UCI University of California, Irvine

CENTER FOR EPIGENETICS AND METABOLISM

NEWSLETTER | SUMMER 2020

CEM MEMBERS

Pierre Baldi, Ph.D.
Tallie Z. Baram, M.D., Ph.D.
Bruce Blumberg, Ph.D.
Emiliana Borrelli, Ph.D.
Rémi Buisson, Ph.D.
John Chaput, Ph.D.
Xing Dai, Ph.D.
Michelle Digman, Ph.D.
Tim Downing, Ph.D.
Enrico Gratton, Ph.D.
Klemens Hertel, Ph.D.
Cholsoon Jang, Ph.D.
Peter Kaiser, Ph.D.
Kai Kessenbrock, Ph.D.
Devon Lawson, Ph.D.
Gina Lee, Ph.D.
Andrej Luptak, Ph.D.
Fabio Macciardi, Ph.D.
Selma Masri, Ph.D.
Ali Mortazavi, Ph.D.
Nick Pannunzio, Ph.D.
Suzanne Sandmeyer, Ph.D.
Paolo Sassone-Corsi, Ph.D.
Marcus Seldin, Ph.D.
Yongsheng Shi, Ph.D.
Rob Spitale, Ph.D.
Joan Steffan, Ph.D.
Leslie Thompson, Ph.D.
Marcelo Wood, Ph.D.
Kyoko Yokomori, Ph.D.

HIGHLIGHTS

- **Marcus Seldin, Ph.D.,** received the NIH NIDDK: dkNET Pilot Program in Informatics Grant
- **Robert Lewis** was awarded the ICAN National Institute on Drug Abuse (NIDA) T32 Training Grant in Substance Use and Use Disorders
- **Estee Lauder** announces the scientific collaboration with the **Paolo Sassone-Corsi Laboratory**
- Two **Seed Grants** of $10,000 each are offered by the CEM to fund research in epigenetics
- The CEM welcomes **Cholsoon Jang, Ph.D.** and **Gina Lee, Ph.D.** as our newest members
- The CEM has postponed the **Epigenetic Control of Cellular Plasticity Symposium** for October 2021

AWARDS AND GRANTS

NIH NIDDK

CEM Member and Assistant Professor in the Department of Biological Chemistry, **Marcus Seldin, Ph.D.,** received the NIH NIDDK: dkNET Pilot Program in Informatics grant.

NIDA T32 TRAINING GRANT

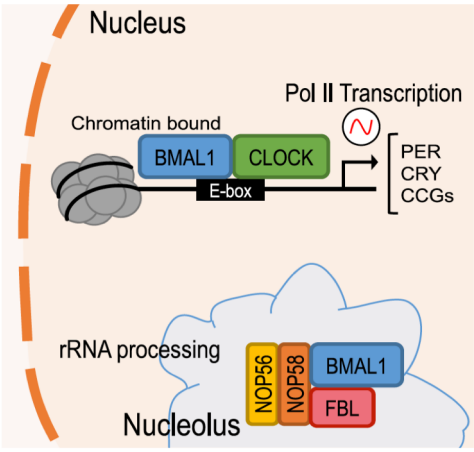
Robert Lewis, a Ph.D. student and member of the Borrelli Laboratory, received the National Institute on Drug Abuse (NIDA) funded ICAN T32 Training Grant in Substance Use and Use Disorders. The goal of this program is to train the next generation of innovative researchers in the field of addiction neuroscience by leveraging the exceptional strength in neuroscience at UCI and the new centers focused on addiction research (ICAN & ICAL) to provide an educational and research experience that will position trainees as new leaders in the field. The objective of Robert's research is to determine how changes in striatal cholinergic interneuron activity by drugs of abuse leads to stable modifications in striatal functions that underlies the transition from casual drug use to abuse.

PUBLICATIONS

iScience

BMAL1 associates with NOP58 in the nucleolus and contributes to pre-rRNA processing

Cervantes, M., Forné, I., Ranjit, S., Gratton, E., Imhof, A., and Sassone-Corsi, P. (2020)



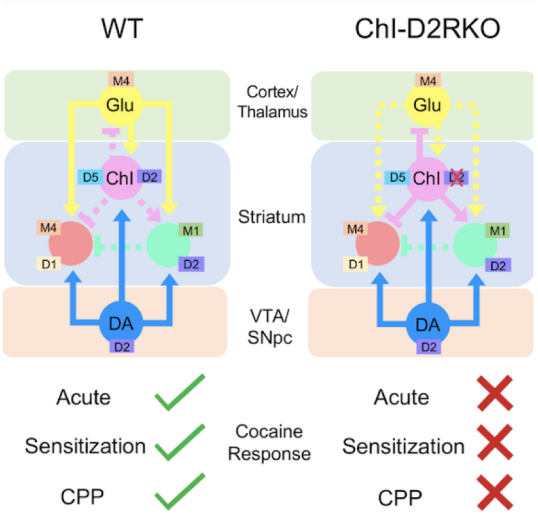
The transcription factor BMAL1 is a core element of the circadian clock that contributes to cyclic control of genes transcribed by RNA polymerase II. By using biochemical cellular fractionation and immunofluorescence analyses a previously uncharacterized nucleolar localization for BMAL1 was revealed. These findings identify an unsuspected function of BMAL1 in the nucleolus that appears distinct from its canonical role in the circadian clock system.

Cell Reports

Dopaminergic Control of Striatal Cholinergic Interneurons Underlies Cocaine-Induced Psychostimulation

Lewis, R.G., Serra, M., Radl, D., Michalak, S.E., Vanderwal, C.D., and Borrelli, E. (2020)

Cocaine drastically elevates dopamine (DA) levels in the striatum, a brain region that is critical to the psychomotor and rewarding properties of the drug. DA signaling regulates intrastriatal circuits connecting medium spiny neurons (MSNs) with afferent fibers and interneurons. While the cocaine-mediated increase in DA signaling on MSNs is known, that on cholinergic interneurons (ChIs) has been more difficult to assess. Using combined pharmacological, chemogenetic, and cell-specific ablation approaches, the findings show that D2R-dependent inhibition of acetylcholine (ACh) signaling is fundamental to cocaine-induced changes in behavior and the striatal genomic response. Thus, D2R-dependent control of striatal ChIs enables the motor, sensitized, and reinforcing properties of cocaine. Also, this study highlights the importance of the DA- and D2R-mediated inhibitory control of ChIs activity in the normal functioning of striatal networks.

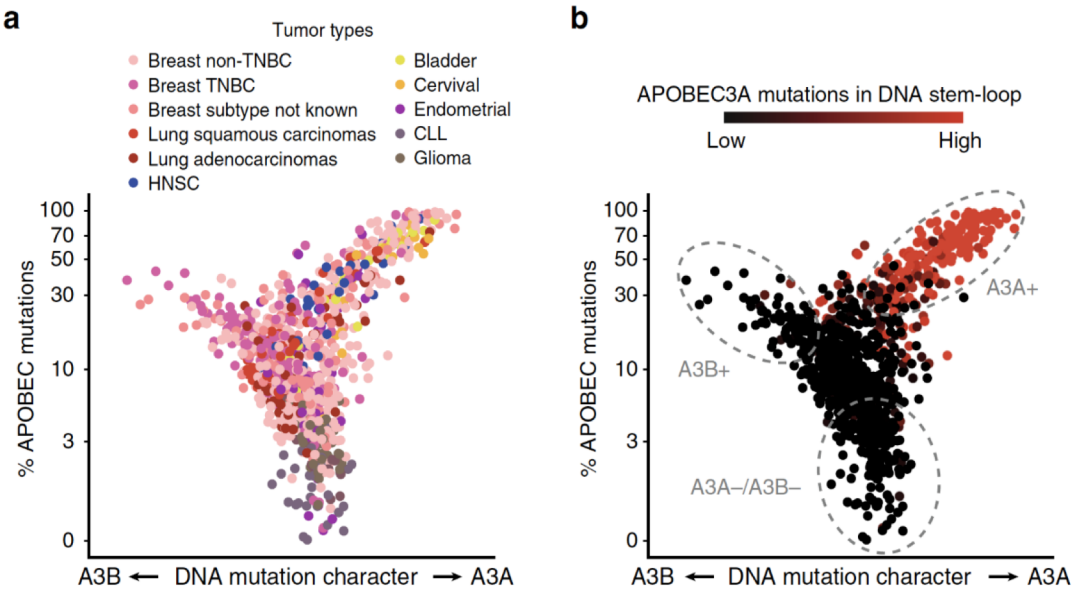


PUBLICATIONS

Nature Communications

Quantification of ongoing APOBEC3A activity in tumor cells by monitoring RNA editing at hotspots

Jalili, P., Bowen, D., Langenbucher, A., Park, S., Aguirre, K., Corcoran, R., Fleischman, A., Lawrence, M., Zou, L., and Buisson, R. (2020)



APOBEC3A is a cytidine deaminase driving mutagenesis, DNA replication stress and DNA damage in cancer cells. While the APOBEC3A-induced vulnerability of cancers offers an opportunity for therapy, APOBEC3A protein and mRNA are difficult to quantify in tumors due to their low abundance. A quantitative and sensitive assay was developed to measure the ongoing activity of APOBEC3A in tumors. Using hotspot RNA mutations identified from APOBEC3A-positive tumors and droplet digital PCR, the RNA-editing activity of APOBEC3A was quantified. This assay is superior to APOBEC3A protein- and mRNA-based assays in predicting the activity of APOBEC3A on DNA. Importantly, this RNA mutation-based APOBEC3A assay is applicable to clinical samples from cancer patients. This study presents a strategy to follow the dysregulation of APOBEC3A in tumors, providing opportunities to investigate the role of APOBEC3A in tumor evolution and to target the APOBEC3A-induced vulnerability in therapy.

PUBLICATIONS

Journal of Experimental Medicine

Commentary on Personalized Medicine and Circadian Rhythms

Greco, C. and Sassone-Corsi, P. (2020)

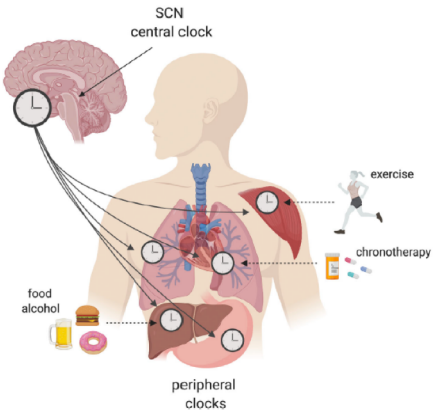
JEM Journal of Experimental Medicine

VIEWPOINT

Personalized medicine and circadian rhythms: Opportunities for modern society

Carolina Magdalen Greco and Paolo Sassone-Corsi

Circadian rhythms govern physiology and metabolism, leading to controlled homeostasis. We discuss the impact of circadian rhythms on society and the challenges for the imminent future of personalized medicine.



Neuroscience

Homer1a Undergoes Bimodal Transcriptional Regulation by CREB and the Circadian Clock

Sato, S., Bunney, B.G., Vawter, M., Bunney, W.E., and Sassone-Corsi, P. (2020)

Accumulating evidence points to a significant link between disrupted circadian rhythms and neuronal dysfunctions, though the molecular mechanisms underlying this connection are virtually unexplored. The transcript *Homer1a*, an immediate early gene related to postsynaptic signaling, has been demonstrated to exhibit robust circadian oscillation in the brain, which supports the hypothesis that *Homer1a* mediates the communication between circadian inputs and neuronal activity. This study elucidates how the circadian clock is implicated in *Homer1a* gene regulation by using circadian clock *Bmal1*-mutant mice either in the presence or absence of stress stimulation. The *Homer1* gene generates multiple transcripts, but only the short variant *Homer1a* responds to acute stress with sleep deprivation (SD) in mice. Chromatin immunoprecipitation assays revealed that both transcription factor CREB and the circadian clock component BMAL1 bind to the *Homer1*promoter in mouse brain. Importantly, circadian *Homer1a* gene expression is unaltered in the absence of BMAL1, while its immediate early response to SD relies on BMAL1. Deletion of *Bmal1* results in attenuated CREB activity in mouse brain, which appears to contribute to decreased expression of *Homer1a* in response to SD. Thus, *Homer1a* undergoes bimodal control by the circadian clock and CREB.

PARTNERSHIP

NEWS RELEASE 2-JUN-2020

Estée Lauder announces scientific collaboration with Dr. Paolo Sassone-Corsi

Estée Lauder to conduct research with world renowned expert in epigenetics and circadian rhythm

To further advance over a decade of circadian rhythm research in skin, the Estée Lauder brand announces a scientific collaboration with Dr. Paolo Sassone-Corsi, Director of the Center for Epigenetics and Metabolism at the University of California, Irvine. Dr. Sassone-Corsi is a world leader in epigenetics and the body clock, having published numerous articles and books on the subjects, and is highly sought after for his expert commentary by both scientific and news media. This research collaboration connects Estée Lauder's skin biology research program with the unmatched expertise and complementary research focus of Dr. Sassone-Corsi.

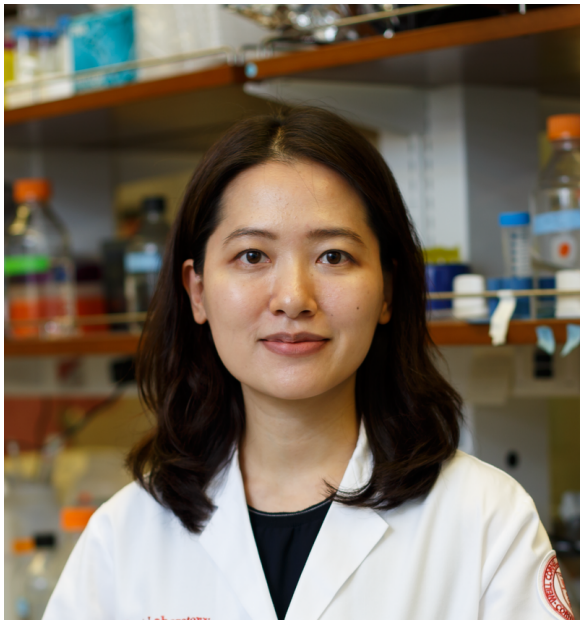
This new Estée Lauder collaboration with the Sassone-Corsi laboratory will build upon Estée Lauder's skin research and contribute to its recent findings by investigating additional molecular mechanisms related to a newly identified micro signaling molecule. The two laboratories will independently explore the interaction between this molecule and other skin activities, including circadian machinery, to deepen the understanding of how skin acts and communicates. This research seeks new information about how this powerful micro signaling molecule interacts with essential skin pathways, in order to better understand how to impact the "memory" of skin to help it act and look younger.

NEW CEM MEMBERS

Gina Lee, Ph.D.

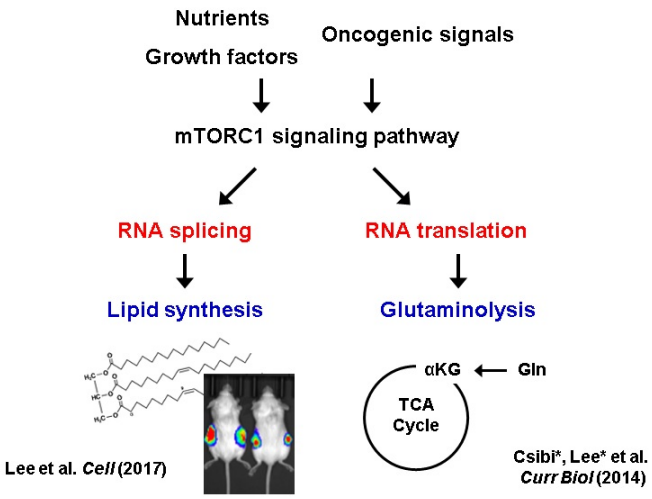
Research

The Lee lab studies signaling and metabolic pathways that control RNA biogenesis. Our work revealed that growth factors and nutrient signaling pathways promote glutamine and lipid metabolism by enhancing RNA splicing and translation of key metabolic enzymes to support tumor growth. Our current focus is another important, yet poorly understood RNA processing, the epigenetic modification of RNA. We study 1) how oncogenic signaling and metabolic pathways control chemical modifications of RNA; and 2) how the RNA epitranscriptome rewires cellular transcriptome, proteome and metabolome to govern cell growth, survival and differentiation. We will uncover new, exciting links between signal transduction, metabolism and the RNA epitranscriptomic landscape, inspiring novel therapeutic avenues for human diseases.

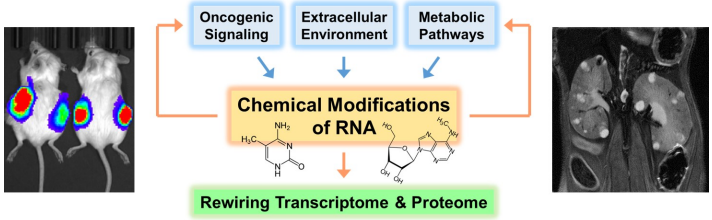


Gina Lee, Ph.D.

Regulation of RNA biogenesis for metabolic adaptation of cancer cells



Rewiring of RNA epitranscriptome by metabolic and signaling networks



NEW CEM MEMBERS

Cholsoon Jang, Ph.D.

Research

Cholsoon Jang, Ph.D.

Diet is one of most important factors that determine our health. The Jang lab studies 1) how the metabolism of dietary nutrients happen in our body, not only by our organs but also by gut microbiota, and 2) how its failure triggers human disease. We focus on clinically relevant, disease-associated nutrients such as alcohol, fructose, and branched-chain amino acids in the context of metabolic diseases (obesity, diabetes, fatty liver) and associated cancers. To quantitatively determine the metabolic fates of nutrients and organ destinations, we use liquid chromatography mass spectrometry (LC-MS)-based metabolomics, lipidomics, and stable isotope tracing in disease animal models and human patients. This comprehensive approach leads us to identify pathogenic metabolites and their impacts on signaling pathways as well as genomic/epigenomic landscapes. Our studies will directly influence public dietary guidelines for safe nutrient consumption and improved preventive and therapeutic strategies. Our technical expertise and knowledge in mass spectrometry, metabolic flux analysis, analytical chemistry, and pathophysiology are the foundation to achieve these goals.

Recently Awarded Grants

Seed Grant, The Center for Epigenetics and Metabolism, 05/01/2020 - 04/30/2021
Differential effects of dietary fiber and fructose on histone acetylation dynamics, Role: PI

Seed Grant, The UCI Microbiome Initiative, 05/01/2020 - 04/30/2021
Elucidating dynamics of microbiota-host interactions using gut-specific ketohexokinase-C knockout mice, Role: PI

Pinnacle Research Award in Liver Disease, AASLD, 07/01/2020 - 06/30/2023
The protective role of small intestinal fructose metabolism in hepatic steatosis, Role: PI

Recent Publication with UCI Affiliations

Jang C*,#, Wada S*, Yang S, Gosis B, Zeng X, et al. (2020). The small intestine shields the liver from fructose-induced steatosis. ***Nat. Metab***. (In press, expected to be online 6/22/20). **#corresponding author**

FUNDING OPPORTUNITIES

2020 CEM SEED GRANTS

UCI

Center for Epigenetics and Metabolism

2020 CEM Seed Grants

Two Seed Grants of $10,000 each are offered by the Center for Epigenetics and Metabolism to fund epigenetics research. A review committee composed of experts external of UCI will select the awarded proposals.

Required Documents:

-Current CV

-Project proposal not exceeding one page

All CEM members and School of Medicine faculty are encouraged to apply. Please note, prior recipients of CEM Seed Grants are ineligible for this award.

Deadline: October 2nd, 2020

Please send all documents to Lauren Stokes at: **lgih@hs.uci.edu**

UPCOMING EVENTS

Epigenetic Control of Cellular Plasticity Symposium

Out of an abundance of caution in regard to the public health crisis, our **Epigenetic Control of Cellular Plasticity Symposium** has been postponed until October 2021