CEMMA

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NEWSLETTER No3 January 2021

Dear CEMMA members,

Get to know what is new!
The 3rd edition of our GRK 1789 newsletter has slightly changed in style - we are working on it.

Against all odds, we can still report on a couple of activities from the past months. We went online for most of them and we would like to report on our experiences.

We will also introduce latest first author publications from the GRK 1789.
As usual, you will find other interesting recent publications on aging and other relevant topics in the Journal Club.

Please also check out the interesting online education platforms. We have listed and hyperlinked them at the end of this newsletter.

Enjoy the 3rd edition.

-- Sabine Wörndle --

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CEMMA welcomes new students

Sruthi Krishnamurthy,
Supervisor: Francesco Roselli
Department Neurology, Ulm University Medical Center.

We cordially welcome Sruthi, the new RTG-PhD and wish a lot of success for her project!

She moved from India to Ulm and started her PhD in October 2020 under the supervision of Francesco Roselli at the Department of Neurology.

For more information about GRK1789 (CEMMA) members and their projects, please visit our CEMMA website.

The Research Training Group (RTG) 1789 “Cellular and molecular mechanisms of ageing” (CEMMA) is funded by the German Science Foundation (DFG) July 2013 to June 2022.

Scientific Retreat

In 2020 the annual Aging-meeting of the CEMMA members took place via Zoom, on Friday 6th November.
The retreat was opened by the speaker of the GRK Hartmut Geiger. After a short introduction round he moderated through oral presentations and also started the discussion round.
In the presentations from the 11 working groups of the GRK the broad thematic spectrum of the Graduate College CEMMA was demonstrated by the talks given by the doctoral students and the scientific results were discussed with all participating supervisors and PhDs.

CEMMA - Retreat 2020

9:00 – 9:15	Hartmut Geiger	Welcome Introduction
9:15 – 9:35	Heike Schreier AG Wiesmüller	"Endonuclease G and the mechanism of DNA maintenance in mitochondria – impact on aging"
9:35 – 9:55	Habib Rahimi AG Buske	"Deciphering critical changes in the methylome of hematopoietic stem cells in age-related clonal hematopoiesis and myeloid leukemogenesis"
9:55 – 10:15	Tanja Schuster AG Geiger	"Quantitative analysis of polarity"
10:15 – 10:35	Dominik Pflumm AG Schirmbeck	"Induction of SARS-CoV-2 specific antibodies in aging mice"
10:35 – 11:05	BREAK	
11:05 – 11:25	Tamara Phan AG Iben	" TFIIEβ mutation in Trichothiodystrophy effects rRNA synthesis and performance"
11:25 – 11:45	Konstantinos Tsesmelis AG Wirth	"The impact of astroglial redox imbalance on CNS homeostasis and aging"
11:45 – 12:05	David Bayer AG Roselli	"Disruption of hypothalamic projections in murine ALS models and human patients"
12:05 – 12:25	Verena Bopp AG Danzer	"The role of aging and alpha-synuclein oligomer load on Parkinson's Disease pathogenesis."
12:25 – 13:00	BREAK	
13:00 – 13.20	Nicole Wiederspohn AG Liss	"Single-cell RNAscope expression analysis of Parkinson's disease-affected brain regions"
13:20 – 13:40	Smitha Srinivasachar AG Kirchhoff	HIV-1 infection activates endogenous retroviral promoters regulating antiviral gene expression.

As a summary of the retreat in ZOOM format, it can be said that it worked well, but we hope to be able to organize retreats in person again in the future to further strengthen the team spirit of the group.

Scientific Workshop

The Scientific Workshop **Basics in bioinformatics and functional genomics using R and Bioconductor, given by Medhanie Mulaw** (Ulm University), was a great success for the participating PhDs.
The workshop took place from September to December 2020, on nine dates on Tuesday afternoons for 2 hours. External scientists also participated in the course. After the 4th date, the training was run through ZOOM due to social distancing rules.

