12. EphA4 Antagonists Stabilized by Non-Covalent Intramolecular Interactions (Unpublished)

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EphA4 is a receptor tyrosine kinase essential to the CNS throughout development and for mediating synaptic function. Recently, it was discovered that blocking EphA4 signaling is associated with reversing synaptic dysfunction in Alzeimer's Disease mouse models (Fu et al., 2014). Research has shown that macrocyclic 12 amino acid peptide APY-d3 serves as an effective EphA4 antagonist with a relatively long half-life in plasma and nanomolar binding affinity in vitro (Olson et al., 2016). When bound to EphA4 ligand binding domain (-LBD), APY-d3 adopts a ß-hairpin conformation stabilized by an essential intramolecular disulfide bridge. In particular, flexibility for the ß-turn is granted by ß-Ala8 while residues Cys4 and Cys12 form the covalent disulfide bond that stabilize the macrocycle in the bioactive ß-hairpin conformation, as confirmed by X-ray crystallography of the complex between the peptide and EphA4-LBD. Through Structure-Activity Relationship (SAR) studies, computational structure-based design strategies and experimental isothermal calorimetry (ITC) measurements, the Pellecchia Laboratory has made several hypotheses on how to obtain novel agents that can adopt a ß-hairpin without the need of the redox-susceptible disulfide bond. Our hypothesis is that these strategies may yield novel and more effective EphA4 antagonistic agents. The project entailed iterative steps of synthesis and purification of test agents, followed by experimental evaluation of their thermodynamics of binding to recombinant EphA4-LBD. This information, together with solution NMR spectroscopy-based conformational studies on selected test agents, will be interpreted to guide follow-up iterations until potent EphA4 antagonistic agents are obtained that possess comparable or greater affinity for EphA4 as APY-d3.

13. Allergic lung inflammation affects glutamatergic inputs in NTS in sex-specific manner

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Alternaria alternata (alternaria) is a fungi that is associated with allergic lung inflammation; it generates an inflammatory response in the tissue and affects breathing patterns during acute exposure. Long-term exposure has been correlated with asthma symptoms. Here, mice were exposed to non-infectious particles extracted from alternaria via inhalation in an exposure chamber for 7 days. Analysis of lungs confirm allergic inflammation with an increased eosinophil, T cell and B cell in BALF of animals after alternaria exposure. The lungs are connected to the brainstem via vagal nerve afferents, fibers arrive at the nucleus tract solitary (NTS) and synapse within the brainstem to regions that control breathing and the inflammatory response of peripheral organs. Brainstem of males and females show no apparent changes in the gene expression of inflammatory genes, but do show sex-specific effects. Puncta quantification of synaptophysin and vglut2 in NTS are decreased in females after Alternaria exposure, but not males. Regions responsible for controlling breathing patterns BotC and pre-BotC have no altered synaptic puncta numbers. The alterations seem to be NTS specific, as females show in the NTS alterations in pAKT and downstream signaling effector proteins without changes in microglial nor astroglial reactivity. Males also have similar protein pathways activated in NTS. Collectivelly, the data suggests synaptic plasticity mechanisms would happen in NTS region, that are not driven by brain inflammation and sex-specific effects would be present. In conclusion, allergic lung inflammation impacts the NTS region by decreasing vglut2 in females only.

14. Fragile X Gene Mutation Alters Hypothalamic GnRH Neuron Activity with Consequences on Reproductive Function

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Mutations in the Fragile X mental retardation (FMR1) gene cause the most common form of inherited intellectual disability, Fragile X syndrome (FXS), due to the loss of Fragile X mental retardation protein (FMRP) in the central nervous system. However, the role of FMR1 on hypothalamic functions has not been examined. A population of hypothalamic neurons that express gonadotropin-releasing hormone (GnRH) and regulate reproduction may be particularly affected by FMR1 mutation, since people with FMR1 mutations also have reproductive issues, such as early cessation of reproductive function in women and enlarged testes in men. We use the Fmr1 knockout (KO) mouse model to determine the role of the FMR1 gene in the hypothalamus and, in particular GnRH neurons. Our data demonstrate that Fmr1KO mice have increased GABAA receptor levels in the hypothalamus. Specifically, in GnRH neurons, the number of GABAergic boutons is increased. GABA, although the primary inhibitory neurotransmitter in the central nervous system, is excitatory to GnRH neurons. We then analyzed the physiological consequences of altered GnRH neuron connectivity. GnRH regulates reproduction by stimulating the synthesis and section of gonadotropin hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gonadotrope cells, which in turn regulate gonadal function. Given that GABAergic afferents in part control GnRH neuron function, alterations in GABAergic stimulation can change the synthesis and secretion of FSH and LH. Fmr1KO females have different serum gonadotropin levels with higher FSH, and LH levels. This may have consequences on ovarian function in females, especially since FSH stimulates the growth of ovarian follicles, while LH primarily stimulates steroidogenesis and ovulation. We determined that Fmr1KO female mice had larger litters and a higher number of ovulated follicles in their ovaries, indicating increased follicular recruitment. This increase in ovulated follicles and larger litter size correlates with high FSH and LH observed in serum analysis. Fmr1KO female mice experienced early cessation of reproductive function and stopped reproducing earlier than control females, which corresponds to findings in the human population. We analyzed whether premature ovarian senescence is due to developmentally lower ovarian follicle reserve by analyzing primordial follicles at 3 weeks of age and found no difference in Fmr1KO and control mice. This indicates that ovarian follicles develop normally during development but are depleted faster in adulthood in the absence of Fmr1. Our data suggest that GnRH neuron function is dysregulated due to FMR1 mutations leading to altered serum gonadotropin levels. In turn, this may lead to increased follicle recruitment in the ovaries and premature cessation of reproductive function. In summary, our results reveal a novel mechanism whereby FMR1 mutations alter GABAergic neurotransmission in the hypothalamus leading to downstream reproductive defects and early menopause.

