Preisverleihung 2023

STIFTUNG PROFESSOR DR. MAX CLOËTTA

Heft Nr. 51

Prof. Dr. Sebastian Jessberger

«New neurons for old brains:
mechanisms underlying lifelong neurogenesis»

Prof. Dr. Christoph Hess

«Metabolic regulation of T cell function»

STIFTUNG
PROFESSOR DR. MAX CLOËTTA

fünfzigste Preisverleihung

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VORWORT

Prof. Dr. Fritjof Helmchen

Für die Stiftung Prof. Dr. Max Cloëtta ist das Jahr 2023 ein besonderes Jahr, da sie ihr 50-jähriges Jubiläum feiert. Aus diesem Anlass fand am 28. September 2023 bereits ein Jubiläumssymposium in Rüschlikon statt, an dem in einem bunten Programm nicht nur zurückgeschaut, sondern der Blick vor allem auch in die Zukunft gerichtet wurde. Unter dem Thema '*Pushing Frontiers in Medicine*' wurden die vielfältigen Herausforderungen der medizinischen Forschung in den kommenden Jahren und Jahrzehnten diskutiert. Ein Höhepunkt des Symposiums war die Verleihung des speziell ausgeschriebenen Cloëtta-Jubiläumspreis 2023 an die beiden ETH-Professorinnen Prof. Tanja Stadler und Prof. Barbara Treutlein für ihre herausragenden Arbeiten auf den Gebieten der Phylogenetik bzw. Stammzellforschung. Dazu nochmals herzlichen Glückwunsch! Wir freuen uns, dass wir zusätzlich zu dieser festlichen Jubiläums-Veranstaltung im Spätsommer nun die Vergabe der jährlichen Cloëtta-Preise in Basel feiern. Bei dieser 50. Preisvergabe werden zwei Forschungspersönlichkeiten ausgezeichnet, die mittels ihrer herausragenden Arbeiten insbesondere die Bedeutung des zellulären Stoffwechsels für die Regulation des Aktivitätszustandes bestimmter Zelltypen hervorheben konnten:

Prof. Dr. Christoph Hess vom Universitätsspital Basel und dem Departement Biomedizin der Universität Basel hat in seiner Forschung bedeutende Beiträge zum Verständis der Aktivität von Immunzellen, insbesondere der weissen Blutkörperchen, geleistet. Er konnte zeigen, wie Immunantworten auf Änderungen im Stoffwechsel dieser Immunzellen basieren und wie sie durch Beeinflussung des Stoffwechsels reguliert werden können. Dank seiner klinischen Tätigkeit konnte Prof. Hess mit seiner Gruppe genetische Defekte in seltenen Immunkrankheiten identifizieren und die resultierenden Fehlmechanismen im Stoffwechsel aufklären. Diese wichtigen Erkenntnisse können neue Möglichkeiten für therapeutische Ansätze eröffnen.

Prof. Dr. Sebastian Jessberger von der Universität Zürich erforscht die Funktion von neuronalen Stammzellen während der Entwicklung sowie im erwachsenen und alternden Gehirn. Einer seiner wichtigen Forschungsbeiträge ist der Befund, dass die Aktivität von Stammzellen massgeblich vom Stoffwechsel, insbesondere dem Fettstoffwechsel, reguliert wird. Ein weiteres Forschungsinteresse von Prof. Jessberger gilt der Neubildung von Nervenzellen auch im Erwachsenen, der sogenannten adulten Neurogenese. Seine Gruppe konnte diesen Vorgang zum ersten Mal live im Hippocampus des Mausgehirns beobachten. Auch kraft methodischer Neuentwicklungen trägt Prof. Jessberger zum Fortschritt der Stammzellforschung bei.

Beide diesjährigen Preisträger haben mit ihren originellen wissenschaftlichen Beiträgen ihre jeweiligen Forschungsfelder entscheidend vorangebracht. Zur Würdigung ihres wissenschaftlichen Erfolgs erhalten Prof. Hess und Prof. Jessberger, wie alle Vorgänger:innen, auch einen Eintrag in das Goldene Buch der Cloëtta Stiftung, welchen sie bei der Preisverleihung unterzeichnen werden. Das grossformatige Goldene Buch begleitet die Stiftung schon seit ihrem Beginn. Über 49 Jahre hinweg wurden die Texte in wunderschöner kalligraphischer Ausführung von Peter Friedli gestaltet (siehe Abbildung rechts). Nach dem letzten Eintrag und somit Abschluss des ersten Bands im letzten Jahr, ist beim Jubiläumssymposium der zweite Band des Goldenen Buchs mit den Würdigungen der Jubiläumspreisträgerinnen eröffnet worden. Dass diese schöne Tradition somit in den kommenden Jahrzehnten fortgesetzt wird, freut mich sehr! Die kalligraphische Feder wurde dabei von Peter Friedli an seine Nachfolgerin, Gabriela Hess, übergeben und ich möchte ihm an dieser Stelle nochmals ausdrücklich und sehr herzlich für seine treue, stets zuverlässige, und immer wunderbar kunstvolle Arbeit danken.

Bei Anja Witte, der Geschäftsführerin der Stiftung Prof. Dr. Max Cloëtta, und ihrem Team möchte ich mich in diesem Jahr ganz besonders bedanken, galt es doch neben den regulären Sitzungen des Stiftungsrates gleich zwei grosse Feiern zu organisieren, mit Vergabe von insgesamt vier Cloëtta-Preisen. Die Zusammenarbeit und der Austausch über vielfältige Themen im Zuge der Vorbereitungen hat mir grosse Freude bereitet. Herzlichen Dank!

Ihnen allen wünsche ich eine anregende Lektüre dieser Brochüre und viel Freude bei der Feier für unsere diesjährigen Preisträger.

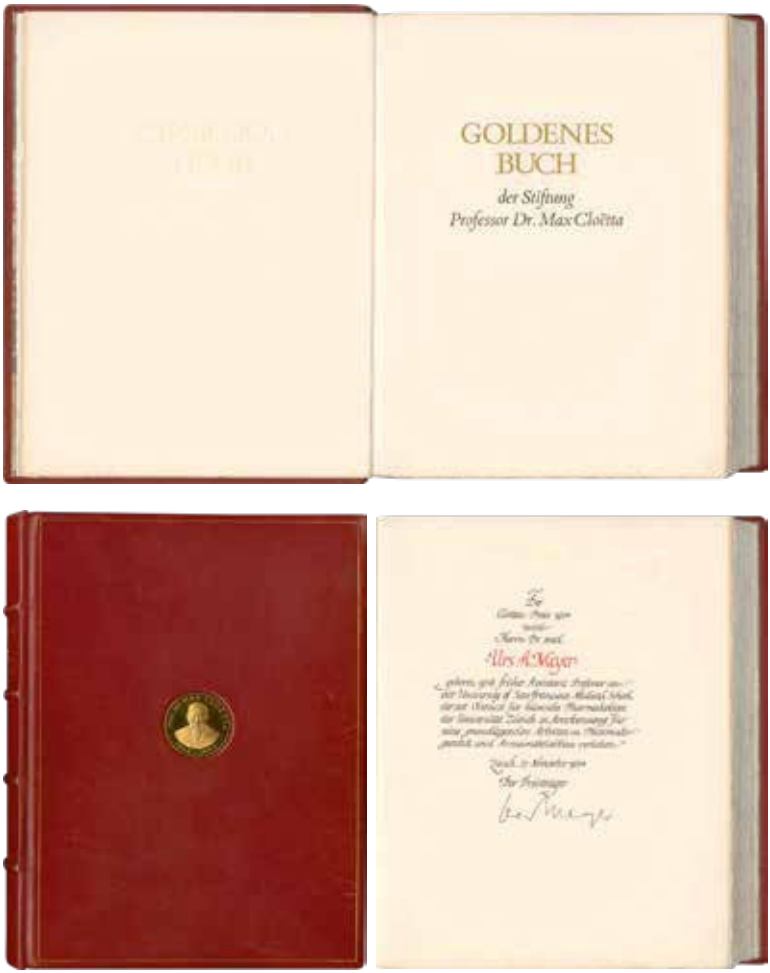


Abbildung: Das Goldene Buch der Cloëtta Stiftung. Frontseiten (oben) und Buchdeckel sowie die Würdigung des ersten Preisträgers aus dem Jahr 1974 (unten).

Anja Witte

Geschäftsführerin

Stiftungsrat

Im Jahr 2023 gab es keine Veränderungen in der Zusammensetzung des Stiftungsrates. Dem Gremium gehören, wie bereits langjährig bewährt, sechs hochkarätige Medizinprofessorinnen und -professoren sowie drei anerkannte Experten auf dem Gebiet der Finanzen und des Rechts an.

Einmal mehr bedanken wir uns ausdrücklich bei den Mitgliedern des Stiftungsrates, die engagiert ihr Fachwissen und ihre Erfahrung einbringen, sowie bei den externen Expertinnen und Experten, deren Gutachten die Entscheidungsfindung auch bei der Auswahl der Cloëtta-Preistragenden unterstützen. Erst diese breit abgestützte Kompetenz ermöglicht es der Stiftung, ihren Zweck wirkungsvoll umzusetzen und die medizinische Forschung sowie die damit verbundenen naturwissenschaftlichen Hilfsdisziplinen in der Schweiz und im Ausland zu fördern und zu unterstützen.