Course description:

Medhanie A. Mulaw (Jun.-Prof. Dr.) medhanie.mulaw@uni-ulm.de

Basics in bioinformatics and functional genomics using R and Bioconductor

Scentific data analysis and presentation play a pivotal role in biological sciences and molecular medicine. Clinical decisions, including patient diagnosis and prognosis, are based on proper quantitative and qualitative analysis of various molecular and histological data. Integrated analysis of Large-scale whole-genome, transcriptome, and epigenome datasets are providing novel insights into disease initiation, progression, and treatment in clinical settings. Additionally, functional studies using animal models and *in vitro* experiments have seen a paradigm shift with the advent of next-generation sequencing.

This course will introduce participants to methods of data retrieval and preprocessing using R and Bioconductor. Participants will use published and in-house datasets and familiarize themselves with biostatistical methods in bioinformatics and functional genomics.

Target: Be able to understand the basics of acquisition, analysis, and presentation of small- and large-scale high throughput sequencing data. Hypothesis-specific data analysis design; a quick overview of data analysis considerations depending on the biological source (DNA, RNA, histone ...) and platform (bulk, single-cell, sequencing method ...) will be covered.

Desired background: Basic knowledge of experimental design in scientific research; theoretical background in biological data analysis and bioinformatics; basic understanding of computer operating systems (esp. Linux/Unix); some hands-on experience in R or related data analysis packages is a plus. Participants are strongly encouraged to read reviews and introductory textbooks related to biostatistics, bioinformatics, and functional genomics.

Methodology: R and Bioconductor; public and in-house -omics datasets. The lecture will be held once per week. Participants will have practical questions to work on until the next session. At the end of the lecture series, participants (in a group of 3 to 4) will work on a dataset related to a selected scientific question. They will work as a team to come up with a concise and clear plan on how to tackle the problem and undertake the data analysis. Each group will finally give a presentation (~15 minutes) followed by a discussion with the attendees.

References:

Gentleman et al. (Eds.) (2005). Bioinformatics and Computational Biology Solutions Using R and Bioconductor / R.
Singer et al. (2017). Bioinformatics for precision oncology *Briefings in Bioinformatics*, bbx143, https://doi.org/10.1093/bib/bbx143.
Michael F. Berger & Elaine R. Mardis (2018). The emerging clinical relevance of genomics in cancer medicine. *Nature Reviews Clinical Oncology,*
volume 15, pages353–365 (2018).
Michael Agostino (2012). Practical Bioinformatics. Garland Science.

Scientific Workshop

Some impressions

GRK 1789 related first authorship publications

In 2020:

HIV-1 infection activates endogenous retroviral promoters regulating antiviral gene expression

Smitha Srinivasachar Badarinarayan, Irina Shcherbakova, Simon Langer, Lennart Koepke, Andrea Preising, Dominik Hotter, Frank Kirchhoff, Konstantin M J Sparrer, Gunnar Schotta, Daniel Sauter
Nucleic Acids Research, Volume 48, Issue 19, 4 November 2020, Pages 10890–10908, Published: 06 October 2020

Full text: https://doi.org/10.1093/nar/gkaa832

Abstract
Although endogenous retroviruses (ERVs) are known to harbor *cis*-regulatory elements, their role in modulating cellular immune responses remains poorly understood. Using an RNA-seq approach, we show that several members of the ERV9 lineage, particularly LTR12C elements, are activated upon HIV-1 infection of primary $CD4^+$ T cells. Intriguingly, HIV-1-induced ERVs harboring transcription start sites are primarily found in the vicinity of immunity genes. For example, HIV-1 infection activates LTR12C elements upstream of the interferon-inducible genes *GBP2* and *GBP5* that encode for broad-spectrum antiviral factors. Reporter assays demonstrated that these LTR12C elements drive gene expression in primary $CD4^+$ T cells. In line with this, HIV-1 infection triggered the expression of a unique *GBP2* transcript variant by activating a cryptic transcription start site within LTR12C. Furthermore, stimulation with HIV-1-induced cytokines increased GBP2 and GBP5 expression in human cells, but not in macaque cells that naturally lack the *GBP5* gene and the LTR12C element upstream of *GBP2*. Finally, our findings suggest that GBP2 and GBP5 have already been active against ancient viral pathogens as they suppress the maturation of the extinct retrovirus HERV-K (HML-2). In summary, our findings uncover how human cells can exploit remnants of once-infectious retroviruses to regulate antiviral gene expression.