15. PANDORA-seq Reveals a Hidden Regulatory Small RNA Landscape Associated With Atherosclerosis Development In Hypercholesterolemic LDL Receptor-deficient Mice

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Small non-coding RNAs (sncRNAs) have been demonstrated to have diverse roles in regulating molecular processes. While the standard RNA sequencing (RNA-seq) method has advanced sncRNA discovery, many RNA modifications can interfere with library construction procedures, preventing the discovery of a subset of highly modified sncRNAs including transfer RNA-derived small RNAs (tsRNAs) and ribosomal RNA-derived small RNAs (rsRNAs) that may have important functions in disease development. To address this technical obstacle, we recently developed a novel PANDORA-seq method to overcome RNA modification-elicited sequence interferences (Nat Cell Biol 2021:424-436). This study aims to identify novel sncRNAs that are associated with atherosclerosis development by using PANDOR-seq. To identify sncRNAs associated with atherosclerosis development, LDLR-/- mice were fed a low-cholesterol diet (LCD; 0.02% cholesterol) or high-cholesterol diet (HCD; 0.5% cholesterol) for 9 weeks. Total RNA isolated from intima was subjected to both traditional RNA-seq and PANDORA-seq, and the sequencing data were analyzed by sncRNA analyzing software SPORTS1.1. By overcoming RNA modification-elicited limitations, PANDORA-seq unveiled a rsRNA- and tsRNA-enriched sncRNA landscape in the atherosclerotic intima of LDLR-/- mice which was strikingly different from that detected by traditional RNA-seq. While micro-RNAs (miRNAs) were the dominant sncRNAs detected by traditional RNA-seq (55.9% of total sncRNAs), PANDORA-seq substantially increased the reads of rsRNAs and tsRNAs which account for 77.4% and 5% of total sncRNAs, respectively. PANDORA-seq also detected 1,383 differentially expressed sncRNAs induced by HCD feeding including 1160 rsRNAs and 195 tsRNAs but traditional RNA-seq only detected 16 differentially expressed rsRNAs and tsRNAs. Thus, PANDORA-seq revealed the hidden rsRNAs and tsRNAs associated with atherosclerosis development, and the functions of those previously underexplored sncRNAs warrant future investigations.

16. Mapping cellular pathways targeted by Crimean-Congo Hemorrhagic Fever Virus vOTU

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Crimean-Congo Hemorrhagic Fever Virus (CCHFV) is a tick-borne virus widespread in Africa, parts of Asia and Europe with no currently approved vaccine or treatments available.
CCHFV RNA L-segment encodes for a RpRd and a viral ovarian tumor (vOTU) protease that possess deubiquitinase (DUB) and delSGylase activities, counteracting host innate immune response by reversing post-translational modifications initiated by the cellular ubiquitin (Ub) and the interferon-stimulated gene product 15 (ISG15), essential for type 1 interferon (IFN1) response.
The aim of this study was screening the main cell pathways targeted by CCHFV protease and its interactions with Ub and ISG15. vOTU wild type (WT) and C40A (catalytically inactive) were solely or co-expressed with human ISG15 (V5-tagged) using A549 KO (ISG15 knocked out) cells. Cell antiviral state was stimulated or not by adding synthetic RNA (Poly I:C). Proteins were isolated by immunoprecipitation against Ub, ISG15 (V5-tag) or vOTUs (HA-tag) followed by mass spectrometry.
Several pathways associated with signal transduction, cell cycle control, trafficking, and cytoskeleton were identified when overexpressing vOTUs alone or simultaneously with ISG15, which can be associated with the transport of these transient proteins through the cell. Proinflammatory (p38 MAPK), TGF (T-cell activation) pathways were identified for vOTU-WT and vOTU-WT-ISG15, regardless cell antiviral state induction. Proteasome pathway was identified under vOTU-C40A and vOTU-C40A-ISG15 transfection, both lacking DUB activity.
This study represents the kickstart of a series of experiments that will enhance our knowledge about the mechanisms by which CCHFV can evade the immune response, thus, revealing new targets for therapeutic intervention.

17. Single-cell analysis identifies specific platelet subpopulations in COVID-19, sepsis, and systemic lupus erythematosus drive the disease severity

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Dysregulation of the immune system is a primary mechanism of many diseases from sepsis to autoimmune diseases and, recently, COVID-19. While most of the attention in the analysis of the diseases of the immune system is focused on the professional immune cells, recently abnormal platelets have been implicated in severe outcomes is several of them. Here, we identify and compare the expression signatures of platelets in individuals with COVID-19, sepsis, and SLE using an integrated analysis of single-cell transcriptomes from several publicly available datasets. We identify platelet subtypes specifically over- and under-represented in fatal and less severe disease cases that could be used both as a benchmark to identify patients with negative prognosis and, potentially, provide targets for intervention. Our analysis gives cellular and molecular insights on platelet responses to severe immune system dysregulation and offers potential path to therapeutic intervention aimed for improving outcomes for subsets of patients with severe forms of several diseases.

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