The 2023 Korean-Nordic Workshop and Meeting in the Life Sciences



Thursday, 27 April 2023

Stockholm – Frösundavik, Sweden

Sponsored and organized through **KNTEC**

(Korea Nordic Science and Technology Cooperation Center)

http://kntec.org

Stockholm Office: Frösundaviks allé 1 (hus 4, plan 6), SE-169 70 Solna

KNTEC

Korea-Nordics Science & Technology Cooperation Center

Local KNTEC representatives and organizers in Stockholm:

Sarah Bengtsson [choi.kntec@gmail.com]

Sung-Jong Lee [chris@nrf.re.kr]

Scientific organizers:

Peter Swoboda (Karolinska Institute, Stockholm, Sweden) [peter.swoboda@ki.se]

Junho Lee (Seoul National University, Seoul, Korea) [elegans@snu.ac.kr]

List of scientific participants (in alphabetical order):

Korea

Jongkyeong Chung, Seoul National University (SNU)

DaeHee Hwang, Korea Advanced Institute of Science and Technology (KAIST)

Junho Lee, Seoul National University (SNU)

Dae-Sik Lim, Korea Advanced Institute of Science and Technology (KAIST)

Jiwon Shim, Hanyang University (HYU)

Hanseul Yang, Korea Advanced Institute of Science and Technology (KAIST)

Nordic – Finland and Sweden

Ville Hietakangas, University of Helsinki (UH)

Volker Lauschke, Karolinska Institute (KI)

Jette Lengefeld, University of Helsinki (UH)

Mathias Rask-Andersen, Uppsala University (UU)

Pelin Sahlén, Royal Institute of Technology (KTH)

Peter Swoboda, Karolinska Institute (KI)

Ulrich Theopold, Stockholm University (SU)

Schedule of events

WEDNESDAY, 26 April: Arrival (Quality Hotel Friends, Råsta Strandväg, Solna)

Dinner (TBD)

THURSDAY, 27 April: **Scientific meeting day at KNTEC**

Frösundaviks allé 1 (hus 4, plan 6), Solna

09:00 – 09:30: **Anders Hektor**, Science Counselor at the Swedish Embassy in Korea

Opening and welcome address

Jenny Cho and **Sung-Jong Lee,** NRF and KNTEC Representatives

Brief overview of programs and initiatives

NRF – National Research Foundation of Korea

KNTEC – Korea Nordic Science and Technology Cooperation Center

Lena Renner, VR Representative

Brief overview of programs and initiatives

VR – Swedish Research Council (*Vetenskapsrådet*)

09:30 – 10:00: talk 1 – **Junho Lee**, *The mind of a dauer: comparative connectomics reveals developmental plasticity*

10:00 – 10:30: talk 2 – **Ulrich Theopold**, *Drosophila as a tumor model*

10:30 – 10:45: BREAK

10:45 – 11:15: talk 3 – **Jiwon Shim**, *Spatio-temporal regulation of blood progenitor cell fate in the Drosophila lymph gland*

11:15 – 11:45 talk 4 – **Volker Lauschke**, *Organotypic and microphysiological models for translational pharmacology*

11:45 – 12:15: talk 5 – **Pelin Sahlén**, *Enhancer mutations in a congenital heart disease*

12:15 – 13:30: LUNCH BREAK

13:30 – 14:00: talk 6 – **Dae-Sik Lim**, *Hippo-YAP/TAZ signaling controls cell plasticity for tissue homeostasis*

14:00 – 14:30: talk 7 – **Ville Hietakangas**, *Stem cell growth directs region-specific cell fate decisions during intestinal nutrient adaptation*

14:30 – 14:45: BREAK

14:45 – 15:15: talk 8 – **Hanseul Yang**, *Hair follicle stem cells and skin regeneration*

15:15 – 15:45: talk 9 – **Jette Lengefeld**, *Cellular enlargement - A new hallmark of aging?*

15:45 – 16:15: talk 10 – **DaeHee Hwang**, *YAP overcomes serum deprivation-induced translation restriction by restoring mTORC1 activity*

16:15 – 16:30: BREAK

16:30 – 17:00: talk 11 – **Mathias Rask-Andersen**, *The genetic architecture of complex traits: from association studies to function to utility*

17:00 – 17:30: talk 12 – **Jongkyeong Chung**, Regulation of ER calcium release by the PINK1-Parkin pathway

17:30 – 18:00: talk 13 – **Peter Swoboda**, *Modeling human * Binge Eating * in the worm C. elegans*

18:00 – 19:30: Concluding remarks, practical information, BREAK and TRANSFER

19:30: DINNER (Quality Hotel Friends, Råsta Strandväg, Solna)

FRIDAY, 28 April: Breakfast (Quality Hotel Friends, Råsta Strandväg, Solna)

Informal meetings and departure

Time slots for talks are 30 minutes. The speakers are kindly requested to set up their presentations in such a way, to allow for questions and short discussions within that 30-minute time frame.

Please bring your talk also on a **USB-stick**, so that in case of computer/projector trouble we have an **instant back up** at hand.

Please observe that the meeting participants are of mixed scientific background. One can thus expect that next to no-one will be sufficiently specialized in the field of research of a given speaker.

Location of venues and events

See overleaf for maps.

Meeting venue: **A**

KNTEC, Frösundaviks allé 1 (hus 4, plan 6), SE-169 70 Solna

Hotel accommodation and Thursday dinner: **B**

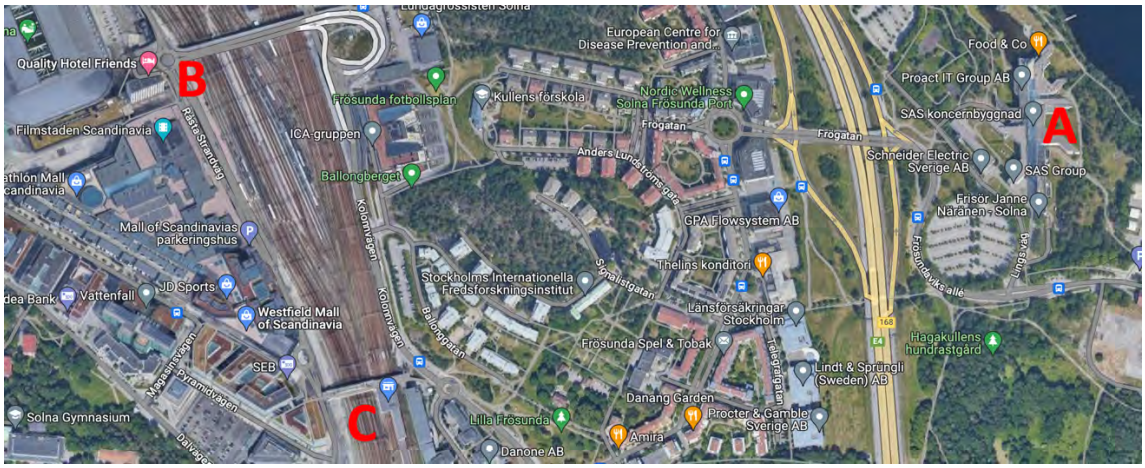
Quality Hotel Friends, Råsta Strandväg 1, SE-169 56 Solna