GRK 1789 related first authorship publications

In 2021:

Aging of human hematopoietic stem cells is linked to changes in Cdc42 activity

Amoah, A., Keller A, Emini R, Hoenicka M, Liebold A, Vollmer A, Eiwen K, Soller K, Sakk V, Zheng Y, Florian MC, Geiger H. (2021) 'Aging of human hematopoietic stem cells is linked to changes in Cdc42 activity', *Haematologica Early view Jan 14, 2021*

Full text: https://doi.org/10.3324/haematol.2020.269670

Abstract
In this study, we characterize age-related phenotypes of human hematopoietic stem cells (HSCs). We report increased frequencies of HSC, HPC and lineage negative cells in the elderly but a decreased frequency of multi-lymphoid progenitors. Aged human HSCs further exhibited a delay in initiating division ex vivo though without changes in their division kinetics. The activity of the small RhoGTPase Cdc42 was elevated in aged human hematopoietic cells and we identified a positive correlation between Cdc42 activity and the frequency of HSCs upon aging. The frequency of human HSCs polar for polarity proteins was, similar to the mouse, decreased upon aging, while inhibition of Cdc42 activity via the specific pharmacological inhibitor of Cdc42 activity, CASIN, resulted in re-polarisation of aged human HSCs with respect to Cdc42. Elevated activity of Cdc42 in aged HSCs thus contributed to age-related changes in HSCs. Xeno-transplants, using NBSGW mice as recipients, showed elevated chimerism in recipients of aged compared to young HSCs. Aged HSCs treated with CASIN ex vivo displayed an engraftment profile similar to recipients of young HSCs. Taken together, our work reveals strong evidence for a role of elevated Cdc42 activity in driving aging of human HSCs, and similar to mice, this presents a likely possibility for attenuation of aging in human HSCs.

Journal Club - Publications of interest

To use the LINK, you have to log into the campus network of the university (from home via VPN).

Aging and covid vaccines
https://media.nature.com/original/magazine-assets/d41586-020-02856-7/d41586-020-02856-7.pdf

In vivo base editing rescues Hutchinson–Gilford progeria syndrome in mice
https://www.nature.com/articles/s41586-020-03086-7

Opportunities for organoids as new models of aging
https://rupress.org/jcb/article-pdf/217/1/39/1377466/jcb_201709054.pdf

The Organoid Cell Atlas
https://www.repository.cam.ac.uk/bitstream/handle/1810/316095/41587_2020_Article_762.pdf

The distribution of cellular turnover in the human body
https://www.nature.com/articles/s41591-020-01182-9

WHEN ANTIBODIES MISLEAD: THE QUEST FOR VALIDATIONResearch antibodies don't always do what it says on the tin. Test for true signals before you start your experiment. By Monya Baker
https://media.nature.com/original/magazine-assets/d41586-020-02549-1/d41586-020-02549-1.pd

Single-cell multimodal omics: the power of many
https://www.nature.com/articles/s41592-019-0691-5

How to Write Your First Research Paper
https://poorvucenter.yale.edu/sites/default/files/files/hows_to_write_your_first_research_paper_2011.pdf

The CellAge database of cell senescence-related genes is available at:
https://genomics.senescence.info/cells/?m=1

Online – Courses

All about mice, on demand webinars
https://learn.education.jax.org/browse/jaxge-online/

Webinars of topics that relate to the research and development of antibodies.
https://www.antibodysociety.org/learningcenter/

Training on how to choose and use antibodies
https://www.abcam.com/content/abcam-antibody-basics-training

For students and researchers in the natural sciences who are new to peer review or wish to refresh their skills
https://masterclasses.nature.com/online-course-on-peer-review/16507836

Last but not least: some Science-Fun: