2022 전미 한인 생명과학자의 날

KOREAN-AMERICAN BIOSCIENCE FORUM 2022

미국내 대표 한인 생명과학자 협회
NEBS, NYKB, KOLIS, KLAM 합동 온라인 컨퍼런스

2022. 1. 22. Saturday

1:00 PM – 5:00 PM (EST) 10:00 AM – 2:00 PM (PST)

Registration link

CONTACT US

NEBS 회장 이재교: president@nebskorea.com
NYKB 회장 양종원 : nybk2008@gmail.com
KOLIS 회장 김선기: kolis.president@gmail.com
KLAM 회장 노승언 : klam21205@gmail.com

NEBS 홈페이지: http://www.nebskorea.com
NYKB 홈페이지: http://nykb.org
KOLIS 홈페이지: https://www.kolis.org
KLAM 홈페이지: https://klamus.org/

2022 KOREAN-AMERICAN BIOSCIENCE FORUM SPEAKERS

노승언 박사 (Seung-Eun Roh)
Johns Hopkins University
Imaging immediate early gene NPTX2 at synapses *in vivo* during critical period plasticity and behavior relevant to schizophrenia

김은하 박사 (Eunha Kim)
Harvard Medical School
Maternal gut bacteria drives intestinal inflammation in offspring with neurodevelopmental disorders by altering the chromatin landscape of CD4+ T cells

이상수 박사 (Sang Soo Lee)
Johns Hopkins University
Plasticity of an excitatory thalamic circuit controls homeostatic SWS persistence

윤혜진 박사 (Haejin Yoon)
Harvard Medical School
Dynamic regulation of mitochondrial metabolism in metabolic disease

김태완 박사 (Taewan Kim)
Memorial Sloan Kettering Institute
Human Pluripotent Stem Cell based Platform to Study and Treat Parkinson's Disease

김헌석 박사 (Heonseok Kim)
Stanford University
Single cell characterization of CRISPR-modified transcript isoforms with nanopore sequencing

박정환 박사 (Jung Park)
Columbia University
Novel experience resets brain circuitry to facilitate cognitive flexibility

윤혁석 박사 (John Yoon)
University of California Davis
Molecular Control of Thermogenesis and Energy Balance

2022 KOREAN-AMERICAN BIOSCIENCE FORUM SPONSOR

한국 보건산업 진흥원

KHIDI
Korea Health Industry Development Institute

한국보건산업진흥원
미국지사장 박순만

존경하는 NEBS, NYKB, KOLIS, KLAM회원 여러분,

한국보건산업진흥원 미국지사장 박순만입니다.

2022년 임인년 새해에 제 2회 전미생명과학자의 날을 맞아 회원님들께 인사드립니다.

앞으로 대한민국 생명과학에 중추역할을 하게될 차세대 한인 생명과학자들이 한자리에 모이는 전미한인생명과학자의 날에 공동으로 주관하게 해주신 회장님과 임원진에게 감사의 말씀을 드립니다.

지난 2년은 코로나19로 인해 전 세계가 경제 및 사회적으로 큰 어려움을 겪었습니다.

코로나가 지속됨에 따라 우리나라 기업들의 바이오헬스 분야진출 관심이 더욱 증가하고 있습니다. 진흥원 미국지사는 이런 시기에 우리 기업들이 전 세계 보건산업 시장규모 제약분야 1위 및 글로벌 리더쉽 분야 최상위국인 미국진출에 기여하는 것을 뜻깊게 생각하고 있습니다.

진흥원 미국지사는 한국과 미국의 교두보로 자리매김을 함으로서 우리나라 보건산업의 위대함을 미국에 알리고, 다양한 보건산업 영역들을 지원해 시너지를 높일 수 있도록 최선을 다하겠습니다.

진흥원을 통해 여러 한국 기업들이 성공적으로 한단계 도약해 추후 미국 진출을 꿈꾸는 다른 기업들에게 새로운 희망을 줄 수 있는 계기가 되었으면 좋겠습니다.

비록 비대면으로 진행되는 행사라 모든 분들을 실제로 뵙지는 못하겠지만, 행사 기간동안 NEBS, NYKB, KOLIS, KLAM 에서 마련해주신 네트워크를 기반으로 교류와 협력의 장이 되길 기원합니다.

2022년 올 한해도 진흥원 미국지사가 성장해 우리나라 보건산업 발전에 힘이 될 수 있도록 지속적인 관심과 협조를 부탁드립니다.

감사합니다.
한국보건산업진흥원 미국지사장 박순만

회장단 인사말

NEBS 회장 이재교 박사

안녕하십니까. 뉴잉글랜드 생명과학 협회 (NEBS) 회장 이재교입니다. 무엇보다 2022 전미 한인 생명과학자의 날을 KOLIS, NYKB, KLAM 그리고 KHIDI와 함께 주최하게 되어 너무 큰 영광이라고 생각합니다. 쉽게 그 끝을 알 수 없는 COVID-19의 여파로 미국 내 한인 과학자분들의 학술 교류가 계속 제약받고 있음이 안타깝지만, 이렇게 온라인 플랫폼으로 미국 동부, 서부 그리고 올해에는 Maryland 지역을 포함한 한인 생명과학자분들의 학술 교류에 도움을 드릴 수 있으매 이번 행사의 의미가 크다고 생각이 듭니다. 또한 각 분야의 뛰어난 학술적 성과를 성취하신 여덟 분의 연사들과, 비록 이번에는 저희들이 선정해 드리지 못하였지만 그에 못지않은 너무나 훌륭한 내용으로서 지원해 주신 지원자분들께도 진심 어린 감사의 말씀을 드리고 싶습니다. New England 지역의 한인 생명과학자 커뮤니티에 큰 축을 맡고 있는 저희 NEBS는 앞으로도 한인 과학자분들의 학술교류 및 네트워킹에 기여할 수 있는 많은 기회를 만들고, 참여하도록 노력하겠습니다. 앞으로도 저희 NEBS를 항상 응원해 주시고, 여러분들의 적극적인 참여 또한 부탁드리겠습니다. 끝으로, 이러한 소중한 기회를 만들고 진행하는 데 있어 많은 도움을 주신 KOLIS, NYKB, KLAM 및 보건산업진흥원과 NEBS 임원진 여러분께 다시 한번 진심으로 감사의 말씀을 전하고 싶습니다.

NEBS 39대 회장,
이재교 올림

KOLIS 회장 김선기 박사

안녕하세요. 2022년 KOLIS 회장을 맡고 있는 김선기입니다.
최근 COVID-19 바이러스가 여러 변이로 인해 예측이 어려워진 상황에서 인류가 직면한 문제를 해결하기 위해 생명과학의 중요성은 날로 더 커져가고 있습니다. 장기화되고 있는 판데믹 상황에서 저희 생명과학자들은 각자의 자리에서 할 수 있는 일들을 묵묵히 해나가고 있습니다. 힘든 상황 속에서도 열심히 노력하여 결실을 맺은 한인 생명과학자들의 학술성과를 서로 소개할 수 있는 기회를 만들고자 미국 생명과학자 협회들이 다시 모여 제 2회 전미 한인 생명과학자의 날을 기획하였습니다. 온라인 컨퍼런스를 통해 한인 생명과학자들이 거리에 구애받지 않고 활발하게 최신 연구성과를 교류하고 배울 수 있는 기회가 되길 바랍니다. 미국 서부 베이 지역의 스탠포드, UC 버클리, UC 데이비스, UC 샌프란시스코 소속 한인 생명과학자들로 구성된 단체인 KOLIS 역시 전세계 생명과학자들과의 학술교류와 네트워킹에 힘쓰겠습니다.
전미생명과학자의 날이 앞으로도 생명과학을 선도하고 교류의 중심이 되어 계속해서 발전하는 행사가 될 수 있기를 기원합니다.

KOLIS 회장 김선기 올림

회장단 인사말

NYKB 회장
양종원, PhD candidate

안녕하세요. 뉴욕한인생명과학자 협회 (NYKB) 회장 양종원 입니다. 계속되는 변이 바이러스로 인하여 팬데믹이 길어지는 가운데 많은 전미 한인과학자분들의 한땀한땀의 노력들이 더욱 소중하게 느껴집니다. 모두가 힘들고 어려운 시기에도 불구하고 새로운 온라인세대에 맞춰 작년에 시작된 전미한인생명과학자의 날을 이번년도에도 이어나 갈수 있어서 참 좋습니다. 특히 이번 년도에는 KLAM (Korean Life Scientists Association of Maryland)에서 새롭게 함께 해주셔서, 제2 전미한인과학자의 날이 작년보다 더욱 기대가 됩니다. 동부와 서부의 다양한 분야의 한인 생명과학자분들이 함께 학술교류를 하고 네트워킹이 이루어지는 좋은 기회가 될 것 같습니다. 뉴욕과 뉴저지(Rutgers University)의 많은 학교와 연구소들의 협력의 중심이 되는NYKB는 앞으로도 한인 생명과학의 발전과 생명과학자분들의 좋은 학술교류, 네트워킹을 위해 힘쓰고 노력하겠습니다.

제13대 뉴욕한인생명과학자 협회 회장

양종원 올림

KLAM 회장 노승언 박사

안녕하세요. 2022년 KLAM의 회장을 맡게 된 노승언입니다 (JHU Neuroscience). 먼저는 NEBS, NYKB, 그리고 KOLIS에서 작년부터 이러한 훌륭한 포럼을 시작해 주셔서 감사하고, KLAM도 이번부터 참여하게 되어 기쁘게 생각합니다. 더불어 공동주최해주신보건산업진흥원 미국지사에 감사합니다. 미국에서 각 지역을 대표하는 분들이 모두 모인 이 자리가 참 뜻 깊은 것 같습니다. 비록 온라인이지만 다른 지역의 새로운 분들을 뵐 수 있는 자리를 갖게 된다니 저 또한 많은 기대가 되었습니다. 그리고 훌륭하신 한인 과학자 분들이 참 많구나, 하는 것도 새삼 느끼게 되면서 한인으로서의 자부심도 갖게 됩니다. 참여하시는 분들 모두 평소 가질 수 없었던 네트워크를 형성하는 기회가 될 것이라 생각합니다. 또한 앞으로 더욱 많은 단체와 한인 과학자분들과 만날 수 있는 귀한 소통의 장이 되기를 바랍니다. KLAM에서도 하나된 네트워킹을 위해 협력하도록 하겠습니다.

KLAM 회장 노승언 올림

2022 KOREAN-AMERICAN BIOSCIENCE FORUM AGENDA

Opening remark

1:00 - 1:06pm NEBS, NYKB, KOLIS and KLAM 단체장 인사말
1:06 - 1:10pm 축사: *보건산업진흥원 (박순만 지사장님)*

Scientific session I

1:10 -1:35pm NEBS awardee I
Speaker: 노승언 박사 (Johns Hopkins University)
Moderator: 고현용 박사 (Boston Children's Hospital, NEBS)

1:35 - 2:00pm KOLIS awardee I
Speaker: 김태완 박사 (Memorial Sloan Kettering Institute)
Moderator: 김선기 박사 (UC Berkeley, KOLIS)

2:00 - 2:25pm NYKB awardee I
Speaker: 김은하 박사 (Harvard Medical School)
Moderator: 윤태진 박사 (NYU, NYKB)

2:25 - 2:50pm KLAM awardee I
Speaker: 김헌석 박사 (Stanford University)
Moderator: 장민혁 박사 (Johns Hopkins University, KLAM)

2:50 - 3:10pm Networking session I
Q&A room 1: NEBS, KOLIS speakers
Q&A room 2: NYKB, KLAM speakers
Networking rooms

Scientific session II

3:10 - 3:35pm NEBS awardee II
Speaker: 이상수 박사 (Johns Hopkins University)
Moderator: 유창현 박사 (MIT, NEBS)

3:35 - 4:00pm KOLIS awardee II
Speaker: 박정환 박사 (Columbia University)
Moderator: 이현철 박사 (UC Berkeley, KOLIS)

4:00 - 4:25pm NYKB awardee II
Speaker: 윤혜진 (Harvard Medical School)
Moderator: 윤태진 박사 (NYU, NYKB)

4:25 - 4:50pm KLAM awardee II
Speaker: 윤현석 박사 (University of California Davis)
Moderator: 장민혁 박사 (Johns Hopkins University, KLAM)

4:50 - 5:10pm Networking session II
Q&A room 1: NEBS, KOLIS speakers
Q&A room 2: NYKB, KLAM speakers
Networking rooms

5:10 - 5:30pm Raffle event
Moderators: Drs. 정현국 (NYKB), 이현철(KOLIS), 박진석 (NEBS), 장지현(KLAM)

* Times in Eastern Standard time (EST)

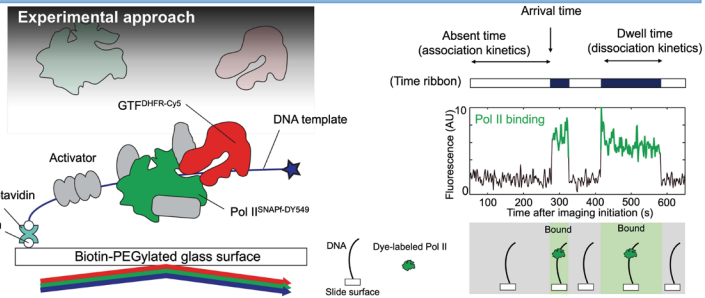
Single molecule studies of RNA polymerase II transcription

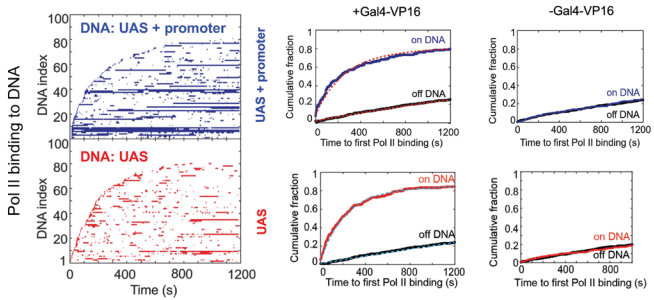
How is mRNA synthesized?

Inwha Baek, M.S., Ph.D., inwhabaek@g.harvard.edu
Harvard Medical School, Boston, MA, USA

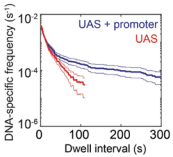
Background

RNA polymerase II (Pol II) transcription is a highly regulated and dynamic process involving multiple steps. To successfully produce mRNA, distinct transcription initiation, elongation, and termination factors need to be recruited to and released from Pol II in a timely manner. However, the kinetics of these factors are poorly characterized because past studies utilized ensemble assays, which can only reveal the averaged behavior of individual molecules. Using single-molecule fluorescence imaging, we examined the dynamics of Pol II and general transcription factors (GTFs) during preinitiation complex (PIC) assembly in nuclear extracts, a complex environment recapitulating transcription activator-dependent Pol II transcription.

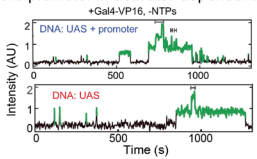




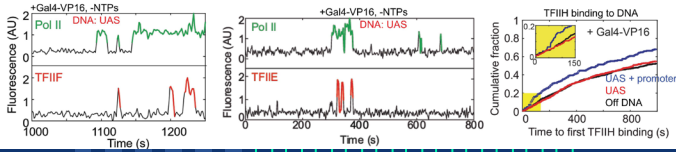
(UAS: Upstream activating sequence)
Pol II recruitment does not require core promoter in activator-dependent transcription.



Pol II binding to DNA is more stable when core promoter is present.



Activator can form a Pol II cluster at enhancer (UAS).



Summary

- In an activator-dependent PIC assembly, Pol II, TFIIF and TFIIE can preassemble on enhancer-bound activators before loading into PICs at promoter.
- TFIIH binding is dependent on the core promoter.
- Activators can recruit multiple Pol II molecules at enhancer.

More details: Baek, et al., *Molecular Cell*, 2021, Rosen* & Baek*, et al., *PNAS*, 2020

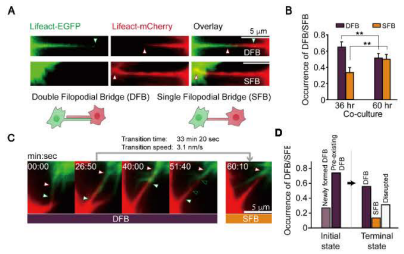
Formation of Intercellular Tunneling Nanotubes

Minhyeok Chang, Ph.D (mchang60@jhmi.edu)
Johns Hopkins University, Baltimore, MD 21205, USA

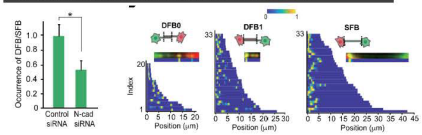
Background

Tunneling nanotubes (TNTs) are sub-micrometer thin routes that directly connect distant cells. However, the formation mechanism of TNT is poorly understood.

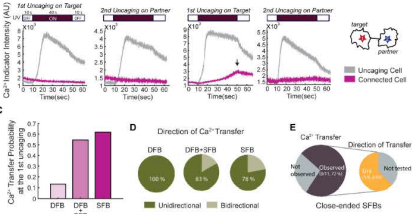
DFB transition into an SFB



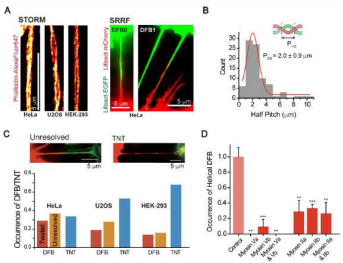
N-cadherin interaction of FB



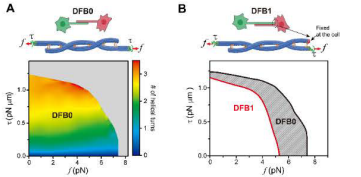
SFB as a close-ended TNT



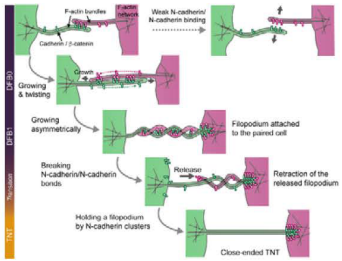
Helical deformation of DFB



Model of DFB transition to a TNT



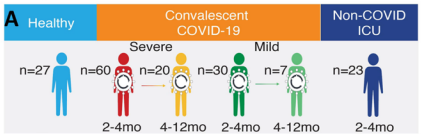
Summary

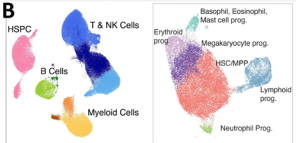


Durable Alterations of Hematopoiesis and Chromatin post-COVID-19

Jin Gyu Cheong, jic2016@med.cornell.edu
Weill Cornell Graduate School, New York, NY

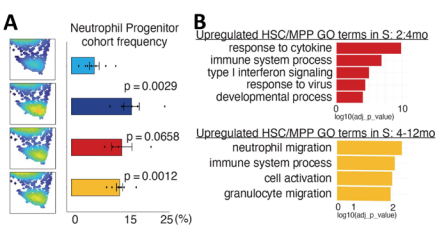
Backgrounds : SARS-CoV-2 infection is often associated with extended systemic inflammatory features that are well-established to influence hematopoiesis and epigenetic memory of inflammation in innate immune cells and their progenitors. To study this, we performed combined snRNA/ATAC-seq on 197K of PBMCs, including 28K of HSPCs from convalescent COVID-19 patients.



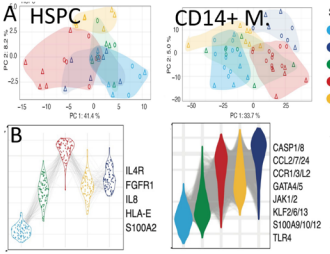


A) Cohorts.
B) UMAP of all PBMCs(L) and HSPCs(R).