Public Transport: **C**

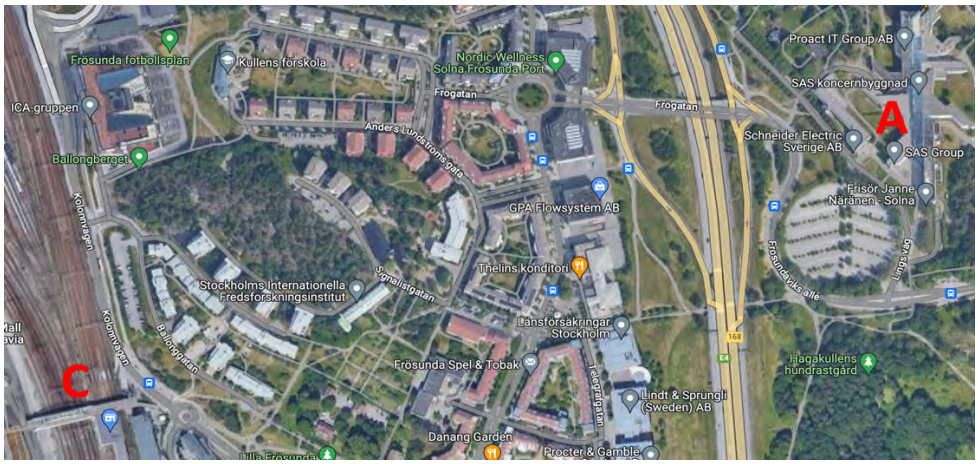
Commuter train (*Pendeltåg*) station SOLNA

(if you come from the Arlanda airport, take the exit on the * *tail end* * of the train)

(if you come from the city of Stockholm, take the exit on the * *front end* * of the train)


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Filmstaden Scandinavia
Frösunda fotbollsplan
Kullens förskola
ICA-gruppen
Ballongberget
Nordic Wellness Solna Frösunda Port
European Centre for Disease Prevention and...
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SAS koncernbyggnad
Schneider Electric Sverige AB
SAS Group
Frisör Janne Naranen - Solna
CPA Flowsystem AB
Thelins konditori
Mall of Scandinavias parkeringshus
JD Sports
Vattenfall
Westfield Mall of Scandinavia
SEB
Stockholms Internationella Fredsforskningsinstitut
Länsförsäkringar Stockholm
Frösunda Spel & Tobak
Lindt & Sprüngli (Sweden) AB
Hagakullens hundrastgård
Danang Garden
Procter & Gamble Sverige AB
Lilla Frösunda
Amira
Danone AB
Solna Gymnasium
Rästa Strandväg
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Magasinsvägen
Pyramidvägen
Dalvägen
Frogatan
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Signalistgatan
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SAS Group
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GPA Flowsystem AB
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Kolonnvägen
Ballonggatan
Signalistgatan
Telegrafgatan
Frösundaviks allé
Lyrgatan
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Scientific profiles of participants

Korea



Jongkyeong Chung



Professor, Department of Biological Sciences
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Current Research

Using mammalian cell biology and Drosophila as model systems, my lab is studying:

- Molecular mechanism of Parkinson's disease
- Mitochondria and PINK1-Parkin signaling pathway
- ER/mitochondrial calcium channels and intracellular calcium homeostasis
- Cell signaling for growth regulation

Representative Publications

Su Jin Ham, Lee, D., Xu, W. J., Cho, E., Choi, S., Min, S., Park, S., **Jongkyeong Chung** (2021). Loss of UCHL1 rescues the defects related to Parkinson's disease by suppressing glycolysis**. Science Advances**

Su Jin Ham, Lee, D., Yoo, H., Jun, K., Shin, H., **Jongkyeong Chung** (2020). Decision between mitophagy and apoptosis by Parkin via VDAC1 ubiquitination. **Proceeding of the National Academy of Sciences USA**

Wonho Kim, Jang, Y. G., Yang, J., **Jongkyeong Chung** (2017). Spatial activation of TORC1 is regulated by Hedgehog and E2F1 signaling in the Drosophila eye. **Developmental Cell**

Regulation of ER calcium release by PINK1-Parkin pathway

Jongkyeong (JK) Chung
Department of Biological Sciences, Seoul National University

Although defects in intracellular calcium homeostasis are known to play a role in the pathogenesis of Parkinson's disease (PD), the underlying molecular mechanisms remain unclear. Here, we show that the loss of PTEN-induced kinase 1 (PINK1) and Parkin leads to dysregulation of inositol 1,4,5-trisphosphate receptor (IP_3R) activity, robustly increasing ER calcium release. In addition, we identify that CDGSH iron sulfur domain 1 (CISD1, also known as mitoNEET) functions downstream of Parkin to directly control IP_3R. Both genetic and pharmacologic suppression of CISD1 restore the increased ER calcium release in PINK1 and Parkin null mammalian cells and flies, demonstrating the evolutionarily conserved regulatory mechanism of intracellular calcium homeostasis by the PINK1-Parkin pathway. More importantly, suppression of CISD1 in PINK1 and Parkin null flies rescues PD-related phenotypes including defective locomotor activity and dopaminergic neuronal degeneration. Based on these data, we propose that the regulation of ER calcium release by PINK1 and Parkin through CISD1 and IP_3R is a feasible target for treating PD pathogenesis.

DaeHee Hwang



Post-doctoral researcher
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Current Research

- Upstream mechanisms of Hippo pathway regulation
- Physiological consequences of YAP/TAZ activation
- Role of mRNA translation in diseases and determination of cell fate

Hwang, D., Kim, M., Kim, S., Kwon, M.R., Kang, Y.-S., Kim, D., Kang, H.-C., Lim, D.-S. (2021) AMOTL2 mono-ubiquitination promotes contact inhibition by facilitating LATS activation. *Life Science Alliance* **4**(10) e202000953

Choi, W., Kim, J., Park, J., Lee, D., **Hwang, D.**, Kim, J.-H., Ashktorab, H., Smoot, D., Kim, S.-Y., Choi, C., Koh, GY., Lim, D.-S. (2018) YAP/TAZ Initiates Gastric Tumorigenesis via Upregulation of MYC. *Cancer Research* **78**(12): 3306

Kim, HB.*, Kim, M.*, Park, Y.-S., Park, I., Kim, T., Yang, S.-Y., Cho, C., **Hwang, D.**, Jung, J.-H., Markowitz, S., Hwang, S.W., Yang, S.-K., Lim, D.-S.#, Myung, S.-J.# (2017) Prostaglandin E2 Activates YAP and a Positive-Signaling Loop to Promote Colon Regeneration After Colitis but Also Carcinogenesis in Mice. *Gastroenterology* **152**(3): 616-630 *Co-first authors #Co-corresponding authors

Kim, T.*#, **Hwang, D.***, Lee, D., Kim, J.-H., Kim, S.-Y., Lim, D.-S.# (2016) MRTF potentiates TEAD-YAP transcriptional activity causing metastasis. *The EMBO Journal* **36**(4): 520-535 *Co-first authors #Co-corresponding authors

Kim, T., Yang, S.-J., **Hwang, D.**, Song, J., Kim, M., Kim, S.K., Kang, K., Ahn, J., Lee, D., Kim, M-Y., Kim, S., Koo, J.S., Koh, S.S., Kim, S.-Y., Lim, D.-S. (2015) A basal-like breast cancer-specific role for SRF-IL6 in YAP-induced cancer stemness. *Nature Communications* **6**(1): 10186

YAP overcomes serum deprivation-induced translation restriction by restoring mTORC1 activity

DaeHee Hwang[1], Jeeyoon Chang[1], Seonguk Baek[1], Taejun Seol[1], Bomin Ku[1], Hongseok Ha[1], Suhyeon Cho[1], Yoon Ki Kim[1], Dae-Sik Lim[1*]

[1] Department of Biological Sciences, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Republic of Korea

The Hippo pathway downstream effectors YAP and TAZ display oncogenic potential via their transcriptional co-activator function, mediated primarily by binding to TEAD transcription factors. Many studies have focused on identifying YAP/TAZ-TEAD target genes, but their role in the regulation of protein synthesis has remained largely unexplored. Here we show that YAP activation is sufficient to overcome the global translation restriction of 5'TOP-containing mRNAs, which is induced by serum deprivation and dependent on the inactivation of mTORC1. We found that YAP/TAZ repressed the expression of DDIT4, a negative regulator of mTORC1 whose expression is otherwise upregulated by serum deprivation. Forced expression of DDIT4 was sufficient to suppress translation and transformative potential of serum-unresponsive uveal melanoma cells, which harbor G protein mutations. Our findings highlight crosstalk between Hippo-YAP/TAZ and mTORC1 pathways in the regulation of translation and offer a new perspective towards understanding YAP/TAZ-driven malignancies.

Junho Lee



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Current Research

Using C. elegans as a model organism, my lab is studying:

- Biology of animal dispersal strategy: nictation behavior of nematodes
- Developmental plasticity of the nervous system as a whole in *C. elegans*
- Alternative lengthening of telomeres in the nematode and mouse embryonic stem cells / chromosome evolution
- Korean nematode collection for studying phenotypic diversity and novelty in evolution
- Establishment of a new *Caenorhabditis* genetics model using a new Korean nematode species
- Hippo signaling and premature neuronal aging
- RFX isoforms and a subroutine regulatory module for specific ciliated neuron sets
- Biological significance of Htt (Huntingtin) in the nematode

Representative Publications

Bo Yun Lee, Jun Kim, **Junho Lee** (2022). Intraspecific de novo gene birth revealed by presence–absence variant genes in Caenorhabditis elegans**. *NAR Genomics and Bioinformatics***

Soungyub Ahn, Heeseung Yang, Sangwon Son, Hyun Sik Lee, Dongjun Park, Hyunsoo Yim, Hee-Jung Choi, Peter Swoboda, **Junho Lee** (2022). The C. elegans Regulatory Factor X (RFX) DAF-19M module: a shift from general ciliogenesis to cell-specific ciliary and behavioral specialization. **Cell Reports**

Eunkyeong Kim, Jun Kim, Chuna Kim and **Junho Lee** (2021). Long-read sequencing and de novo genome assemblies reveal complex chromosome end structures caused by telomere dysfunction at the single nucleotide level. **Nucleic Acids Research**

Chuna Kim, Sanghyun Sung, Jong-Seo Kim, Hyunji Lee, Yoonseok Jung, Sanghee Shin, Eunkyeong Kim, Jenny J. Seo, Jun Kim, Daeun Kim, Hiroyuki Niida, V. Narry Kim, Daechan Park and **Junho Lee** (2021). Telomeres reforged with non-telomeric sequences in mouse embryonic stem cells. **Nature Communications**

Heeseung Yang, Bo Yun Lee, Hyunsoo Yim and **Junho Lee** (2020). Neurogenetics of nictation, a dispersal strategy in nematodes. **Journal of Neurogenetics**

Hanee Lee, Junsu Kang, Soungyub Ahn and **Junho Lee** (2019). The Hippo Pathway Is Essential for Maintenance of Apicobasal Polarity in the Growing Intestine of Caenorhabditis elegans. **Genetics**

Chuna Kim, Jun Kim, Sunghyun Kim, Daniel E. Cook, Kathryn S. Evans, Erik C. Andersen, and **Junho Lee** (2019). Long-read sequencing reveals intra-species tolerance of substantial structural variations and new subtelomere formation in C. elegans. **Genome Research**

Mind of a dauer: Comparative connectomics reveals developmental plasticity

Junho Lee
Department of Biological Sciences, Seoul National University

A fundamental question in neurodevelopmental biology is how flexibly the nervous system can change during development. To address this, we reconstructed the complete chemical connectome of dauer, an alternative developmental stage of nematodes with distinct behavioral characteristics, by volumetric reconstruction and automated synapse detection using deep learning. With the basic architecture of the nervous system preserved, structural changes in neurons, large or small, were closely associated with connectivity changes, which in turn evoked dauer-specific behaviors such as nictation. Graph theoretical analyses revealed higher clustering of motor neurons and more motor-to-sensory feedback connections in the dauer connectome. We suggest that the nervous system in the nematode, probably animals in general, has evolved to respond to harsh environments by reversibly developing a quantitatively and qualitatively differentiated connectome.

Dae-Sik Lim



Professor & Director
Creative Research Initiatives Center for Cell Plasticity, KAIST Stem Cell Center,
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Current Research

Using a Mouse as a model organism, my lab is studying:

- Hippo-YAP signaling in tissue development and regeneration
- Hippo-YAP signaling in Tumorigenesis and senescence
- Cell Plasticity in the lung, liver, and adipose tissue

Representative Publications

Jeon, H. Y., Choi, J., Kraaier, L., Kim, Y. H., Eisenbarth, D., Yi, K., ... & **Lim, D. S.** (2022). Airway secretory cell fate conversion via YAP-mTORC1-dependent essential amino acid metabolism. **The EMBO Journal**, e109365.

Park, J., Eisenbarth, D., Choi, W., Kim, H., Choi, C. Lee, D. and **Lim, D.S.** YAP and AP-1 Cooperate to Initiate Pancreatic Cancer Development from Ductal Cells in Mice. **Cancer Research** (2020) 80(21), 4768-4779.

Sun-Hye Jeong ... H-S. Choi & **Lim, D. S.** Hippo-mediated suppression of IRS2/AKT signaling prevents hepatic steatosis and liver cancer. **J Clin Invest**. (2018) 128(3):1010–1025

Jang, W., Kim, T., Koo, J. S., Kim, S. K., & **Lim, D. S.** Mechanical cue-induced YAP instructs Skp2- dependent cell cycle exit and oncogenic signaling. **The EMBO Journal** (2017). e201696089.

Kim* TH, Hwang DH, Lee D, Kim JH, Kim SY, and **Lim* D.-S**., MRTF potentiates TEAD-YAP transcriptional activity for cancer metastasis. **The EMBO journal** 36.4 (2017): 520-535.

Lee D.H., Park J.O.Kim SY., & **Lim, D.-S.,** LATS-YAP/TAZ controls lineage specification by regulating TGF [beta] signaling and Hnf4 [alpha] expression during liver development. **Nature Communications**, (2016) 7. doi:10.1038/ncomms11961

Kim, T., Yang, S.J., Hwang D., et al. Koh, S.-S., Kim, S-Y., and **Lim D.-S.,** A basal-like breast cancer-specific role for SRF-IL6 in YAP-induced cancer stemness. **Nature Communications**. 2015 10.1038/NCOMMS1018

Hippo-YAP/TAZ signaling controls cell plasticity for tissue homeostasis

Dae-Sik Lim
National Creative Research Initiatives Center,
KAIST Stem Cell Center, Department of Biological Sciences,
Korea Advanced Institute of Science and Technology (KAIST)

The Hippo-YAP/TAZ signaling pathway is a critical developmental program that controls adult stem/progenitor cell proliferation, organ size, and regeneration. We and others revealed that activation of YAP typically leads to the hyperproliferation of precursor cells, inhibition of differentiation, the proliferation of surrounding cells, and cancer development. However, the role of this pathway in regulating cell fate changes or cell plasticity during tissue regeneration has yet to be fully characterized in vivo. Recently, we found that activation of YAP in specific cell types induces dedifferentiation and transdifferentiation, rather than hyperproliferation, of precursor cells. Based on our preliminary data, we hypothesize that YAP confers “cell plasticity” to certain types of differentiated cells in several tissues. In the lung secretory cells, we showed that sustained activation of YAP/TAZ reprograms secretory cells to lose their cellular identity and convert into squamous alveolar type 1 (AT1) cells via the distinct transitional cell state of Damage-Associated Transient Progenitors (DATPs). In the adipocytes, sustained activation of YAP/TAZ in mature adipocytes induces de-differentiation into adipose progenitor-like cells expressing progenitor markers. We will discuss how Hippo-YAP/TAZ signaling affects cell fate dynamics of stem/progenitor cells in the lung and adipose tissue. YAP confers “cell plasticity” to specific differentiated cells.

Jiwon Shim



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School of Natural Science
Hanyang University, Korea
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Email: jshim@hanyang.ac.kr

Current Research

Using Drosophila melanogaster as a model organism, my lab is studying the physiological functions of immune cells and their differentiation trajectories from stem/progenitors.
Specific aims include:

- Metabolic function of chemosensory receptors in Drosophila blood cells
- Respiratory role of myeloid blood cells in Drosophila
- ROS and NO-mediated maintenance of myeloid stem/progenitor cell quiescence
- Integration of environmental inputs into myeloid stem/progenitors via inter-organ interactions
- Evolution of myeloid stem/progenitors and mature blood cells in Drosophila subspecies
- Identification of novel myeloid cell types in innate immunity

Representative Publications

B Cho, M Shin, E Chang, S Son, and **J Shim** (2023) Spatio-temporal regulation of blood progenitor cell fate by EGFR S-nitrosylation, ***submitted***

SH Yoon, B Cho, D Lee, H Kim, **J Shim*** and JW Nam* (2023) Molecular traces of *Drosophila* hemocyte evolution, ***under review***

M Shin[1], E Chang[1], D Lee, B Cho, F Koranteng, H Na, **J Shim** (2023) Immune cells maintain internal oxygen homeostasis in *Drosophila*, ***under revision***

H Li#, J Janssens#, M De Waegeneer, SS Kolluru, K Davie, V Gardeux, W Sealens, F David, M Brbic, J Leskovec, C McLaguphlin, Q Xie, R Jones, K Brueckner, **J Shim**, SG Tattikota, F Schnorrer, K Rust, T Nystul, Z Carvalho-Santos, C Ribeiro, S Pal, TM Przytycka, A Allen, S Goodwin, CW Berry, MT Fuller, H White-Cooper, E Matunis, S DiNardo, A Galenza, LE O'Brien, JAT Dow, H Jasper, B Oliver, N Perrimon*, B Deplancke*, S Quake*, L Luo*, and S Aerts*, FCA Consortium (2022) Fly Cell Atlas: a single-nucleus transcriptomic atlas of the adult fruit fly, **Science**, 375(6584), eabk2432

S Madhwal, M Shin, M Joshi, A Kapoor, P MR R ehman, K Gor, **J Shim*** and T Mukherjee* (2020) Metabolic control of immune-competency by odors in *Drosophila*, **eLife**, 10, e60376

B Cho*, SH Yoon*, D Lee, F Koranteng, SG Tattikota, N Cha, M Shin, H Do, Y Hu, SY Oh, SJ Moon, N Perrimon, JW Nam*, and **J Shim*** (2020) Single-cell transcriptome maps of myeloid blood cell lineages in *Drosophila*, **Nature Communications**, 11(1), 4483

SG Tattikota, B Cho, Y Hu, Y Liu, V Barrera, M Steinbaugh, SH Yoon, A Comjean, F Li, F Dervis, RJ Hung, JW Nam, Sui SH, **J Shim** and N Perrimon (2020) A single-cell survey of *Drosophila* blood, **eLife**, 9, e54818

M Shin*, N Cha*, F Koranteng*, B Cho, and **J Shim** (2020) Subpopulation of macrophage-like plasmatocytes attenuates systemic growth via JAK/STAT in the *Drosophila* fat body, **Frontiers in Immunology**, 11:63

B Cho, CM Spratford, S Yoon, N Cha, U Banerjee* and **J Shim*** (2018) Systemic control of immune cell development by integrated hypoxia chemosensation in *Drosophila*, **Nature Communications**, 9(1):2679

Shim J*, Mukherjee T*, Mondal BC, Liu T, Young G, Wijewarnasuriya D and Banerjee U (2013) Olfactory control of blood progenitor maintenance. **Cell**, 155(5): 1141-1153 (*co-first authors)
Highlighted as Cover article and Featured article

Shim J, Mukherjee T and Banerjee U (2012) Direct sensing of systemic and nutritional signals by hematopoietic progenitors in *Drosophila*. **Nat. Cell. Biol**., 14(4): 394-400

Spatio-temporal regulation of blood progenitor cell fate in *Drosophila* lymph gland

Jiwon Shim
Department of Life Science, Hanyang University, Seoul, Korea

The *Drosophila* lymph gland contains blood progenitors, akin to myeloid progenitors in vertebrates, which give rise to multiple blood cell types that play a role in innate immune response, sense stress and injury. During early development, blood progenitors undergo proliferation to expand, but later become quiescent to maintain their multipotent state before the onset of differentiation. While various signaling factors have been shown to maintain the blood progenitor fate, it remains unclear how the progenitor cells remain poised until they resume differentiation. Here, we find that Nitric oxide synthase (Nos) is expressed in the lymph gland progenitors, where it generates nitric oxide (NO) to post-translationally modify protein cysteine residues through S-nitrosylation of proteins in the hematopoietic progenitors. The presence of this modification activates the Ire1/xbp1-dependent unfolded protein response (UPR), leading to an arrest in the G2 phase of the cell cycle, a characteristic of blood progenitors in the lymph gland. More specifically, we identified the epidermal growth factor receptor (EGFR) as one specific target of S-nitrosylation, which traps the protein in the endoplasmic reticulum (ER), preventing its receptor function and inducing an UPR. Overall, our findings demonstrate that the blood progenitor cells utilize NO to activate UPR through S-nitrosylation, maintaining progenitor cell fate by inhibiting cell cycle progression.

Hanseul Yang



Assistant Professor
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Current Research

Focusing on adult stem cells and tissue regeneration, my lab is studying:

- tissue homeostasis and wound healing in skin and endometrium
- how the functions of adult stem cells are supported by both intrinsic factors and external signaling cues
- how adult stem cells crosstalk with their micro- and systemic-environment to govern their identity and state changes
- how adult stem cell maintenance, self-renew, fate choices and differentiation are coordinated within the cellular network
- the epigenetic mechanisms underlying adult stem cell functions

Representative Publications

Adam RC*, **Yang H***, Ge Y, Infarinato NR, Gur-Cohen S, Miao Y, Wang P, Zhao Y, Lu CP, Kim JE, Ko JY, Paik SS, Gronostajski RM, Kim J, Krueger JG, Zheng D, Fuchs E (2020). NFI transcription factors provide chromatin access to maintain stem cell identity while preventing unintended lineage fate choices. **Nature Cell Biology**

Adam RC*, **Yang H***, Ge Y, Lien WH, Wang P, Zhao Y, Polak L, Levorse J, Baksh SC, Zheng D, Fuchs E. (2018). Temporal Layering of Signaling Effectors Drives Chromatin Remodeling during Hair Follicle Stem Cell Lineage Progression. **Cell Stem Cell**

Yang H, Adam RC, Ge Y, Hua ZL, Fuchs E (2017). Epithelial-mesenchymal micro-niches govern stem cell lineage choices. **Cell**

Yang H*, Schramek D*, Adam RC, Keyes BE, Wang P, Zheng D, Fuchs E (2015). ETS family transcriptional regulators drive chromatin dynamics and malignancy in squamous cell carcinomas. **eLIFE**