1. Using snRNA/ATAC-seq of PBMC and HSPC, we defined distinct cell types as well as HSPC subtypes.

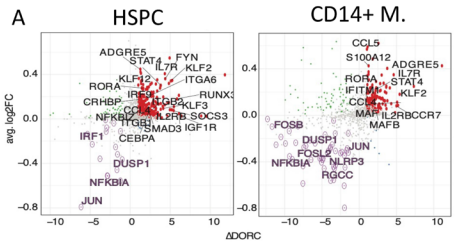


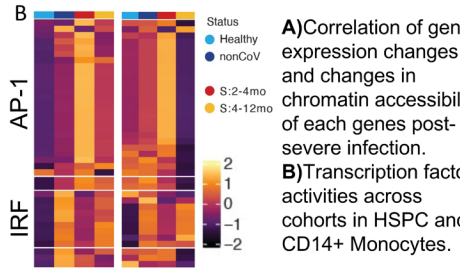
2. Cohort frequency in neutrophil progenitor cluster**(A)** and GO analysis of transcriptomic data of HSPC**(B)** displays altered hematopoiesis post-severe COVID-19.



A)PCA of ATAC-seq data
B)Normalized logFC of peaks with epigenetic memory

3. Epigenetic memory persists in HSPC and CD14+ monocytes post-COVID-19.





A)Correlation of gene expression changes and changes in chromatin accessibility of each genes post-severe infection.
B)Transcription factor activities across cohorts in HSPC and CD14+ Monocytes.

4. Gene activity(gene expression and chromatin accessibility) of AP-1 family is decreased post-COVID-19, as well as their TF activity, however TF activity of IRF family is persistently increased in post-severe COVID-19

Cell Subtype Specific Role of Nab2 in Cocaine Self-administration

Eric Y. Choi, B.A., eric.choi@som.umaryland.edu

University of Maryland School of Medicine, Baltimore, MD, USA

Background

- Basal ganglia circuitry is critical for mediating motivation for natural reward. This Circuitry is disrupted by drugs of abuse, such as cocaine, which induces adaptations at the molecular level and underlie motivational drive geared toward seeking drugs.
- Previous studies have shown an opposing role for Egr3 in nucleus accumbens(Nac) cell subtypes in cocaine action
- Here we study the D2-medium spiny neuron specific role of Nab2, a co-regulator of Egr3, in cocaine self-administration and seeking behavior

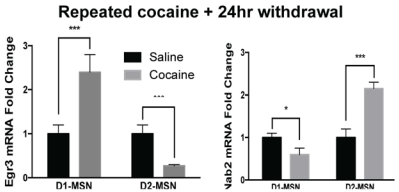


Figure 1: Nab2, the corepressor of Egr3, displays opposite regulation to Egr3 in D2-MSN subtypes after repeated exposure to cocaine in mice. IP injection of cocaine (7 days, 20mg/kg) in mice n=6. *p<0.05, ***p<0.001

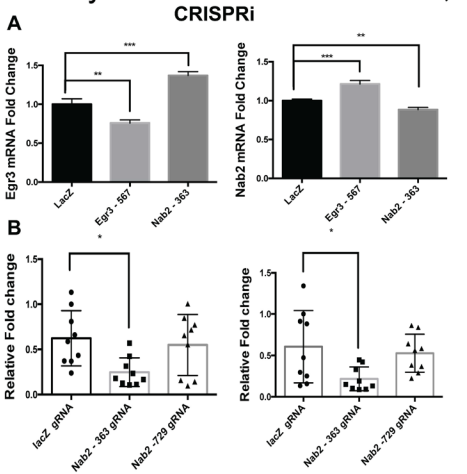


Figure 2: **A**. dCas9-KRAB CRISPRi system targeted by Nab2 and Egr3 gRNA mimics the bidirectional regulation of Nab2 and Egr3 mRNA expression shown in a cocaine IP injection model. **B.** H3K4me3 and H3K27ac enriched Cut & Run shows decreased enrichment of Nab2 chromatin. Experiments performed in Neuro2A cell line. *p<0.05, **p<0.01, ***p<0.001

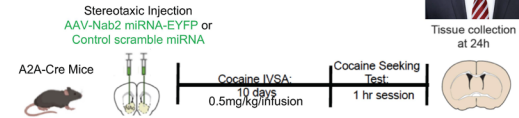


Figure 3: Timeline of *in vivo* cocaine intravenous self-administration experiment

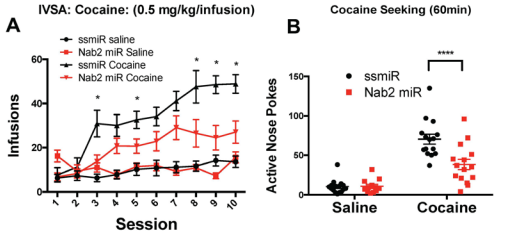


Figure 4: **A**. 10 Days of cocaine self-administration shows Nab2 KD in D2-MSNs lead to lower cocaine intake. **B**. Mice with Nab2 KD in D2-MSNs mice made significantly lower active nose pokes during 1hr cocaine seeking test. *p < 0.05 at least, ****p < 0.0001. ssmiR saline n=16, ssmiR cocaine n=15, Nab2 saline n=12, Nab2 cocaine n=15

Future Directions

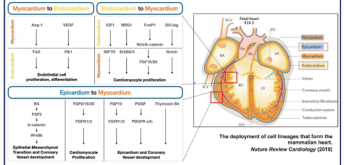
We plan to use the tissue punches from cocaine self-administered mice for single nuclei RNA-seq to elucidate Nab2 driven transcriptomic changes that occur during cocaine seeking. From those findings we further study the downstream mechanisms that lead to this attenuated cocaine intake and seeking.

Epicardial histone deacetylase 3 (Hdac3) promotes myocardial growth through a novel microRNA pathway

Jihyun Jang, PhD, jhjang@som.umaryland.edu
University of Maryland School of Medicine, Baltimore, MD, USA

Background

Signaling communication between myocyte and nonmyocyte



The deployment of cell lineages that form the mammalian heart.
Nature Review Cardiology (2016)

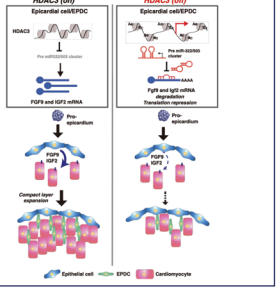
Epicardium orchestrate myocardium development

During Development

- **Molecular regulation of epicardial Epithelial-to-Mesenchymal Transition by Epicardial-derived cell (EPDC)**
- **Epicardial-derived secretome**

The role of the epicardium during heart development and repair.
Circulation Research (2020)

Our working model



Results

Fig.1 Specific inactivation of Hdac3 in developing epicardium results in ventricular wall hypoplasia

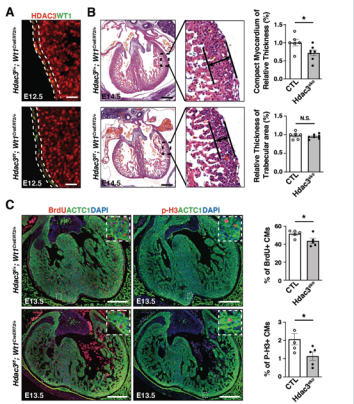


Fig.2. Reduction of Epicardial Derived Cell (EPDCs) in Hdac3 epicardial knockout hearts.

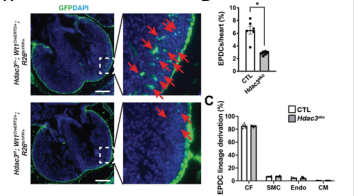


Fig.3 Hdac3 deletion resulted in downregulation of FGF9 and IGF2.

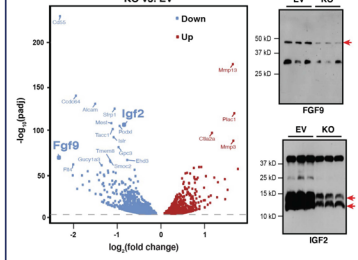


Fig.4. Supplementation of FGF9 or IGF2 rescues cardiomyocyte proliferation defects.

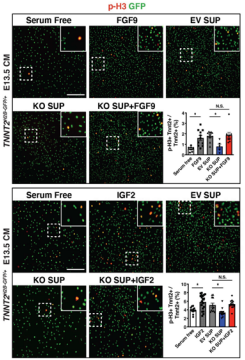
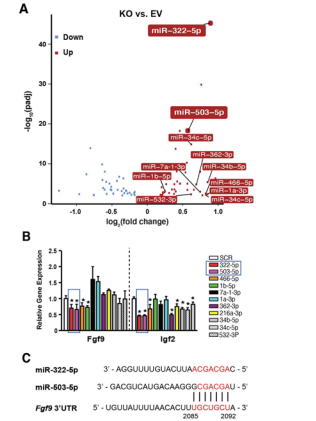


Fig.5. miR-322 and miR-503 repress the expression of FGF9 and IGF2



Summary

- **Hdac3 in the epicardium defines epicardial lineage derivation**
- **Epicardial Hdac3 is important for myocardial growth.**
- **Hdac3 induces expression of FGF9 and IGF2 by suppressing miR-322 and 503.**

Our findings reveal a critical signaling pathway in which epicardial HDAC3 promotes compact myocardial growth by stimulating FGF9 and IGF2 through repressing miR-322/miR-503, providing novel insights in elucidating etiology of congenital heart defects, and conceptual strategies to promote myocardial regeneration.

For more detail

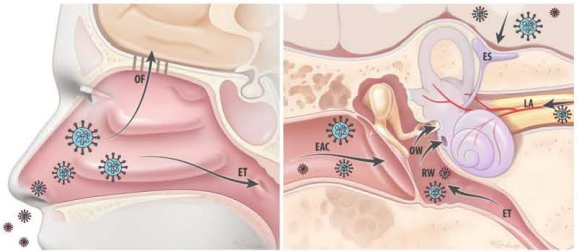
Jang J, Song G, Li Q, Song X, Cai C, Kaushal S, Li D. Epicardial histone deacetylase 3 promotes myocardial growth through a novel microRNA pathway. *BioRxiv* [Preprint]

Direct SARS-CoV-2 infection of the human inner ear

Minjin Jeong, Ph.D, jeongm@stanford.edu, Stanford University

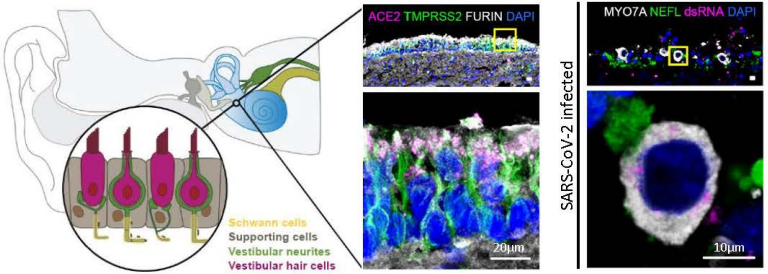
Background

COVID-19 is an infectious disease caused by the novel coronavirus SARS-CoV-2. A growing number of sensory symptoms have been linked to this illness. Here, we describe patients with COVID-19 and new-onset of hearing loss, tinnitus and/or dizziness. To investigate whether these symptoms might be due to direct infection of audiovestibular structures, we examined the expression of SARS-CoV-2 cell entry-related genes and proteins in human and mouse inner ear tissue, and we infected human vestibular tissue to identify target cell types of SARS-CoV-2.



Potential paths for SARS-CoV-2 entry into the inner ear.

Results



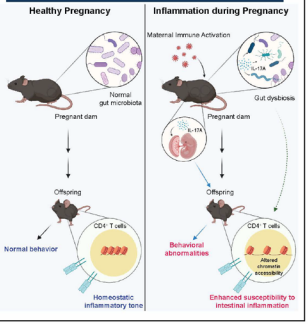
SARS-CoV-2 infection in human inner ear. Surgical specimens of human vestibular end organs from the inner ear include vestibular hair cells, supporting cells, Schwann cells, and vestibular neurons. SARS-CoV-2 entry-related proteins (ACE2, TMPRSS2, and FURIN) are expressed in MYO7A+ hair cells especially at their apical regions. At 48 hours post-infection, we observed viral double-stranded RNA (dsRNA) in hair cells and not in vestibular neurites.

For more details, Jeong, M. *et al.* Direct SARS-CoV-2 infection of the human inner ear may underlie COVID-19-associated audiovestibular dysfunction. *Commun Med* **1**, 44 (2021).

Maternal gut bacteria drives intestinal inflammation in offspring with neurodevelopmental disorders by altering the chromatin landscape of CD4⁺ T cells

Eunha Kim, Ph.D., Eunha_Kim@hms.harvard.edu
Department of Immunology, Blavatnik Institute, Harvard Medical School, Boston, MA 02115, USA

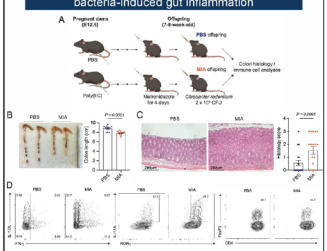
Abstract



Back ground

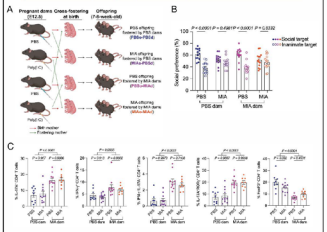
- Prenatal and early life experiences are critical determinants for human health.
- Viral infection during pregnancy correlates with an increased frequency of autism spectrum disorders (ASD) in offspring.
- Individuals with ASD are also known to display a broad range of non-neurological comorbidities, including immune and gastrointestinal (GI) dysfunction.
- However, the mechanisms by which inflammatory phenotypes manifest as comorbid symptoms of neurodevelopment disorders are largely unknown.
- The viral mimetic polyinosinic:polycytidylic acid (poly[I:C]) induced maternal immune activation (MIA) rodent model has been established to study neurodevelopmental and behavioral abnormalities of the offspring.
- We leveraged this model to investigated the long-term immunological consequences of prenatally-experienced inflammation of the offspring.

MIA offspring show increased susceptibility to bacteria-induced gut inflammation



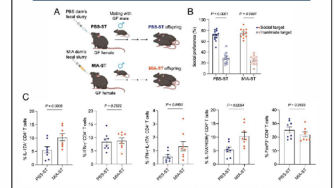
(**A**) Seven to eight-week-old offspring (PBS and MIA offspring) born to PBS- or poly(I:C)-injected dams at E12.5 were pre-treated with metronidazole for four days and then infected with 2 x 10^8 colony forming units (CFUs) of *C. rodentium*. All analyses were done ten days post-infection with *C. rodentium*. (**B–C**) Colon length (**B**), H & E staining of the colons and the associated histology scores (**C**) of PBS and MIA offspring. (**D**) The composition of colonic lamina propria T cells was analyzed by flow cytometry. Representative flow plots of IL-17A- and IFN-γ-producing CD4⁺ T cells, RORγ⁺ IL-17A-producing CD4⁺ T cells and FoxP3⁺ regulatory T cells. All flow plots were gated on live, CD45⁺, TCRβ⁺, CD4⁺, CD8⁻ and CD19⁻ cells.

The increased immune susceptibility of MIA offspring is postnatally determined



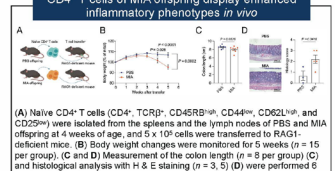
(**A**) PBS and MIA offspring were cross-fostered upon birth (P0). Seven to eight-week-old offspring were used for behavioral tests, followed by *C. rodentium* infection experiments. (**B**) Percentage of interaction in the three-chamber sociability test of PBSo-PBSd, MIAo-PBSd, PBSo-MIAd, and MIAo-MIAd offspring. (**C**)The composition of colonic lamina propria T cells was analyzed by flow cytometry. Quantifications of IL-17A-, IFN-γ-, and IL-17A- and IFN-γ-producing CD4⁺ T cells, RORγ⁺ IL-17A-producing CD4⁺ T cells, and FoxP3⁺ regulatory T cells of PBSo-PBSd, MIAo-PBSd, PBSo-MIAd, and MIAo-MIAd offspring.

Transfer of MIA-associated microbiota induces primed immune phenotypes in offspring



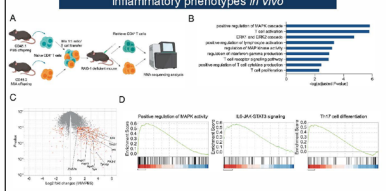
(**A**) Female B6 GF mice were colonized with fecal bacteria of stool samples collected at E14.5 from either PBS or MIA dams (PBS-ST [stool-transferred] and MIA-ST, respectively) and a week later mated to male B6 GF mice. Offspring (PBS-ST offspring and MIA-ST offspring, respectively) from the mating were subjected to behavioral analyses followed by *C. rodentium* infection at 7–8-weeks-of age. (**B**) Percentage of interaction i in the three-chamber sociability test of PBS-ST and MIA-ST offspring. (**C**)The composition of colonic lamina propria T cells was analyzed by flow cytometry. Quantifications of IL-17A-, IFN-γ-, and both IL-17A- and IFN-γ-producing CD4⁺ T cells, RORγ⁺ IL-17A-producing CD4⁺ T cells, and FoxP3⁺ regulatory T cells.

CD4⁺ T cells of MIA offspring display enhanced inflammatory phenotypes *in vivo*



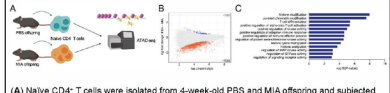
(**A**) Naïve CD4⁺ T cells (CD4⁺, TCRβ⁺, CD45RB^{high}, CD44^{low}, CD62L^{high}, and CD25^{low}) were isolated from the spleens and the lymph nodes of PBS and MIA offspring at 4 weeks of age, and 5 x 10^5 cells were transferred to RAG1-deficient mice. (**B**) Body weight changes were monitored for 5 weeks (n = 15 per group). (**C** and **D**) Measurement of the colon length (n = 8 per group) (**C**) and histological analysis with H & E staining (n = 3, 5) (**D**) were performed 6 weeks after the transfer.

CD4⁺ T cells of MIA offspring display enhanced inflammatory phenotypes *in vivo*



(**A**) Naïve CD4⁺ T cells were isolated from 4-week-old CD45.1 PBS and CD45.2 MIA offspring. PBS and MIA naïve CD4⁺ T cells were mixed in a 1:1 ratio and transferred into RAG1-deficient mice. Four weeks after transfer, transferred cells were retrieved, sorted by congenic markers, and analyzed by RNA sequencing. (**B**) Graph showing the key GO terms that were enriched in the differentially expressed genes between PBS vs. MIA CD4⁺ T cells. (**C**) Volcano plot displaying log2 fold change vs. *P*-value for each gene. Genes considered significant (P < 0.01 and log2FC > 1) are labeled in orange, and selected genes involved in T cell activation and MAPK activity are labeled in blue. (**D**) GSEA analysis demonstrating significant enrichment of gene sets associated with MAPK activity, IL6-JAK-STAT3 signaling, and Th17 cell differentiation.

MIA naïve CD4⁺ T cells display distinct chromatin accessibility



(**A**) Naïve CD4⁺ T cells were isolated from 4-week-old PBS and MIA offspring and subjected to ATAC-seq analyses. (**B**) Scatter plot represents the differences in chromatin accessibility between PBS and MIA naïve CD4⁺ T cells. Orange dots indicate peaks that are statistically significantly more accessible in MIA naïve CD4⁺ T cells, and blue dots indicate those that are uniquely accessible in PBS naïve CD4⁺ T cells (fold change > 1.5, FDR < 0.05). (**C**)GO terms that were enriched in the differential open chromatin regions (OCRs) of MIA naïve CD4⁺ T cells compared to those of PBS offspring.

Conclusion

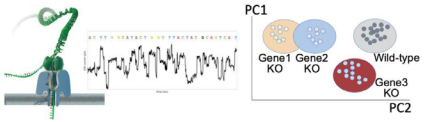
- Mice prenatally exposed to maternal immune activation display immune-primed phenotypes
- Maternal immune activation (MIA) induces changes in the gut microbiota of pregnant mice
- Altered microbiota promote immune priming by affecting T cells' chromatin accessibility
- Maternal IL-17A shapes the immune-primed phenotypes through changes in microbiota

Single cell characterization of CRISPR-modified transcript isoforms with nanopore sequencing

Heonseok Kim, Ph.D., heonseok@stanford.edu, Stanford university, CA, USA

Background

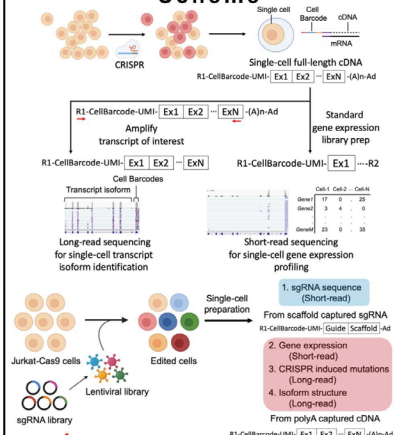
We developed a single-cell approach to detect CRISPR-modified transcript structures. This method assesses how genetic variants at splicing sites and splicing factors contribute to alternative mRNA isoforms. Our method combines long-read sequencing to characterize the transcript structure and short-read sequencing to match the single-cell gene expression profiles.



Oxford nanopore long-read sequencing
Single-cell RNA sequencing
Single-cell CRISPR screen

Combine!

Scheme

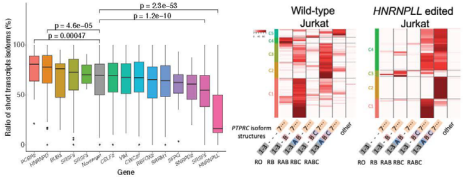


Detect!

Transcript isoform changes
CRISPR induced mutation genotype
Gene expression profile

In a single-cell level

Result



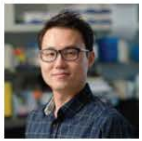
Conclusion

Our approach demonstrates a new method for the characterization of various CRISPR-induced transcript modifications.

For more details

H. S. Kim et al., BioRxiv, 2021
H. S. Kim et al., GenomeBiology, In Press

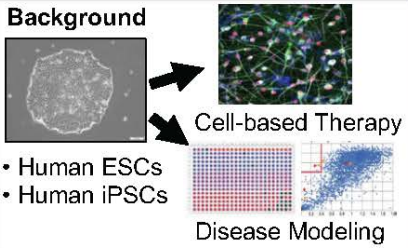
Human Pluripotent Stem Cell (hPSC) based Platform to Study and Treat Parkinson's Disease (PD)



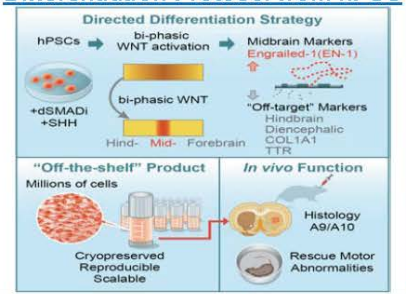
Tae Wan Kim, Ph.D.

The Center for Stem Cell Biology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

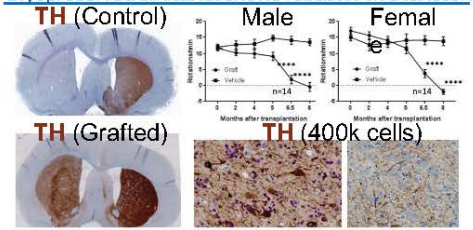
Background



Clinical Grade Dopamine(DA) Neuron Differentiation Protocol from hPSC

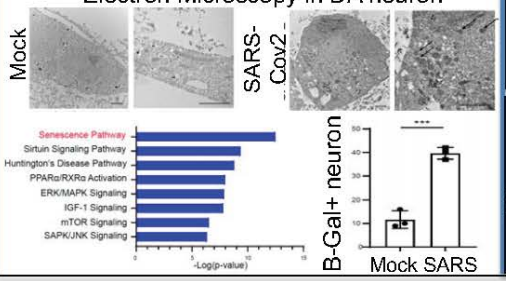


Cryopreserved clinical lot shows robust *in vivo* function

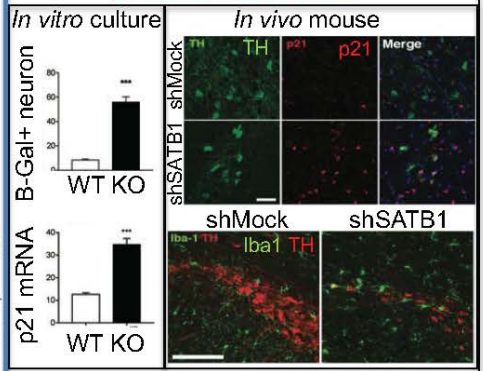


Obtained FDA clearance to initiate clinical trial

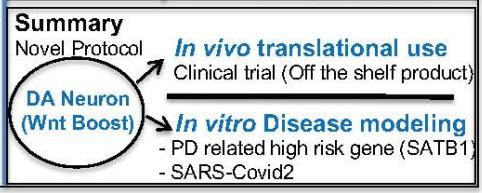
SARS-Covid2 infection to DA neuron trigger senescence



mDA neurons senescence by p21 upon SATB1 depletion



Summary



Resampling analysis of single-cell RNA-seq data using deep learning methods

Kyung Dae Ko, Ph. D, (kok3@nih.gov)
National Institutes of Health, Bethesda, MD, USA.

Introduction

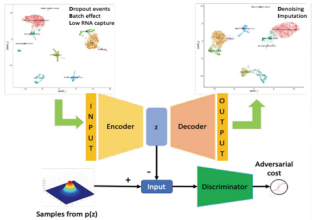


Fig1. The concept and workflow of Adversarial autoencoder for single cell analysis

Procedure

- **Data Preprocess**
  - Normalize UMI matrix
  - Remove all zero's genes
- **Model training**
  - Transform the matrix to input matrix for an input layer
  - Build layers of autoencoder and adversarial layers
  - Calculate costs in adversarial layers during training the autoencoder to find optimal steps
- **Data Reconstruct**
  - Reconstruct a matrix using latent input
  - Validate the reconstruct matrix using Seurat and singleR packages
  - Infer biological functions using GO analysis

Case 1: Atlas of Mouse Muscle Regeneration

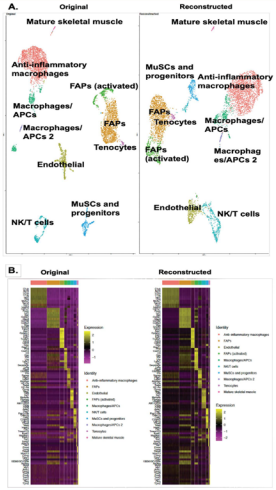


Fig2. (A) UMAP-based clustering (B) heatmaps of original and reconstructed datasets related to atlas of mouse muscle regeneration [1].

Case 2 : The impact of Polycomb to muscle satellite cell

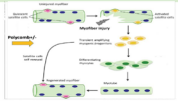


Fig3. The mechanism of skeletal muscle regeneration [2].

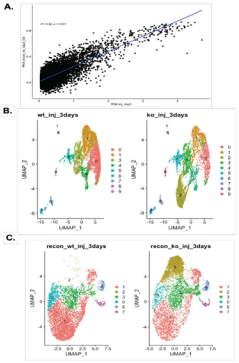


Fig4. (A) Correlation between original and reconstructed datasets. The distribution of the clusters using (B) original and (C) reconstructed datasets between WT and Ezh1KO conditions

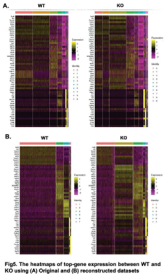


Fig5. The heatmaps of top-gene expression between WT and KO using (A) Original and (B) reconstructed datasets

Summary

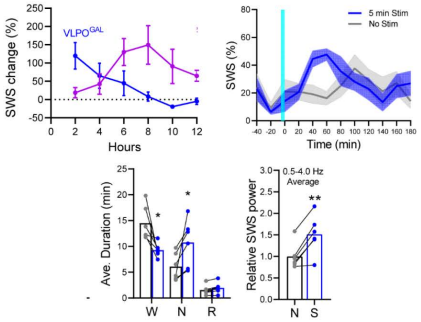
- Adversarial autoencoder can relieve dropout events and low RNA capture through denoising and imputation.
- The salient characteristics of the pipeline are its independence from annotation biases, and improve the accuracy to detect transcriptional signatures and infer the changes of cell status under external environment influence.

Plasticity of an excitatory thalamic circuit controls homeostatic SWS persistence

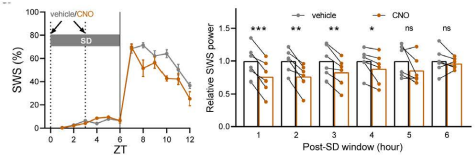
Sang Soo Lee, PhD, slee496@jhmi.edu
Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: Sleep is regulated by both circadian and homeostatic controls. However, the neural architectures underlying homeostatic slow-wave sleep (SWS) are unclear. In this study, we identified a novel excitatory neural circuit in a local thalamic area driving homeostatic SWS persistence.

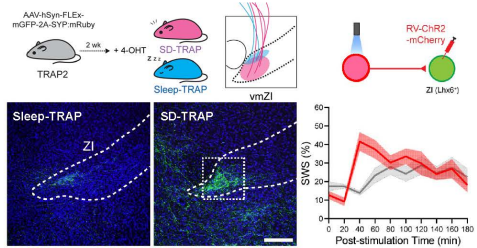
Stimulation of local thalamic VGLUT2⁺ neurons drives persistent SWS



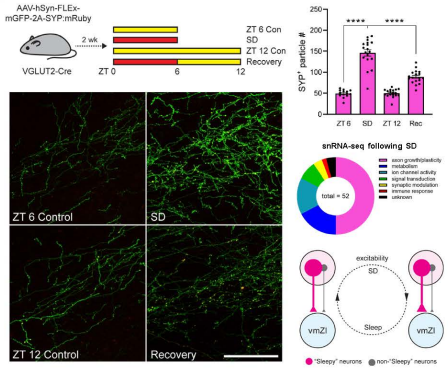
Activity of thalamic VGLUT2⁺ neurons is required for homeostatic SWS



Sleep need-sensitive thalamic neurons project to SWS-promoting ZI

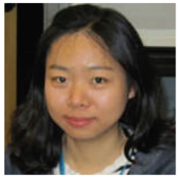


Sleep need induces reversible morphological plasticity of thalamic neurons toward ZI



Summary: Activity of local glutamatergic neurons in the thalamus is sufficient and necessary for driving homeostatic SWS. The SWS persistence is possibly driven by homeostatic neural plasticity.

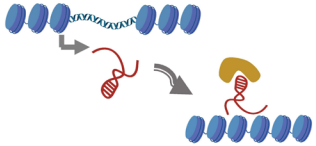
Jpx RNA regulates CTCF anchor site selection and formation of chromosome loops



Hyun Jung Oh, Ph.D. (hjoh@molbio.mgh.Harvard.edu)
Massachusetts General Hospital, Harvard Medical School, Boston, MA

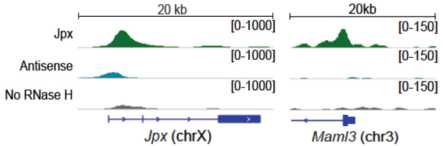
Background

Trans-acting long ncRNA Jpx

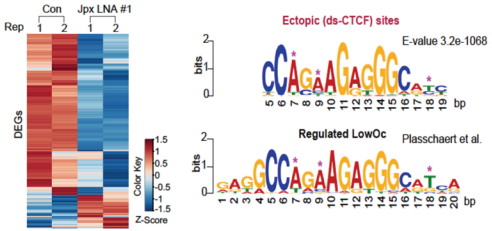


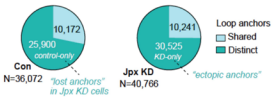
Genome-wide map of Jpx binding sites

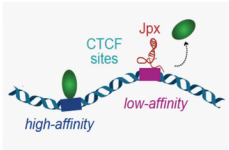
RNA-centric approach: CHART



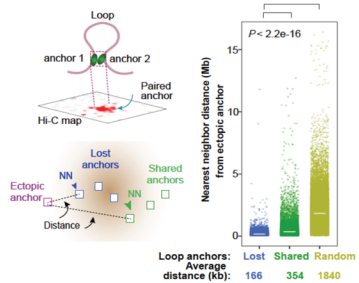
LNA-mediated Jpx depletion results in downregulation of genes, ectopic CTCF and *de novo* loops







CTCF release factor



Summary

Jpx regulates anchor site usage

Oh et al. Cell 2021

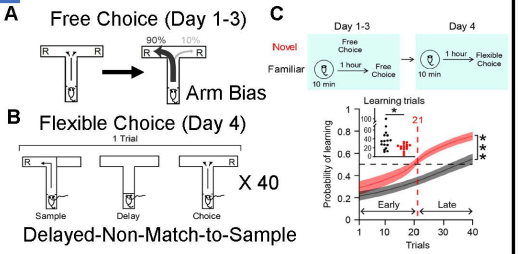
Novel experience resets brain circuitry to facilitate cognitive flexibility

Alan Jung Park, Ph.D., jp3532@columbia.edu
Columbia University, New York, NY, USA

Background

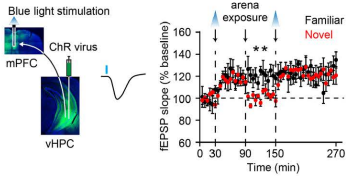
1. Novelty positively affects cognitive function by activating dopamine D1-receptors (D1Rs).
2. Novelty activates the ventral hippocampus (vHPC), and medial prefrontal cortex (mPFC).

1 Novel Experience Enhances Learning



A. Mice (n = 10) established an arm bias after free choice sessions (t-test, $t_{(9)}$ = 8, P < 0.0001). **B.** Flexible choice training. **C.** Mice were exposed to a novel (n = 17) or a familiar (n = 20) arena 1 hour before flexible choice training. The novel group learned more rapidly. Two-way RM ANOVA, $F_{(39,1365)}$ = 2.4, P < 0.0001.

2 Novelty resets vHPC-mPFC Circuitry

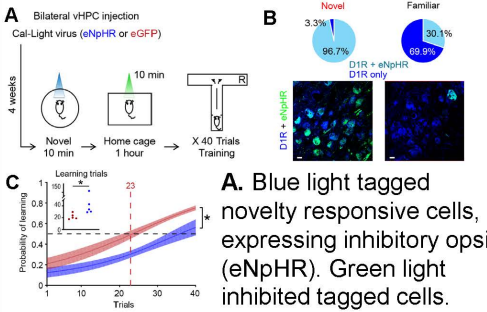


Optogenetic stimulation of vHPC terminals in the mPFC. Novelty weakens vHPC–mPFC field excitatory postsynaptic potentials (fEPSPs) (two-way RM ANOVA, time × group, $F_{(3,24)}$ = 9.2, P = 0.0 003; 5 mice each).

Summary

1. Novelty facilitates learning.
2. Novelty resets vHPC-mPFC circuitry.
3. D1Rs in the vHPC mediate the effects of novelty.

3 Novelty-Responsive D1R-Expressing vHPC Cells Mediate Novelty-Enhanced Learning



A. Blue light tagged novelty responsive cells, expressing inhibitory opsin (eNpHR). Green light inhibited tagged cells.

B. Novelty tags D1R positive cells (blue), expressing eNpHR (green) (novel, n = 628; familiar, n = 611 cells; χ^2 test, P < 0.0001). **C.** Inhibiting tagged cells blocked novelty-enhanced learning (two-way RM ANOVA; n = 5 for each group, $F_{(1,8)}$ = 12.4, P = 0.008).

Reference

Park et al. Reset of hippocampal – prefrontal circuitry facilitates learning. *Nature* (2021)

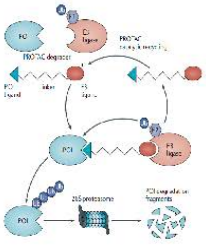
Present and Future of Targeted protein degradation (TPD) technologies

Icahn School of Medicine at Mount Sinai

Kwang-Su Park, Ph.D
Icahn school of medicine at Mount Sinai, NewYork, USA
(kwang-su.park@mssm.edu)

- Background
  - Small molecules that hijack the cellular protein ubiquitination machinery to selectively degrade proteins of interest, so-called degraders, have recently emerged as alternatives to selective chemical inhibitors, both as therapeutic modalities and as powerful research tools.
  - Proteolysis-targeting chimeras (PROTACs) contains two linked moieties with one binding the POI and the other binding an E3 ligase.
  - The formation of an E3–degrader–POI ternary complex results in polyubiquitination of the POI and its subsequent degradation by the 26S proteasome.

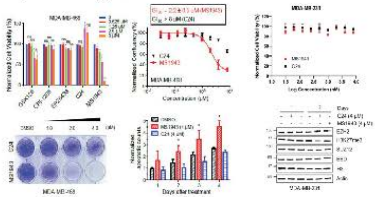
✓ Introduction of PROTAC



Dale B, Cheng M, **Park KS**, et al. *Nat Rev Cancer.* **2021**, 21, 638-654.

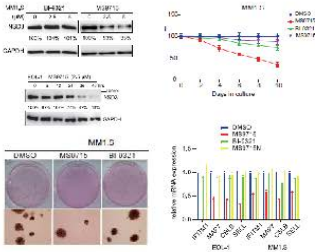
✓ Improvement efficacy compared with conventional inhibitors

1) EZH2 degrader



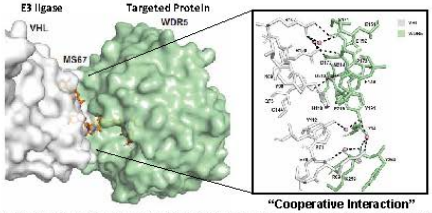
Ma, A.*, Stratikopoulos, E.*, **Park, KS.*** *et al. Nat Chem Biol* **2020,** 16, 214–222

2) NSD3 degrader



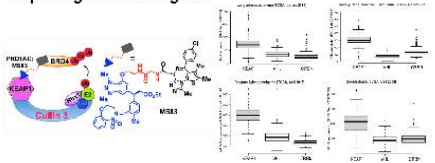
Xu C, Meng F, **Park KS**, et al. *Cell Chem Biol.* **2021**

✓ Mechanism: Chemically induced protein-protein interaction



Yu X, Li D, Kottur J, Shen Y, Kim HS, **Park KS**, et al. *Sci Transl Med.* **2021**, 13, eabj1578.

✓ Exploring New E3 Ligase



Wei J, Meng F, **Park KS**, et al. *J Am Chem Soc.* 2021, 143, 15073-15083.

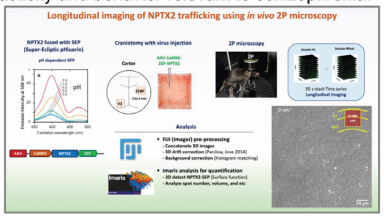
- Summary
  - Targeted protein degradation technologies can overcome hurdles from conventional drug discovery such as off-target effect, drug-resistance and targeting undruggable targets.
  - Inducing new protein-protein interaction is one of key mechanism for targeted protein degradation technologies

Imaging *in vivo* synaptic trafficking of immediate early gene Neuronal Pentraxin 2 (NPTX2) during critical period plasticity and behavior relevant to schizophrenia

Seung-Eon Roh, Ph.D (sroh3@jhmi.edu), Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background

NPTX2 in an immediate early gene secreted from pyramidal neurons onto excitatory synapses of Parvalbumin interneurons (PV-INs), meditating inhibitory circuit homeostatic scaling by clustering AMPAR. Despite its strong implications in synaptic plasticity and neurological diseases such as Alzheimer's disease and psychiatric diseases, the synaptic trafficking has not been examined *in vivo* due to a lack of tools. In addition to electrophysiology, biochemistry and behavioral methods, I used 2-photon microscopy of pH-dependent GFP (Super-ecliptic pHluorin)-fused NPTX2 to monitor dynamics of NPTX2 synaptic trafficking during critical period plasticity and behavior relevant to schizophrenia.



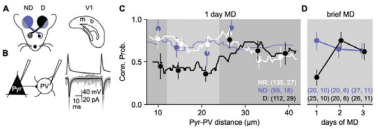


Figure 1. Monocular-deprivation selectively eliminates functional connections between Pyr→PVs in Layer2/3.

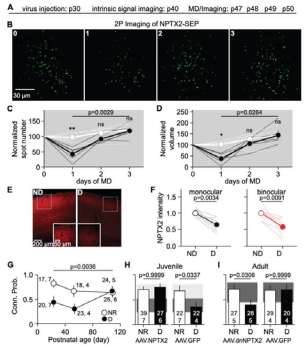


Figure 2. MD-induced disconnections depend on reduced NPTX2 content.

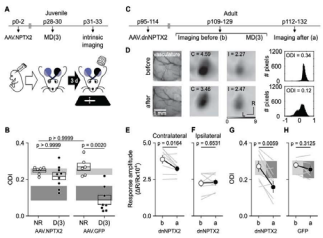


Figure 3. Manipulation of NPTX2 can gate ocular dominance plasticity (ODP).

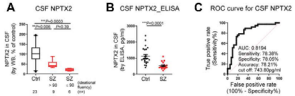


Figure 4. CSF NPTX levels are reduced in individuals with schizophrenia.

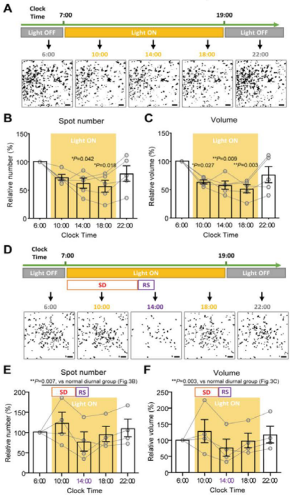


Figure 5. NPTX2 trafficking is linked to behavioral activity and sleep.

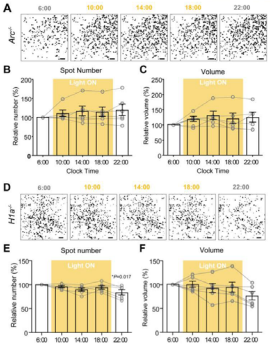


Figure 6. Diurnal NPTX2-SEP trafficking is abolished in *Arc*-/- and *Homer1a*-/- mice.

Summary

1. MD-induced Pyr→PV disconnections depend on NPTX2 reduction.
2. NPTX2 manipulation gates ODP.
3. CSF level of NPTX2 is reduced in schizophrenia patients.
4. Normal diurnal oscillation of NPTX2 trafficking is impaired in schizophrenia animal models.

Conclusion NPTX2 trafficking that gates ODP is impaired by schizophrenia genetic factors, creating vulnerability to stress and environmental factors.

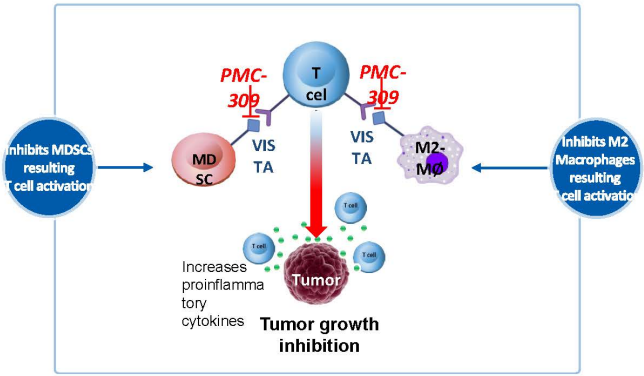
Clinical Development of Olinvacimab and Others

Jin-San Yoo jinsan.yoo@PharmAbcine.com

PharmAbcine
Antibody Therapeutics for Life

Olinvacimab & Pembrolizumab combo (mTNBC)	Phase Ib (2018.10~ ongoing) Australia • 2 patients still receiving treatment • The study will be finalized in 4Q21	Phase II (In preparation) Australia, South Korea • 36 patients planned • HREC approval expected in 3Q21
Olinvacimab mono	Phase IIa (2019.11~ ongoing) Australia, U.S • Delay in patient recruitment due to COVID-19 • 12 out of 36 patients recruited • The study to be finalized by 2023	
Olinvacimab & Pembrolizumab combo (rGBM)	Phase Ib (2018.10~ ongoing) Australia • SD: 44%, (1 pt. in SD over 21 months) • 1 patient still receiving treatment • The study will be finalized in late 2021	Will not proceed to phase II for right now! Looking for co-development Partner!

Anti-VISTA Ab restores immune activity of T cells through inhibition of VISTA interaction



* MDSCs (Myeloid-derived suppressor cells) : Interact with T cells and inhibit immune response
* VISTA (V-domain Ig suppressor of T cell Activation) : An immune checkpoint molecule overexpressed on MDSC

PHD3 loss promotes exercise capacity and fat oxidation in skeletal muscle

Haejin Yoon[1], Jessica B. Spinelli[1], Elma Zaganjor[1], Samantha J. Wong[1], Allen Clermont[2], Nathalie Y. R. Agar[2], Laurie J. Goodyear[2], Reuben J. Shaw[4], Steven P. Gygi[1], Johan Auwerx[3], and Marcia C. Haigis[1]

[1]Department of Cell Biology, Harvard Medical School, Boston, [2]Section on Integrative Physiology and Metabolism, Joslin Diabetes Center, Boston,
[3]Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, [4]The Salk Institute for Biological Studies, 10010 N. Torrey Pines Road, La Jolla, [5]Laboratory of Integrative and Systems Physiology, École Polytechnique Fédérale de Lausanne

1 INTRODUCTION and ABSTRACT: PHDs and the cellular fuel choices

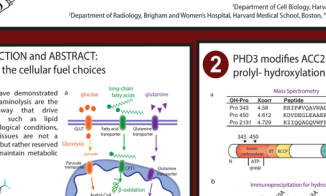
Countless studies have demonstrated that glycolysis and glutaminolysis are the main metabolic pathway that drive biosynthetic pathways, such as lipid synthesis. Under physiological conditions, fatty acids in many tissues are not a predominant fuel choice, but rather reserved nutrient deprivation to maintain metabolic homeostasis (a).

Prolyl hydroxylase domain family members (PHDs, also called EGLN1-3) are implicated in metabolic reprogramming. PHDs are well known to modulate metabolism through the master transcriptional regulator hypoxia inducible factor (HIF). However, in most cell types PHD3 is not a major HIF hydroxylase and is less sensitive to low oxygen than other PHDs (b).

Abstract: Rapid alterations in cellular metabolism allow tissues to maintain homeostasis during changes in energy availability. The central metabolic regulator acetyl-CoA carboxylase 2 (ACC2) is rapidly phosphorylated during cellular energy stress by AMP-activated protein kinase (AMPK) to relieve its suppression of fat oxidation. While ACC2 can also be hydroxylated by prolyl hydroxylase 3 (PHD3), the physiological consequence thereof is poorly understood.

We find that ACC2 phosphorylation and hydroxylation occur in an inverse fashion. ACC2 hydroxylation occurs in conditions of high energy and represses fatty acid oxidation. PHD3-null mice demonstrate loss of ACC2 hydroxylation in heart and skeletal muscle and display elevated fatty acid oxidation. Whole body or skeletal muscle-specific PHD3 loss enhances exercise capacity during an endurance exercise challenge. In sum, these data identify an unexpected link between AMPK and PHD3, and a role for PHD3 in acute exercise endurance capacity and skeletal muscle metabolism.

2 PHD3 modifies ACC2 by site-specific prolyl- hydroxylation (OH-Pro)

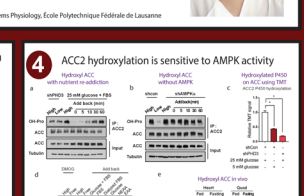


- Since PHD3 regulates FAO but we saw no effect on fat synthesis, we hypothesized PHD3 modifies ACC2.
(a) LC-MS/2 identified putative OH-Pro sites at Pro 343, 450 and 2131.
(b) Pro to Ala mutants were generated at each site, P450A mutagenesis most dramatically decreased ACC2 OH-Pro. (c) Hydroxylation assays showed recombinant PHD3 hydroxylates a synthetic ACC2 peptide containing P450. (d) the P450A mutant had blunted ability to repress FAO.

3 PHD3 and the ACC2 hydroxylation site P450 promote ACC2 activity and ATP binding

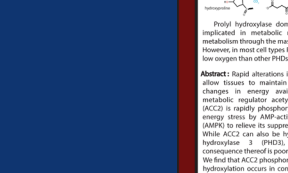
- Our data support the model that PHD3 activates ACC2 via hydroxylation of P450 in order to repress FAO. PHD3 promotes ATP-binding by ACC2.
(a) P450 is conserved from yeast to human in the ATP-grasp domain of the biotin carboxylase domain. (b) Mapping P450 in the published human ACC2 biotin carboxylase domain crystal structure (3JRW). Superposition with the e. coli ATP-bound ACC biotin carboxylase domain (1DV2) showed P450 is in close proximity to catalytic ATP. (c) PHD3 overexpression amplified WT ACC2 activity, but not the P450A variant by in vitro radioactivity-based ACC assays. (d) ACC2 lacking the major hydroxylation site showed decreased ATP-binding versus WT by IP with ATP-agarose. This suggests PHD3 activates ACC2 by enabling greater affinity for ATP. (e) ACC is a pivotal regulator of fat metabolism that directs the cell to catabolize or synthesize fatty acids by generating malonyl-CoA. PHD3 represses long chain fatty acid oxidation by ACC hyroxylation.

4 ACC2 hydroxylation is sensitive to AMPK activity



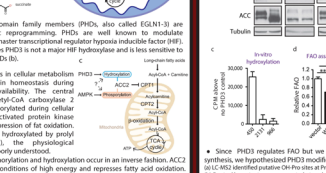
- ACC2 hydroxylation is energy-sensitive and negatively regulated by AMPK.
(a) ACC2 hydroxylation was strongly decreased following nutrient depletion and increased after 5 minutes of returning cells to high nutrient conditions. (b) PHD3 hydroxylated ACC2 during low glucose condition in AMPK knockdown MEFs. (c) Representative tandem mass tag signals of hydroxylated P450 on ACC2 in 293T cells in control, 5 mM glucose or PHD3 knockdown cells. (d) ACC2 hydroxylation in MEFs in high versus low glucose, and in the indicated fast. 1 mM DMOG, High, 25 mM glucose with serum; -Glu/-FBS, no glucose without serum; Glucose+FBS, 25 mM glucose with serum; FBS, no glucose with serum; Dialyzed FBS, Dialyzed FBS; Glucose, 25 mM glucose only; NEAA, 1% non-essential amino acids; EAA, 1% essential amino acid. (e) Hydroxylation was decreased fasted in mice compared to fed. (f) ACC2 hydroxylation and phosphorylation was oppositely regulated in WT mouse muscles in fed and fasted conditions, and PHD3 KO mouse. (g) Hydroxyl ACC2 was increased in AMPK KO mice quad.

5 PHD3 binds with ACC2 in an AMPK-dependent manner



- ACC2 phosphorylation affects the PHD3-ACC2 interaction.
(a) Schematic figure of the ACC2 protein. Posttranslational modifications by AMPK (phosphorylation, red) and PHD3 (hydroxylation, blue) are highlighted. BC, biotin carboxylase domain; BCCP, biotin carboxyl carrier protein; CT, carboxyltransferase domain; N-terminus domain contains ATP-grasp domain. (b) The model was generated by superposition of human ACC2 biotin carboxylase domain (PDB: 3JRW). The distance between phosphorylation (S222, red) and hydroxylation (P450, blue) sites is approximately 47 Å. (c) PHD3 and ACC2 interaction with ACC2 WT, ACC2 P450A or S222A. (d) ACC activity assay in MEFs overexpressing WT ACC2, ACC2 P450A, ACC2 S222A or PHD3 (n = 3). (e) In vitro hydroxylation assay for PHD3 enzymatic activity with recombinant protein about ACC2 WT, ACC2 P450A, S222A, or S222E, and PHD3 (n=3).

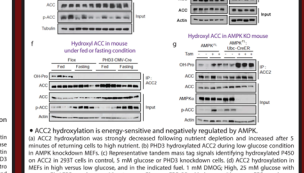
6 PHD3 and AMPK have opposing effects on fat metabolism



(a) Schematic of the regulation of long chain fatty acid oxidation by PHD3 and AMPK. (b) Palmitate oxidation assay in MEFs with overexpressed ACC2 WT, ACC2 P450A, ACC2 S222A or ACC2 P450A/S222A double mutant (n = 3) using FAO analysis. (c) Relative abundance of acylcarnitines in MEFs depleted of PHD3 (red) and AMPK (blue) compared to control cells. For all comparisons two-tailed t test was used. N = 4, P < 0.05. (d) Flowchart of the metabolomics analysis in WT or PHD3 KO mouse quadriceps under fed or fasted condition. (e) Matrix-assisted laser desorption/ionization imaging mass spectrometry imaging (MALDI-MSI) of palmitoylcarnitine (C16 acyl-carnitine, m/z 400.3420 in WT or PHD3 KO mouse quadriceps under fed or fasted conditions, alongside H&E stained serial sections. (f) The scatter dot plot indicates the relative abundance of palmitoyl-carnitine under each condition. (g) Palmitate oxidation in WT or PHD3 KO mice quadriceps under fed or fasted condition using ^{14}C-labeled palmitate and CO_2 capture analysis (n=4).

- AMPK and PHD3 depletion cause opposing changes in acyl carnitine levels.

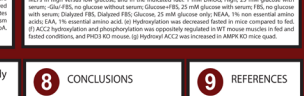
7 Loss of PHD3 increases body energy expenditure and exercise capacity.



- PHD3 KO mice have high oxigen consumption and are sensitive to exercise.
(a) Flowchart of the endurance exercise experiments. PHD3 KO mice demonstrated increased exercise tolerance compared to WT after repetitive treadmill running (n = 8). Mean whole-body maximum oxygen consumption (b), the individual exhaustion time (c), and total running distanc (d). (e) FAO assay in WT or PHD3 KO mice quadriceps in pre- or post-exercise (n=5).

8 CONCLUSIONS

Here, our work demonstrates that PHD3 may improve energy homeostasis and skeletal muscle performance during a wide range of physiological stresses.



- PHD3 presents a metabolic barrier to fatty acid utilization by activating ACC2 and repressing FAO.
- PHD3 hydroxylates Pro450 in the ATP-binding domain of ACC2 to result in full ATP binding and activation of ACC2 enzymatic activity.
- AMPK inhibits PHD3 activity and regulates FAO by phosphorylating S222 on ACC2.
- Loss of PHD3 and AMPK coordinate fat metabolism through ACC2. FAO is increased in low serum free media compared to high glucose media.
- PHD3 null mice demonstrate loss of ACC2 hydroxylation in heart and skeletal muscle and display elevated fatty acid oxidation.
- Whole body or skeletal muscle-specific PHD3 loss endows mice with increased endurance exercise capacity.

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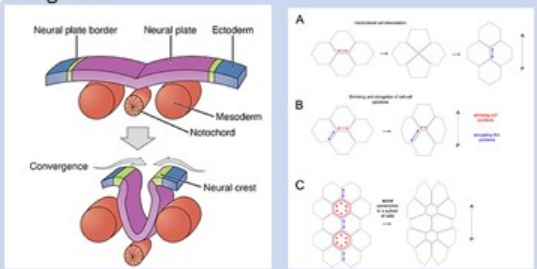
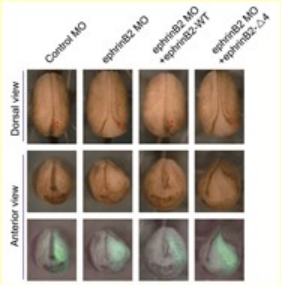
EphrinB2/Ror2 interaction regulates neural tube closure.

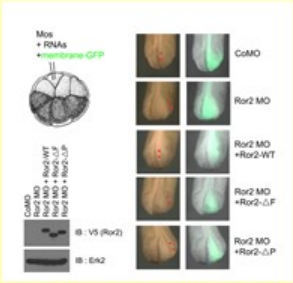
Jaeho Yoon Ph.D., jaehoyoon25@gmai.com
Cancer & Developmental Biology Laboratory (CDBL), CCR, NCI, NIH MD

Background

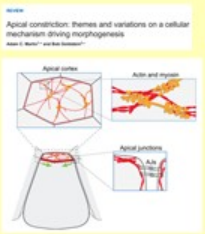


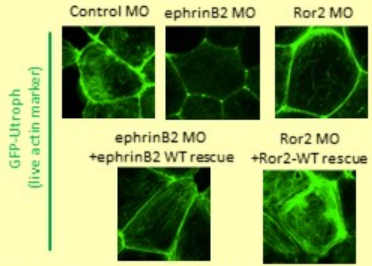


PDZ binding motif of ephrinB2 is required for proper neural tube closure



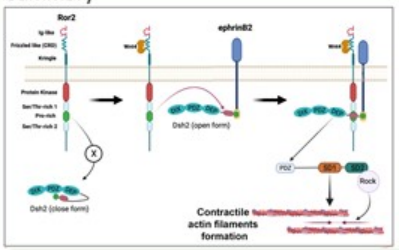
Frizzled domain and PRD domain of Ror2 are required for proper neural tube closure

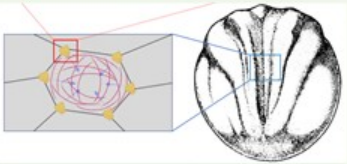




Ror2 regulates contractile actin bundles during apical constriction

Summary



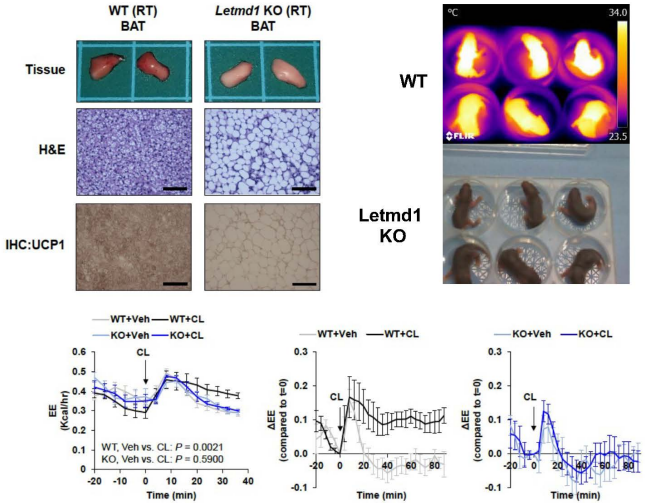


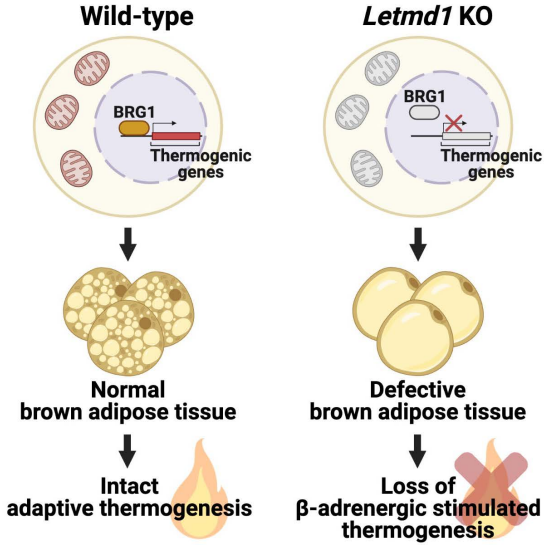
A model for
Apical constriction protein complex

Molecular Control of Thermogenesis and Energy Balance

John Yoon, M.D., Ph.D., jcyoon@ucdavis.edu
University of California Davis School of Medicine

- β-adrenergic stimulated adipocyte thermogenesis controls energy balance in the body
- Letmd1 is a brown adipocyte protein induced by β-adrenergic signaling
- Loss of Letmd1 abolishes β3-adrenergic-dependent thermogenesis
- Letmd1 interacts with the chromatin remodeler BRG1 to regulate thermogenic genes





Choi KM et al (2021) Cell Reports 37:110104.


Thank you for your participation.
We hope you all have a productive 2022,
and
See you at the 2023 meeting!