Adam RC, **Yang H**, Rockowitz S, Larsen SB, Nikolova M, Oristian DS, Polak L, Kadaja M, Asare A, Zheng D, Fuchs E (2015). Pioneer factors govern super-enhancer dynamics in stem cell plasticity and lineage choice. **Nature**

Gur-Cohen S, **Yang H**, Baksh SC, Miao Y, Levorse J, Kataru RP, Liu X, Cruz-Racelis JD, Mehrara Babak, Fuchs E (2019). Stem cell-driven lymphatic remodeling coordinates tissue regeneration. **Science**

Miao Y, **Yang H**, Levorse J, Yuan S, Polak L, Sribour M, Singh B, Rosenblum M, Fuchs E (2019). Adaptive immune resistance emerges from tumor-Initiating stem cells. **Cell**

Hair follicle stem cells and skin regeneration

Hanseul Yang
Department of Biological Sciences, KAIST

Tissue regeneration relies on resident stem cells, whose activity and lineage choices are influenced by microenvironment. Once activated, stem cells typically give rise to short-lived progenitors, which then progress to differentiate into their lineages. Exploiting the synchronized cyclical bouts of tissue regeneration in hair follicles, we investigated when and how stem cell lineage choices take place. Using temporal single-cell RNA-seq and *in vivo* lineage tracing, we unearthed unexpected heterogeneity among stem cells and their progeny and found that the ability of stem cells to make lineage choices (plasticity) becomes restricted in a sequentially and spatially choreographed program. We traced the roots of lineage restriction to micro-niches located along epithelial-mesenchymal borders, each of which receive slightly different signaling inputs. Instructed by micro-niches signals, hair follicle stem cells reorganize their super-enhancer network to achieve lineage switches. Recently, in addition to intrinsic regulation and local niche factors, we investigate how hair follicle stem cells are regulated by systemic factors such as peripheral nervous systems and hormones. We established a chronic stress mouse model that exhibit mild hypercortisolism (1.5-fold higher glucocorticoid level) by disrupting hypothalamic-pituitary gland-adrenal gland axis. In the model, we identified three functional defects of hair follicle stem cells: 1) premature catagen induction, 2) prolonged telogen phase, 3) hair loss. I will discuss potential mechanisms of how chronic stress damages hair follicles and their regeneration.

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Ville Hietakangas



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Current Research

Our group studies regulation of animal physiology in response to changes in nutrition, using *Drosophila* as the main research model. Our current focus areas are:
-Nutrient regulation of intestinal stem cells
-Physiological roles of gene regulation through intracellular sugar sensing
-New regulators of cell growth and anabolic pathways

Representative publications

Kokki K*, Lamichane N*, Nieminen AI, Ruhanen H, Rovenko B, Havula E, Käkelä R, Hietakangas V. Metabolic gene regulation by Drosophila GATA transcription factor Grain. ***PLoS Genetics***, 2021; 17:e1009855. * Equal contribution

Viitanen A, Gullmets J, Morikka J, Katajisto P, Mattila J, Hietakangas V. LAM – an image analysis method for regionally defined organ-wide cellular phenotyping of the Drosophila midgut. ***Cell Reports Methods***, 2021;1:100059.

Hasygar K, Deniz O, Liu, Y, Gullmets J, Hynynen R, Ruhanen H, Kokki K, Käkelä R, Hietakangas V. Coordinated control of adiposity and growth by anti-anabolic kinase ERK7. ***EMBO Reports***, 2021, 22: e49602.

Melvin RG, Lamichane N, Havula E, Kokki K, Soeder C, Jones C, Hietakangas V. Natural variation in sugar tolerance associates with changes in signaling and mitochondrial ribosome biogenesis. ***eLife*** 2018, 7. pii: e40841.

Liu Y, Mattila J, Ventelä S, Yadav L, Zhang W, Lamichane N, Sundström J, Kauko O, Grénman R, Varjosalo M, Westermarck J, Hietakangas V. PWP1 mediates nutrient-dependent growth control through nucleolar regulation of ribosomal gene expression. ***Developmental Cell*** 2017, 43:240-252.

Teesalu M, Rovenko BM, Hietakangas V. Salt inducible kinase 3 provides sugar tolerance by regulating NADPH/$NADP^+$ redox balance. ***Current Biology*** 2017, 27:458-464.

Mattila J*, Havula E*, Suominen E, Teesalu M, Surakka I, Hynynen R, Kilpinen H, Väänänen J, Hovatta I, Käkelä R, Ripatti S, Sandmann T, Hietakangas V. Mondo-Mlx mediates organismal sugar sensing through Gli-similar transcription factor Sugarbabe. ***Cell Reports*** 2015, 13:350-64.* Equal contribution

Bartok O*, Teesalu M*, Ashwall-Fluss R, Pandey V, Hanan M, Rovenko B, Poukkula M, Havula E, Moussaieff A, Vodala S, Nahmias Y, Kadener S, Hietakangas V. The transcription factor Cabut coordinates energy metabolism and the circadian clock in response to sugar sensing. ***EMBO J.*** 2015, 34:1538-53.* Equal contribution

Stem cell growth directs region-specific cell fate decisions during intestinal nutrient adaptation

The adult intestine is composed of absorptive and secretory cells, constantly renewed by the activity of intestinal stem cells. Moreover, the intestinal size and cellular composition is dynamically adjusted in response to nutrient status. This involves nutrient regulation of intestinal stem cell proliferation and differentiation. While the nutrient control of intestinal stem cell proliferation is well-established, it remains poorly understood how stem cell nutrient sensing is coupled to cell fate decisions. Intestine is a regionalized organ. As distribution of differentiated cells varies between regions, it is conceivable that stem cell regulation reflects the needs of the local tissue environment. How regional control of intestinal stem cells is achieved, has, however, remained unresolved. Here I present our recent work addressing the nutrient regulation of intestinal cells in an organ-wide manner. I discuss the evidence for a mechanism that couples nutrient sensing to cell fate determination throught the control of stem cell size. This regulatory mechanism allows nutrient-responsive control of stem cell differentiation towards absorptive vs. secretory cells in a region-specific manner.

Volker Lauschke



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Current Research

The focus of the Lauschke lab is to design strategies and to engineer tools that can help to narrow the translational gap. To this end, we develop platforms that allow to culture primary patient-derived cells as organotypic microtissues in which physiological phenotypes and functions are maintained ex vivo. We put major emphasis on careful characterization and benchmarking of models to intact human tissues at the molecular, cellular and functional level, as we believe that only models that accurately recapitulate human biology can improve result translation. Specifically, we integrate 3D cell culture systems of primary human cells, microfluidics and comprehensive molecular profiling technologies to discover mechanisms underlying inflammatory conditions (NASH), infectious diseases (COVID-19 and hemorrhagic fevers) and complex metabolic diseases (type 2 diabetes). Furthermore, we identify novel drug targets by integrating tissue engineering with high-throughput drug development.

Representative Publications

Zandi Shafagh R, Youhanna S, Keulen J, Shen JX, Taebnia N, Preiss LC, Klein K, Büttner FA, Bergqvist M, van der Wijngaart W, **Lauschke VM** (2022). Bioengineered pancreas-liver crosstalk in a microfluidic co-culture chip identifies human metabolic response signatures in prediabetic hyperglycemia. ***Advanced Science*** 26:e2203368.

Zhou Y, Arribas GH, Turku A, Jürgenson T, Mkrtchian S, Krebs K, Wang Y, Svobodova B, Milani L, Schulte G, Korabecny J, Gastaldello S, **Lauschke VM** (2021). Rare genetic variability in human drug target genes modulates drug response and can guide precision medicine. ***Science Advances*** 7(36):eabi6856.

Stebbing J, **Lauschke VM** (2021) JAK inhibitors: more than just glucocorticoids. ***New England Journal of Medicine*** 385(5):463-465.

Oliva-Vilarnau N, Vorrink SU, Ingelman-Sundberg M, **Lauschke VM** (2020). A 3D cell culture model identifies Wnt/β-catenin mediated inhibition of p53 as a critical step during human hepatocyte regeneration. ***Advanced Science*** 7(15):2000248.

Stebbing J, Sánchez Nievas G, Falcone M, Youhanna S, Richardson P, Ottaviani S, Shen JX, Sommerauer C, Tiseo G, Ghiadoni L, Virdis A, Monzani F, Rizos LR, Forfori F, Avendaño Céspedes A, De Marco S, Carrozzi L, Lena F, Sánchez-Jurado PM, Lacerenza LG, Cesira N, Caldevilla Bernardo D, Perrella A, Niccoli L, Méndez LS, Matarrese D, Goletti D, Tan YJ, Monteil V, Dranitsaris G, Cantini F, Farcomeni A, Dutta S, Burley SK, Zhang H, Pistello M, Li W, Romero MM, Andrés Pretel F, Simón-Talero RS, García-Molina R, Kutter C, Felce JH, Nizami ZF, Miklosi AG, Penninger JM, Menichetti F, Mirazimi A, Abizanda P, **Lauschke VM** (2020). Janus kinase inhibition reduces SARS-CoV-2 liver infectivity and modulates host cell inflammatory responses to reduce morbidity and mortality. ***Science Advances*** 7(1):eabe4724.

Lauschke VM, Vorrink SU, Moro SM, Rezayee F, Nordling Å, Hendriks DF, Bell CC, Sison-Young R, Park BK, Goldring CE, Ellis E, Johansson I, Mkrtchian S, Andersson TB, Ingelman-Sundberg M (2016). Massive rearrangements of cellular miRNA signatures are key drivers of hepatocyte dedifferentiation. ***Hepatology*** 64(5):1743-1756.

Lauschke VM, Tsiairis CD, François P, Aulehla A (2013). Scaling of embryonic patterning based on phase-gradient encoding. ***Nature*** 2013, 493(7430):101-105.

Organotypic and microphysiological models for translational pharmacology

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Bosch Institute of Clinical Pharmacology, Stuttgart, Germany

The number of successful drug development projects has been stagnant for decades despite major breakthroughs in chemistry, molecular biology and genomics. Unreliable translatability of preclinical in vitro and in vivo models has been identified as a key contributor to these failures. Organotypic and microphysiological culture of primary human cells has emerged as a promising tool kit for preclinical drug development to narrow this translation gap. In this talk I will provide an overview of our recent efforts in developing 3D human tissue cultures and microfluidic models for both efficacy and safety assessments. In addition, the talk will present recent use cases where the use of such organotypic cultures has had direct impacts on market authorizations.



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Jette is an Assistant Professor at the Institute of Biotechnology – HiLIFE at the University of Helsinki (Finland) since 2021 and an Assistant Professor to the Karolinska Institutet (Sweden) since 2023. Jette did her graduate studies at the ETH Zurich (Switzerland) focusing on asymmetric cell division in the lab of Yves Barral. This work started her interest in stem cells. Supported by the SNF, the Jane Coffin Childs Memorial Fund and HHMI, Jette performed her postdoctoral studies at the MIT in the lab of Angelika Amon, where she discovered cell size as aging factor of blood stem cells. Her research team is investigating how blood stem cell fail to maintain their functions during aging and disease.

Current Research

We discovered a new aspect of stem cell ageing *in vivo*: cellular enlargement. With age and damage, stem cells increase in size causing their functional decline. However, we are only beginning to understand how size impacts stem cell fitness and the physiological importance of this process remains unsolved. My team addresses these fascinating questions:

- What pathways cause stem cell dysfunction during their enlargement?
  We use blood (hematopoietic) stem cells of mouse models to identify the molecular mechanisms impairing fitness of large stem cells from a metabolic perspective.
- Can we rejuvenate stem cells after aging and damage?
  We explore approaches to rejuvenate stem cells and investigate the effects on cellular ageing and organismal health.
- Does deregulation of size lead to cancer?
  We utilize blood stem cells from mice and humans to identify factors that facilitate leukemia *in vivo* and to investigate the underlying mechanisms.

Representative Publications

- Davies D, van der Handel K, Bharadwaj S, **Lengefeld J†**, review “Cellular enlargement - a new hallmark of aging?“, Frontiers Cell and Developmental Biology (2022)
- Padovani F, Mairhörmann B, Falter-Braun P, **Lengefeld J**, Schmoller KM “Cell-ACDC: a user-friendly toolset embedding state-of-the-art neural networks for segmentation, tracking and cell cycle annotations of live-cell imaging data”, **BMC Biology** (2022)

- **Lengefeld J**†, Cheng CW, Maretich P, Blair M, Hagen H, McReynolds MR, Sullivan E, Mayors K, Roberts C, Steiner J, Kang JH, Miettinen TP, Manalis SR, Antebi A, Rabinowitz JD, Morrison S, Lees J, Boyer L, Yilmaz O, Amon A "Cell size determines stem cell potential during aging", **Science Advances** (2021)
- Neurohr G, Terry R, **Lengefeld J**, Bonney M, Brittingham G, Moretto F, Miettinen T, Pontano Vaites L, Soares L, Paulo J, Harper W, Buratowski S, Manalis S, van Werven F, Holt L, Novak B, Tyson J, Amon A "Excessive cell growth causes cytoplasm dilution and contributes to senescence", **Cell** (2019)
- **Lengefeld J** and Barral Y "When age learns to write on spindle pole bodies – age of molecules and cells: what are the links beyond budding yeast?", **BioEssays** (2018)
- **Lengefeld J**, Yen E, Chen X, Leary A, Vogel J†, Barral Y † "Spatial cues and not spindle pole maturation drive the asymmetry of astral microtubules between new and pre-existing spindle poles", **MBoC** (2018)
- **Lengefeld J**, Hotz M, Rollins M, Baetz K, Barral Y "Budding yeast Wee1 distinguishes spindle pole bodies to guide their pattern of age-dependent segregation", **Nature Cell Biology** (2017)

Cellular enlargement - A new hallmark of aging?

Jette Lengefeld

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Years of important research has revealed that cells heavily invest in regulating their size. Nevertheless, it has remained unclear why accurate size control is so important. Our recent study using hematopoietic stem cells (HSCs) *in vivo* indicates that cellular enlargement is causally associated with aging. I present an overview of these findings and their implications. Furthermore, I present a broad literature analysis to evaluate the potential of cellular enlargement as a new aging hallmark and I highlight interesting work showing a correlation between cell size and age-related diseases. Taken together, I will present mounting evidence linking cellular enlargement to aging and age-related diseases.

Mathias Rask-Andersen



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Current Research

The study of complex trait genetics, genetic epidemiology, complex disease risk factors in large scale cohorts (UK Biobank)

- Genetics behind human adiposity: body fat accumulation and distribution throughout the body
- Adiposity and disease risk: Cancer and cardio-metabolic disease
- Gene-environment interactions for complex traits
    - Heritability of higher education across socioeconomic deprivation
    - Obesity-associated genetic variation and lifestyle
- Common genetic variation and the molecular biology of age-related hearing loss
- Molecular pharmacology: Trends in drug development and exploitation of novel drug targets

Representative Publications

Rask-Andersen M, Ivansson E, Höglund J, Ek WE, Karlsson T, Johansson Å. Adiposity and Cancer Risk in Males and Females. **Cancer Cell** (Accepted for publication)

Rask-Andersen M, Karlsson T, Ek WE, Johansson Å. Modification of heritability for educational attainment and fluid intelligence by socioeconomic deprivation in the UK Biobank. **American Journal of Psychiatry**, 2021.

Liu W, Johansson Å, Rask-Andersen H, **Rask-Andersen M**. A combined genome-wide association and molecular study of age-related hearing loss in H. sapiens. **BMC Medicine**. vol. 19. 2021.

Rask-Andersen M, Karlsson T, Ek WE, Johansson Å. Genome-wide association study of body fat distribution identifies adiposity loci and sex-specific genetic effects. **Nature communications**, 2019

Karlsson T, **Rask-Andersen M**, Pan G, Höglund J, Wadelius C, Ek WE, Johansson Å. Contribution of genetics to visceral adiposity and its relation to cardiovascular and metabolic disease. **Nature Medicine**. vol.25. 2019.

Hauser AS, Attwood MM, **Rask-Andersen M**, Schiöth HB, Gloriam DE. Trends in GPCR drug discovery: new agents, targets and indications. **Nature reviews Drug discovery** 16 (12), 829-842. 2017.

The Genetic Architecture of Complex Traits: From Association Studies to Function to Utility

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Complex human traits denote an underlying genetic architecture where many factors exert subtle effects that determine a substantial part of the observable variance. Genome-wide association studies (GWAS) on traits such as height, body mass, type 2 diabetes and cardiovascular disease have yielded thousands of associated genetic loci where variation exerts some of the effect. Integrating an individuals genetic variation allows us to quantify the genetic contribution to an individual's particular trait and even assess the risk for disease through the use of polygenic scores. On a larger scale, genetic effects are not static across but influenced by environmental- or lifestyle factors. In our own studies on the UK Biobank (N~500,000) we have found that the genetic predisposition toward higher educational attainment is strongly influenced by socioeconomic factors, where a larger heritability was found in participants from more socioeconomically deprived regions of the United Kingdom. Further studies on body mass also identified gene-environment interactions where lifestyle factors such as physical activity and alcohol consumption frequency attenuated the genetic predisposition towards a higher BMI whereas a higher degree of socioeconomic deprivation amplified genetic effects. We have also delineated the genetic architecure of body fat distribution through large scale GWAS of bioelectrical impedance data in the UK Biobank (N~500,000). Genetic correlation analyses demonstrates that the distribution of body fat, i.e. where fat is deposited and stored in the human body, comprises a trait that is distinct from the accumulation of body fat. Results imply a sex-specific distribution-related mechanistic framework that is active in females, but not in males. Further studies on visceral adipose tissue found it to be an independent risk factor for cardiometabolic disease with a particularly strong effect in Females.

Pelin Sahlén



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Current Research

The research at my lab is aimed at understanding the role of non-coding variation in health, disease and evolution. We use high-resolution chromatin interaction maps to map cis-regulatory networks in clinical samples and commonly used cell lines. We develop and apply experimental and computational methods for functional investigation of enhancer mutations. Our current focus areas

- The role of rare enhancer mutations in congenital heart malformations
- Enhancer mutations as modulators of chemotherapy-induced adverse side effects
- The evolution of enhancer usage during dog domestication
- Functional validation of atherosclerosis-associated common and rare enhancer variants and their target genes
- The dynamics of the cis-interaction landscape of neural differentiation and its relevance for variants associated with neurodevelopmental diseases

Representative Publications

1. **Sahlén P***, Zaugg JB*, Andersson R*, Alberich-Jorda M, de Laat W, Deplancke B, Ferrer J, Mandrup S, Natoli G, Plewczynski D, Rada-Iglesias A, Spicuglia S. Current challenges in understanding the role of enhancers in disease. Nat Struct Mol Biol. 2022 Dec;29(12):1148-1158. doi: 10.1038/s41594-022-00896-3.

2. Freiholtz D, Bergman O, Pradhananga S, Lång K, Poujade F, Granath, C, Olsson C, Franco-Cereceda A, **Sahlén P**, Eriksson P, Björck HM. SPP1/osteopontin, a driver of fibrosis and inflammation in degenerative ascending aortic aneurysm? Journal of Molecular Medicine 2023, manuscript in press

3. Banfi, C, Mallia, A, Ghilardi, S, Brioschi, M, Gianazza, E, Eligini, S, **Sahlén, P**, Baetta, R. Prenylcysteine Oxidase 1 Is a Key Regulator of Adipogenesis. Antioxidants 2023, *12*, 542, https://doi.org/10.3390/antiox12030542

4. Zhigulev A, Norberg Z, Björn N, Udval H, Spalinskas R, Badam TVS, Brandén E, Koyi H, Lewensohn R, De Petris L, Lubovac-Pilav Z, Gustafsson M, Lundeberg J, Gréen H, **Sahlén P***. Rare enhancer mutations modulate the severity of drug-induced myelosuppression in non-small lung cancer patients. (in revision, 03/2023)

5. **Sahlén, P***, Yanhu, L., Xu, J., Kubinyi, E., Wang, G.-D., & Savolainen, P. Variants that Differentiate Wolf and Dog Populations are Enriched in Regulatory Elements. *Genome Biology and Evolution, (2021) 13 (4), evab076,* https://doi.org/10.1093/gbe/evab076

6. **Sahlen, P***, Spalinskas, R., Asad, S., Mahapatra, K. D., Hojer, P., Anil, A., Eisfeldt, J., Srivastava, A., Nikamo, P., Mukherjee, A., Kim, K. H., Bergman, O., Stahle, M., Sonkoly, E., Pivarcsi, A., Wahlgren, C. F., Nordenskjold, M., Taylan, F., Bradley, M., & Tapia-Paez, I. Chromatin interactions in differentiating keratinocytes reveal novel atopic dermatitis- and psoriasis-associated genes. *J Allergy Clin Immunol*. (2021) 147 (5), 1742-1752 https://doi.org/10.1016/j.jaci.2020.09.035

7. Akerborg, O., Spalinskas, R., Pradhananga, S., Anil, A., Hojer, P., Poujade, F. A., Folkersen, L., Eriksson, P. P., & **Sahlen, P***. High-Resolution Regulatory Maps Connect Vascular Risk Variants to Disease-Related Pathways. *Circ Genom Precis Med, (2019) 12*(3), e002353. https://doi.org/10.1161/CIRCGEN.118.002353

8. Anil, A., Spalinskas, R., Akerborg, O., & **Sahlén, P***. HiCapTools: a software suite for probe design and proximity detection for targeted chromosome conformation capture applications. *Bioinformatics, (2018) 34*(4), 675-677. https://doi.org/10.1093/bioinformatics/btx625

9. **Sahlen, P***, Abdullayev, I., Ramskold, D., Matskova, L., Rilakovic, N., Lotstedt, B., Albert, T. J., Lundeberg, J., & Sandberg, R. Genome-wide mapping of promoter-anchored interactions with close to single-enhancer resolution. *Genome Biol, (2015) 16*, 156. https://doi.org/10.1186/s13059-015-0727-9

Abstract

The bicuspid aortic valve (BAV) is a highly heritable congenital valve defect. Only a few coding or GWAS variants have been linked to the disease, explaining only a small portion of the heritability. Given the preponderance of heritability, we hypothesized that rare regulatory variants (MAF < 0.5%) might play a crucial role in BAV pathology.

To this end, 16 tissue samples from patients either with bicuspid (8) or healthy tricuspid (8) aortic valve (TAV) were obtained at the Karolinska Hospital during open-heart surgery. We generated promoter-enhancer interaction (using HiCap) and transcriptome maps of aortic endothelial cells derived from the ascending aorta. Additionally, we sequenced their entire genomes to determine sequence variants.

We found a clear difference in the promoter-enhancer interaction landscape of BAV and TAV samples while their transcriptomes did not differ significantly. We isolated instances where the presence of a rare enhancer variant resulted in making or breaking an interaction with a promoter. We observed a 9- fold enrichment for such cases and they were enriched for binding motifs for transcription factors involved in valve formation during development. Moreover, the target genes of these rare mutations were highly enriched for processes relevant for valve formation and endothelial-to-mesenchymal transition only in BAV patients, whereas TAV patients showed no such enrichment. Resultantly, we produced a battery of genes whose mis-regulation during valve development window could be responsible for the defect. These findings shed light on the genetic component of BAV pathology and provide opportunities for its non-invasive diagnosis.

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Current Research

We use bioinformatics, human cell culture systems and the worm *C. elegans* as models for studying:

- cilia development and cilia function as signaling organelles
- nervous system development, differentiation and behavioral output
- evolutionary aspects of transcription factor mediated gene regulation
- molecular mechanisms underlying human neuro-developmental disorders
- cellular redox state management and its impact on cellular (neuronal) physiology

Representative Publications

A model for human binge eating in the worm C. elegans. Pucci M, D'Addario C, SWOBODA P. Manuscript in preparation.

Primary cilia promote the differentiation of human neurons through the WNT signaling pathway. Coschiera A, Yoshihara M, Lauter G, Ezer S, Kere J, SWOBODA P. Submitted manuscript (bioRxiv; https://doi.org/10.1101/2023.04.06.535895).

The Forkhead transcription factor FKH-8 is a co-regulator of primary cilia in C. elegans. Brocal-Ruiz R, Esteve-Serrano A, Mora-Martinez C, SWOBODA P, Tena J, Flames N. eLife. 2023; in revision (bioRxiv; https://doi.org/10.1101/2021.09.14.460205).

Human LUHMES and NES cells as models for studying primary cilia in neurons. Coschiera A, Watts ME, Kere J, Tammimies K, SWOBODA P. Methods Cell Biol. 2023 May 1;176: in press (https://doi.org/10.1016/bs.mcb.2022.12.012)

The C. elegans Regulatory Factor X (RFX) DAF-19M module: a shift from general ciliogenesis to cell-specific ciliary and behavioral specialization. Ahn S, Yang H, Son S, Lee HS, Park D, Yim H, Choi HJ, SWOBODA P (*), Lee J (*). Cell Rep. 2022 Apr 12;39(2):110661.

Differentiation of ciliated human midbrain-derived LUHMES neurons. Lauter G, Coschiera A, Yoshihara M, Sugiaman-Trapman D, Ezer S, Sethurathinam S, Katayama S, Kere J, SWOBODA P. J Cell Sci. 2020 Nov 9;133(21):jcs249789.

DAF-16/FOXO and HLH-30/TFEB function as combinatorial transcription factors to promote stress resistance and longevity. Lin XX, Sen I, Janssens GE, Zhou X, Fonslow BR, Edgar D, Stroustrup N, SWOBODA P, Yates JR 3rd, Ruvkun G, Riedel CG. Nat Commun. 2018 Oct 23;9:4400.

Characterization of the human RFX transcription factor family by regulatory and target gene analysis. Sugiaman-Trapman D, Vitezic M, Jouhilahti EM, Mathelier A, Lauter G, Misra S, Daub CO, Kere J, SWOBODA P. BMC Genomics. 2018 Mar 6;19:181.

Ciliary dyslexia candidate genes DYX1C1 and DCDC2 are regulated by Regulatory Factor X (RFX) transcription factors through X-box promoter motifs. Tammimies K, Bieder A, Lauter G, Sugiaman-Trapman D, Torchet R, Hokkanen ME, Burghoorn J, Castrén E, Kere J, Tapia-Páez I, SWOBODA P. FASEB J. 2016 Oct;30(10):3578-3587.

Neuropeptidergic signaling and active feeding state inhibit nociception in Caenorhabditis elegans. Ezcurra M, Walker DS, Beets I, SWOBODA P, Schafer WR. J Neurosci. 2016 Mar 16;36(11):3157–3169.

Modeling human * Binge Eating * in the worm *C. elegans*

Mariangela Pucci and Peter Swoboda
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Stress caused by negative environmental input, together with dieting, is a common trigger of human eating disorders, like anorexia nervosa, bulimia nervosa, or binge-eating disorder. Binge eating (BE) is defined as recurring episodes of eating unusually large amounts of food in a short period of time accompanied by a sense of lack of control. We use *C. elegans* and its feeding behaviors under normal and stressful conditions to gain insight into evolutionarily conserved mechanisms (molecular, cellular/neuronal, genetic) controlling food seeking and BE behaviors. Using stressful feeding assays and neurotransmitters governing homeostatic (energy supply) and hedonic (pleasure) eating, we can faithfully model in worms the roles that these systems play in compulsive and addictive feeding behaviors like BE. Our worm model for BE will be highly effective in discovering new BE pathway components. We will thereby better understand the functions of these components in neuronal and brain circuits and the environmental triggers that affect human eating behaviors.

Ulrich Theopold



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We are interested in the innate immune system, its activation, development and interaction with other aspects of physiology. To understand innate immunity at the organismic level, we use the vinegar fly *Drosophila melanogaster.*

The coagulation of insect hemolymph - wound healing and immunity

Arthropods with their open circulatory systems seal wounds and keep bacteria and parasites from entering the hemocoel using efficient clotting systems. We have established a number of methods to study this reaction in *Drosophila melanogaster*. We could show that during Drosophila clotting, extracellular matrices are formed, which immobilize bacteria and prevent their dissemination and the entry of insect-specific nematodes into the hemocoel. Our results lead to a more complete picture of the function and evolution of innate immunity.

The immune response against early stages of tumor development

In this project we study how the innate immune system reacts against tumors. For this we also rely on *Drosophila melanogaster* as a model system. There are a number of mutant fly strains, which develop tumors and we also induce a tumorigenic state genetically. We find that both natural- and experimentally-induced tumors activate immune responses and have characterized this response both at the cellular and humoral level. Genome-wide transcriptional profiling, single-cell sequencing and metabolic profiling reveal similarities to mammalian immune response against tumors, which are being functionally characterized using molecular genetics.

Recent Publications:

Khalili, D, Kunc M, Herbrich S, Mueller, A. **Theopold U**. Chitinase-like proteins promoting tumorigenesis through disruption of cell polarity via enlarged endosomal vesicles. **Front. Oncology** (2023).

Proto-pyroptosis: An Ancestral Origin for Mammalian Inflammatory Cell Death Mechanism in Drosophila melanogaster. Dziedziech A, Theopold U. **J Mol Biol.** 2022

Anti-Fibrotic Activity of an Antimicrobial Peptide in a Drosophila Model. Khalili D, Kalcher C, Baumgartner S, Theopold U. **J Innate Immun.** 2021.

Tissue-autonomous immune response regulates stress signaling during hypertrophy. Krautz R, Khalili D, Theopold U. **Elife.** 2020.

Schmid, MR. Dziedziech A. Arefin B., Kienzle T. Akhter M. Berka J. **Theopold U**. Insect hemolymph coagulation: kinetics of classically and non-classically secreted clotting factors. **Insect Biochem. Mol. Biol**.2019.