Cloëtta-Preis

Zum 50. Mal wird 2023 der Cloëtta Preis verliehen. 94 renommierte Forscherinnen und Forscher haben den mit je CHF 50'000 dotierten Preis seit der ersten Preisverleihung 1974 erhalten. Der Stiftungsrat und die Geschäftsstelle freuen sich, in diesem Jahr zwei Forscher aus den Bereichen der Neurowissenschaften und der Immunologie mit dem Cloëtta-Preis auszuzeichnen: Der erste Preis geht an **Prof. Dr. Sebastian Jessberger,** ordentlicher Professor und Direktor des Instituts für Hirnforschung an der Universität Zürich. Mit Herrn **Prof. Dr. Christoph Hess** wird ein ordentlicher Professor der Universität Basel und Chefarzt der Medizinischen Poliklinik des Universitätsspital Basel geehrt, der das Labor für Immunbiologie leitet und auch mit der Universität Cambridge affiliiert ist. Unser herzlicher Dank gilt den Verantwortlichen der Universität Basel, wo wir erneut zu Gast sein dürfen, und ihrer Vertreterin in unserem Stiftungsrat, Prof. Dr. Daniela Finke, für die tatkräftige Unterstützung bei der Organisation der diesjährigen Preisverleihung.

Forschungsstellen

Die Forschungsstellen der Stiftung Prof. Dr. Max Cloëtta sind für den akademischen Mittelbau in der Schweiz von grosser Bedeutung. Finanziert werden Stellen an schweizerischen Hochschulen, Kliniken oder Instituten für bereits ausgebildete und selbständig arbeitende Forscherinnen und Forscher bis max. 40 Jahre. Mit diesem Programm will die Stiftung den Forschungsnachwuchs in der Schweiz fördern und den Stelleninhabenden helfen, die manchmal nicht einfache Phase bis zur Berufung auf eine ordentliche Professur zu überbrücken. Die Stipendien werden alle zwei Jahre vergeben, im Jahr 2023 erfolgte die Vergabe von zwei Stellen, die nächste Ausschreibung startet im Frühjahr 2024.

2023 finanzierte die Stiftung Prof. Dr. Max Cloëtta folgende Forschende an Schweizer Universitäten mit dreieinhalb- bis fünfjährigen Unterstützungsperioden:

Dr. Sophie Croizier, 1984, Universität Lausanne,
Center for Integrative Genomics.
Projekt: «Stress regulation of energy metabolism»
Unterstützungsdauer: 1.9.2021 – 31.08.2026

Dr. András Jakab, 1985, Universitäts-Kinderspital Zürich,
Center for MR-Research.
Projekt: «From axons to therapy: Characterizing the connectivity of the human thalamus with 3D multi-scale imaging»
Unterstützungsdauer: 1.10.2020 – 31.12.2024

Dr. Paula Nunes-Hasler, 1980, Universität Genf,
Institut für Pathologie und Immunologie.
Projekt: «Exploring the ER-phagosome connection during antigen cross-presentation»
Unterstützungsdauer: 1.10.2019 – 30.9.2024

Dr. Salvatore Piscuoglio, 1982, Universität Basel,
Departement Biomedizin.
Projekt: «Biomarker identification to guide surgical intervention after neoadjuvant chemoradiotherapy in rectal cancer»
Unterstützungsdauer: 1.7.2021 – 30.6.2026

Dr. Joel Zindel, 1986, Universitätsspital Bern,
Departement für Viszerale Chirurgie und Medizin.
Projekt: «Mesothelial cell recruitment in injury repair and post-surgical adhesion formation»
Unterstützungsdauer: 1.5.2023 – 30.04.2028

Dr. Lucas Boeck, 1980, Universitätsspital Basel,
Departement für Biomedizin.
Projekt: «Designing sterilising antibiotic treatments through Antimicrobial Single-Cell Testing (ASCT)»
Unterstützungsdauer: 1.10.2023 – 30.09.2028

Klinische Medizin Plus

Seit 2010 vergibt die Stiftung Prof. Dr. Max Cloëtta Stipendien ‚Klinische Medizin Plus'. Medizinerinnen und Medizinern werden während oder unmittelbar nach Abschluss ihrer Facharztausbildung Stipendien von drei bis maximal zwölf Monaten für die Absolvierung einer Spezialausbildung an einer renommierten, vornehmlich ausländischen Institution ausgerichtet.

2023 kamen folgende Medizinerinnen und Mediziner in den Genuss eines Stipendiums:

Dr. med. Indrit Bègue, 1980, Scientific Chief Resident,
Universität Genf & Universitätsspital Genf.
Projekt: Brain circuitry therapeutics for negative symptoms of schizophrenia with cerebellar transcranial magnetic stimulation
Guest Institution: Beth Israel Deaconess Medical Center & Harvard Medical School and McLean Hospital, Boston, USA,
1.12.2022 – 31.10.2023

Dr. med. Alessandra Bosch, 1989, Clinical Fellow Haematology/ Oncology, Universitäts-Kinderspital Zürich.
Projekt: Clinical & Research subspecialty Fellowship in Paediatric Haemostasis and Thrombosis
Guest Institution: Hospital for Sick Children, Toronto, Canada, 1.7.2022 – 30.6.2023

Dr. med. Corrado Garbazza, 1981, Resident in Psychiatry, Neurologie, Universitäre Psychiatrische Kliniken Basel.
Projekt: Fellowship in Circadian Medicine & Research Appointment in Circadian Pathophysiology
Guest Institution: Beth Israel Deaconess Medical Center, Circadian Medicine Clinic; Brigham and Women's Hospital, Division of Sleep and Circadian Disorders; Harvard Medical School, Boston, USA, 4.4.2022 – 3.4.2023

Dr. med. Lukas Graf, 1989, Assistenzarzt, HNO, Universitätsspital Basel.
Projekt: Ear microsurgery training and development of implantable microphones
Guest Institution: Eaton-Peabody Laboratories, Mass. Eye and Ear, Harvard University, Boston, USA, 1.2.2022 – 31.1.2023

Dr. med. Beat Moeckli, 1989, Senior Resident Surgery, Universitätsspital Genf.
Projekt: Use of AI to predict outcomes after liver transplantation for hepatocellular carcinoma using multimodal data input
Guest Institution: University of California in Los Angeles, USA & University Health Network in Toronto, Canada, 1.10.2023 – 31.1.2024

Dr. med. Sarah Stricker, 1991, Oberärztin, i.V., Department of Neurosurgery, Universitätsspital Basel.
Projekt: Advanced diagnostic and neuroendoscopic surgical management of cerebrospinal fluid (CSF) disorders in children aiming at improved neurocognitive outcome
Guest Institution: Department of Pediatric Neurosurgery at the Neckar Hôpital Enfants Malades, Paris, Frankreich, 1.12.2022 – 31.10.2023

Stiftung feiert 50-jähriges Jubiläum!

Am 27. September 1973 hat Dr. Antoine Cloëtta in Zürich zum Andenken an seinen Vater unter dem Namen Stiftung Professor Dr. Max Cloëtta die Stiftung errichtet. 2023 feiert die Stiftung somit ihr 50jähriges Bestehen! Am 28. September, also fast am Geburtstag der Stiftung, wurde dies gebührend mit einem eintägigen Symposium rund um das Thema 'Pushing Frontiers in Medicine' gefeiert. Das Symposium bot Anlass um mit der Cloëtta-Family von aktuellen und ehemaligen Preisträgerinnen und Preisträgern, Stipendiatinnen und Stipendiaten und allen aktuellen und ehemaligen Mitgliedern des Stiftungsrates sowie unter Einbeziehung von Weggefährtinnen und Weggefährten und Interessengruppen aus Forschung, Wirtschaft, Politik und Gesellschaft die medizinische Forschung zu feiern und um sich angeregt über die zukünftigen Herausforderungen auszutauschen.

Anlässlich des diesjährigen Jubiläums wurde zusätzlich ein 'Cloëtta-Jubiläumspreis 2023' vergeben, das Preisgeld in Höhe von CHF 250'000 ging hälftig an **Prof. Dr. Tanja Stadler** und **Prof. Dr. Barbara Treutlein** von der ETH Zürich für ihre herausragenden wissenschaftlichen Leistungen und in Anerkennung von ihnen als Rising Stars in der biomedizinischen Forschung.

Von Seiten Geschäftsstelle freuen wir uns ausserordentlich darauf, gemeinsam mit dem Stiftungsrat auch in Zukunft – ganz im Sinne von Dr. Antoine Cloëtta – die medizinische Forschung sowie die damit verbundenen naturwissenschaftlichen Hilfsdisziplinen in der Schweiz und im Ausland zu unterstützen und zu fördern sowie jährlich den Cloëtta-Preis zur Auszeichnung schweizerischer und ausländischer Persönlichkeiten, die sich in besonderer Weise um bestimmte Gebiete der medizinischen Forschung verdient gemacht haben, zu verleihen.

THE CLOËTTA PRIZE 2023
IS AWARDED TO

PROFESSOR

SEBASTIAN JESSBERGER

BORN IN 1974 IN MANNHEIM, GERMANY

DIRECTOR OF THE BRAIN RESEARCH INSTITUTE
IN THE FACULTIES OF MEDICINE
AND SCIENCE AT THE UNIVERSITY OF ZURICH

FOR HIS OUTSTANDING CONTRIBUTIONS
IN THE FIELD OF NEURAL STEM CELL BIOLOGY
IN THE DEVELOPING AND ADULT BRAIN

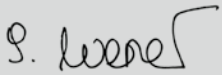
BASEL, 24TH NOVEMBER 2023

IN THE NAME OF THE FOUNDATION BOARD:

THE PRESIDENT

THE VICE PRESIDENT

A MEMBER



SEBASTIAN JESSBERGER

CURRICULUM VITAE

Personal Details
Sebastian Jessberger
Date of birth: March 5, 1974
Swiss / German citizen
Married / two daughters

Current Position
Professor for Neuroscience, Director (since 2014)
Brain Research Institute, Faculties of Medicine and Science
University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland
jessberger@hifo.uzh.ch (www.hifo.uzh.ch/research/jessberger.html)

Degree/Higher Education
- University of Hamburg, Germany,
  Completion of medical thesis 2002 (Dr. med.)
- University of Hamburg,
  Completion of Graduate Studies 2002 (Molecular Biology)
- University of Hamburg, M.D. 2001 (Medicine)
- United States Medical Licensing Examinations
  (USMLE Step I and Step II) 1997, 2000

Professional Career
- Full Professor, University of Zurich, 2019–present
- Associate Professor, University of Zurich, 2012–2019
- Assistant Professor, Institute of Cell Biology,
  Dept. of Biology, ETH Zurich, 2007–2012
- Research Associate, Salk Institute for Biological Studies,
  La Jolla, USA, 2004–2007
- Resident, Clinic of Neurology, Charité University Hospital,
  Berlin, 2002–2004
- Research Associate, Max Delbruck Center for Molecular Medicine,
  Berlin, 2002–2004
- Medical School rotations in New York (USA), Kumi (Uganda), Montpellier (France), Berne (Switzerland), Vienna (Austria), 1995–2001

Honours and Awards

- SNSF Advanced Grant, 2022–2027
- ERC Consolidator Grant, 2016–2021
- Robert Bing Prize of the Swiss Academy of Medical Sciences, 2016
- SNSF Consolidator Grant, 2015–2020
- EMBO Young Investigator Program Award, 2012
- Georg Friedrich Götz Prize, 2013
- Wilhelm Sachsenmair Lecture 2013, ECPS, Innsbruck, A
- John and Lucille van Geest Lecture 2012, Cambridge University, Cambridge, UK
- Jerzy Olszewski Lecture 2010, Canadian Association of Neuropathologists, Toronto, CA
- Fellow MaxnetAging, network on aging of the Max-Planck society, 2005–present
- Postdoctoral fellowship of the American Epilepsy Foundation, Salk Institute, USA, 2006–2007
- Forschungsstipendium of the DFG, Salk Institute, USA, 2004–2006
- Member Graduate program of the DFG, Hamburg, 1997–2000

Professional activities and selected scientific services

- ERC Consolidator Grant panel member, 2019, 2021, 2023
- Member Research Strategy Committee, Medical Faculty UZH, 2020–present
- President board of Betty and David Koetser foundation, 2021–present
- Academic Editor *Life Science Alliance,* 2017–present
- Editorial Board Member *Physiological Reviews,* 2018–present
- Member Auswahlausschuss Alexander von Humboldt Foundation, 2013–2021
- Faculty member *Faculty of 1000* (Neurobiology of Disease & Regeneration), 2015–present
- Member/Head (2018) Gender Equality committee ZNZ, 2015–2020
- Review panel member (chair 2011) Norway Research Council, 2009–2011, 2013, 2015
- *Ad hoc* reviewer for grants submitted to SNSF, ERC, DFG, EMBO, BBSRC, and others.
- *Ad hoc* reviewer for Nature, Science, Cell, Cell Stem Cell, Nature neuroscience, Neuron, PNAS, EMBO J, and others.

Publication summary
- 84 peer-reviewed publications
- 10 book chapters as leading or corresponding author
- 19'206 citations; H-index 49 (Google scholar)

Organisation of scientific meetings
- Co-organizer Monte Verità conference Neurogenesis in health and disease, 2022, Ascona (CH)
- Co-organizer Fusion conferences on Neurogenesis and Neural Disease Modelling, February 2024 Cancun (MX), March 2019 Nassau (BAH), and March 2016 Cancun (MX)
- Co-founder Eurogenesis network (www.eurogenesis.com) Co-organizer Eurogenesis meeting, 2013, 2016, 2019, (planned 2024) Bordeaux (F)

Selected invited lectures (2019–2023)
- EMBO Workshop Gene regulatory mechanisms in neural fate decisions, Sept 2023, Alicante, Spain «Molecular and functional heterogeneity of neural stem cells across lifespan»
- Lund 20th Anniversary Stem Cell Conference, April 2023, Lund, Sweden
- «Intravital imaging to analyse the future (and the past) of adult neural stem cells»
- International Symposium on Neural Development and Diseases, March 2023, Kyoto, Japan «Molecular and functional heterogeneity of hippocampal stem cells»
- Neuroscience School of Advanced Studies, July 2022, Crans Montana, CH «Molecular and functional properties of hippocampal stem cells»
- EMBO Workshop Neural stem cells, June 2022, Kyllini, Greece «Functional diversity of neural stem cells»
- ISSCR Webinar Imaging in Neuroscience (with J Lichtman, X Shen), March 2022, virtual «Using intravital imaging to characterize the dynamics of hippocampal stem cells»

- Queensland Brain Institute Seminar Series, March 2022, virtual
  «Molecular and functional properties of hippocampal stem cells»
- 15th Annual Wisconsin Stem Cell Symposium, April 2021, virtual
  «Molecular and functional control of neural stem cells»
- 15th Clinical Neuroscience Bern meeting (Keynote lecture),
  Oct 2020, virtual
  «Molecular and functional diversity of adult neural stem cells»
- USC Distinguished Speaker Seminar Series, November 2020, virtual
  «Molecular and functional heterogeneity of neural stem cells»
- 42th Annual meeting Molecular biology society of Japan, Dec 2019,
  Fukuoka, Japan
  «Stem cells in the adult brain»
- ISSCR conference, June 2019, Los Angeles, USA
  «Stem cell divisions in the adult brain»
- Marabou Foundation conference, June 2019, Stockholm, Sweden
  «Neural stem cells and aging»
- XVI Portuguese Society for Neuroscience (Keynote lecture),
  May 2019, Lisbon, Portugal
  «Elucidating the molecular and cellular dynamics of neurogenesis»
- DZNE Dresden Opening Symposium (Keynote lecture), May 2019,
  Dresden, Germany
  «Single cell dynamics of adult neural stem cells»
- EMBO conference Neurogenesis, Feb 2019, Bangalore, India
  «Cellular principles of life-long neurogenesis»

Selected extracurricular lectures and public outreach

- 2020 Lecturer, senior citizens Universities of Zurich and Winterthur
- 2018 Participant and planning of *100 Ways of Thinking* exhibition,
  Kunsthalle, Zurich
- 2017 Brain Fair
- 2013 ISSCR Lecture series
  (featuring talks of SJ, J. Knoblich, F.H. Gage, A.R. Kriegstein)
- 2012 Honorary lecture MSc celebrations ETH Zurich
- 2012 Committee member *Falling Walls* lab, Zurich
- 2009 Honorary lecture PhD celebrations ETH Zurich

SELECTED PUBLICATIONS

Knobloch M, Braun SMG, Zurkirchen L, von Schoultz C, Zamboni N, Kovacs WJ, Araùzo-Bravo MJ, Karalay O, Suter U, Machado R, Roccio M, Lutolf MP, Semenkovich CF, Jessberger S (2013) Metabolic control of adult neural stem cell activity by Fasn-dependent lipogenesis. **Nature** 493(7431):226-30

Moore DL, Pilz GA, Araúzo-Bravo MJ, Barral Y, Jessberger S (2015) A mechanism for the segregation of age in mammalian neural stem cells. **Science** 18;349

Pilz GA, Bottes S, Betizeau M, Jörg DJ, Carta S, Simons BD, Helmchen F, Jessberger S (2018) Live imaging of neurogenesis in the adult hippocampus. **Science** 359:658-662

Wegleiter T, Buthey K, Gonzalez-Bohorquez D, Hruzova M, Bin Imtiaz MK, Abegg A, Mebert I, Molteni A, Kollegger D, Pelczar P, Jessberger S (2019) Palmitoylation of BMPR1a regulates neural stem cell fate. **PNAS** 51:25688-25696.

Bowers M, Liang T, Gonzalez-Bohorquez D, Zocher S, Jaeger BN, Kovacs W, Röhrl C, Cramb K, Winterer J, Kruse M, Dimitrieva S, Overall RW, Wegleiter T, Najmabadi H, Semenkovich CF, Kempermann G, Földy C, Jessberger S (2020). FASN-dependent metabolism links neural stem/progenitor cell activity to learning and memory deficits. **Cell Stem Cell** 27:98-109

Bottes S, Jaeger BN, Pilz GA, Jörg DJ, Cole JD, Kruse M, Harris L, Korobeynyk VI, Mallona I, Guillemot F, Helmchen F, Simons BD, Jessberger S (2021) Long-term self-renewing stem cells in the adult mouse hippocampus identified by intravital imaging. **Nature Neuroscience** 24:225-233

Bin Imtiaz MK, Jaeger BN, Bottes S, Machado RAC, Vidmar M, Moore DL, Jessberger S (2021) Decline of Lamin B1 expression mediate age-dependent decreases of hippocampal stem cell activity. **Cell Stem Cell** 18:S1934-5909

Denoth-Lippuner A, Jaeger BN, Liang T, Royall LN, Chie SE, Buthey K, Machado D, Korobeynyk VI, Kruse M, Munz CM, Gerbaulet A, Simons BD, Jessberger S (2021) Visualization of individual cell division history in complex tissues using iCOUNT **Cell Stem Cell** 28:1-15

Gonzalez-Bohorquez D, Gallego Lopez IM, Jaeger BN, Pfammatter S, Bowers M, Semenkovich CF, Jessberger S (2022) FASN-dependent de novo lipogenesis is required for brain development. **PNAS** 119.

Wu Y, Bottes S, Fisch R, Zehnder C, Cole JD, Pilz GA, Helmchen F, Simons BD, Jessberger S (2023) Chronic in vivo imaging defines age-dependent alterations of neurogenesis in the mouse hippocampus. **Nature Aging** 3:380-390.

NEW NEURONS FOR OLD BRAINS: MECHANISMS UNDERLYING LIFELONG NEUROGENESIS

Sebastian Jessberger
Brain Research Institute, UZH

Summary

Neural stem cells generate new nerve cells throughout life in distinct areas of the mammalian brain. One of the brain regions that remains permissive for the lifelong generation of neurons is the dentate gyrus of the hippocampal formation, which is critically involved in certain forms of learning and memory. Failing or altered hippocampal neurogenesis has been associated with a variety of diseases, among others major depression, Alzheimer's disease, and age-related cognitive decline. Thus, understanding the mechanisms underlying lifelong neurogenesis may help developing future therapies targeting adult neural stem cells for endogenous brain repair. We use a multi-pronged, interdisciplinary approach to study the molecular and cellular framework of neural stem cell biology in the developing and adult brain. Aim of our research is to understand how physiologic and disease-associated alterations of neurogenesis are translated into stem cell-associated plastic changes in the brain on a molecular, cellular, and behavioral level.

Introduction

The vast majority of our brain's nerve cells is born during embryonic development. However, neural stem cells (NSCs) are not only responsible for early brain development – they remain active for an entire lifetime. The discovery that new neurons are born throughout life in the 1960s was initially met with substantial skepticism as the idea that, similar to many other organs such as skin, intestines and blood, our brains are also capable to generate their principal cells, i.e., neurons, throughout adulthood was contradictory to a central dogma of the neurosciences: the Nobel prize winning neuroanatomist Ramon y Cajal

coined at the beginning of the 20th century the term: *«Everything may die, nothing may be regenerated»* (Altman, 1962; Altman and Das, 1965; Kuhn et al., 2018). Thus, it took until the end of the 1990s before the neurosciences accepted the presence of cells that retain the capacity to generate new neurons throughout the entire lifespan in the mammalian brain (Gage, 2019).

However, brain regions that remain permissive for lifelong neurogenesis are not widespread but are restricted to a few areas within the mammalian brain. One of the areas where new neurons are generated throughout life is the hippocampus, a brain structure that is critically involved in certain forms of learning and memory, basically deciding what we remember and which experiences or facts we do forget (Squire et al., 2004). Given its key relevance to learning and cognition, the hippocampus is an extensively studied brain region that receives a number of inputs from several cortical association areas. The main input into the hippocampus is via the dentate gyrus (DG) that projects into area 3 of the Cornu ammonis (CA3) from where nerve fibers travel to area CA1 before they project again to cortical association areas (Squire et al., 2004). Using a plethora of approaches, including for example thymidine analogue labeling and genetic lineage tracing methods, previous work showed that the hippocampal DG retains the ability to generate newborn neurons throughout life (Imayoshi et al., 2006; Bonaguidi et al., 2011; Encinas et al., 2011). This process, called adult hippocampal neurogenesis, starts with the activation of NSCs that divide and give rise and generate daughter cells that will eventually differentiate into excitatory, glutamatergic granule cells (Denoth-Lippuner and Jessberger, 2021). Based on their morphology, glia-like cellular properties and gene expression profiles, hippocampal NSCs are often referred to as radial glia-like cells (R cells, or type 1 cells). R cells in rodents are mostly found in a non-proliferative, quiescent state and, once activated, they generate non-radial glia-like progenitors (NR cells, or type 2 cells) that divide again and subsequently differentiate into neurons (Kempermann et al., 2004; Pilz et al., 2018). Within the rodent brain it takes approximately 4–6 weeks before newborn cells fully differentiate into mature neurons, receive excitatory and inhibitory synaptic inputs, and project axons to area CA3 (Denoth-Lippuner and Jessberger, 2021).

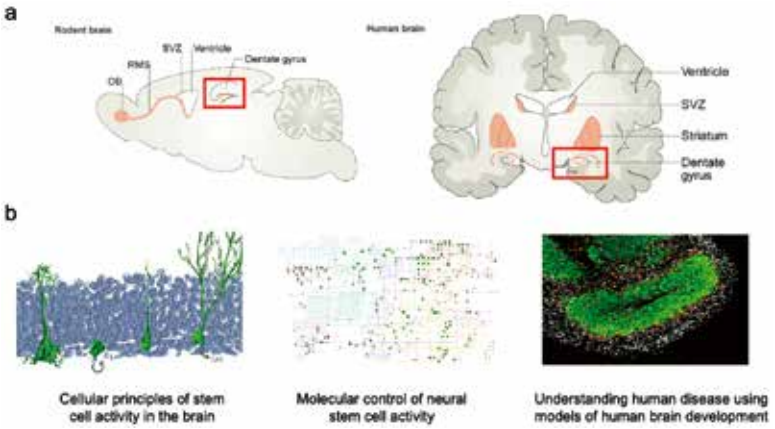


Figure 1. a. *Schematized view of a sagittal section through the mouse brain shows the two main neurogenic areas of the adult rodent brain. The focus of our work is on neurogenesis in the DG of the hippocampus (boxed). The schematic on the right side shows a coronal view of a human brain highlighting areas where neurogenesis has been described.* ***b.*** *Listed are the key areas of research in our laboratory. Parts of the figure adapted from Denoth-Lippuner & Jessberger, 2021.*

The discovery of adult NSCs that generate new neurons throughout life sparked substantial excitement and hopes for future therapeutic approaches to regenerate and heal the injured brain. Indeed, numerous studies found that the number of newly generated neurons is not static but rather dynamically regulated. Whereas, for example, physical activity and housing laboratory rodents in an enriched environment cause an increase in the number of newborn neurons in the hippocampus, many animal models of disease, for example of affective disorders caused by stress, result in a reduction of neurogenesis (Denoth-Lippuner and Jessberger, 2021). Thus, the field speculated that adult neurogenesis may be not only a therapeutic target to replace lost brain cells but that alterations of NSC activity and subsequent neurogenesis may be also associated with the etiology of diseases affecting hippocampal function, such as major depression, Alzheimer's disease, or cognitive aging (Anacker and Hen, 2017; Denoth-Lippuner and Jessberger, 2021). To date there is ample evidence that neurogenesis persists also in the human hippocampus and is,

similarly to the findings based on rodent disease models, dysregulated in the brains of patients with a variety of neurodegenerative and psychiatric diseases (Kempermann et al., 2018; Terreros-Roncal et al., 2021; Zhou et al., 2022). However, causal evidence for functional relevance of lifelong hippocampal neurogenesis in the human hippocampus is still partially missing. This is largely due to the fact that non-invasive measurements of hippocampal neurogenesis, for example using magnetic resonance imaging (MRI) or positron emission tomography (PET), remain highly challenging (Manganas et al., 2007; Pereira et al., 2007). Furthermore, the access to fresh and/or healthy brain – and more specifically hippocampal tissues – is limited. Thus, today's clinical relevance of stem cells in the adult brain remains unclear. At the same time there is no doubt that there are currently hardly any approaches that may help to regenerate the injured brain in the context of acute and chronic neurodegeneration. Two main future avenues hold therapeutic promise: first of all, the activation of endogenous NSCs. Can we replace lost cells, for example in Alzheimer's disease, or compensate for reduced levels of newborn neurons, for example in the context of major depression, by boosting the activation of hippocampal NSCs or by enhancing the integration and survival of newborn neurons? In addition, understanding the mechanisms how newborn neurons find their way to successfully integrate into pre-existing circuits – and this is what they do within the adult DG – may eventually help us to improve, for example, the success of transplants using stem cell-derived cells. How do new neurons find their synaptic targets? What are the signals that tell them where to migrate and where to extend processes? Understanding the molecular and cellular mechanisms will not only further our knowledge regarding a spectacular form of brain plasticity but may indeed help us to pave novel avenues to treat brain diseases (Figure 1). Thus, the aim of our research is to understand how physiologic and disease-associated alterations of neurogenesis are translated into stem cell-associated plastic changes in the brain.

The addition of new neurons into pre-existing hippocampal circuits is a dynamic process, starting with NSC activation, fate commitment, migration of newborn progeny and final neuronal differentiation and integration. Previous analyses of the neurogenic process in the adult brain relied on static, snapshot-based approaches, among other thymidine analogue labeling (e.g., BrdU labeling) and genetic lineage tracing strategies (e.g., using Cre-mediated genetic recombination) (Denoth-Lippuner and Jessberger, 2021). Using such technology, it was possible to reconstruct lineages and developmental timelines by calculating progressions from many individual cells and to build indirectly lineage trees and neuronal maturation steps. However, there is unavoidable ambiguity when recovering lineage information from static pulse-chase lineage tracing assays: no direct proof of an individual cell's behaviour can be directly obtained with such technology, it can only be hypothesized. A methodological problem – that is not unique or specific to NSCs but indeed is prevalent in all somatic stem cell fields – is: how can we assess a dynamic process with static measures? Over the last decade there had been tremendous attempts to use imaging-based approaches with the aim to probe the dynamics of somatic stem cell behaviour in the non-vertebrate nervous system and other stem cell niches including muscle and skin (e.g., Rompolas et al., 2012; Rompolas et al., 2013; Barbosa et al., 2015; Gurevich et al., 2016; Rompolas et al., 2016).

Given the lack of direct, longitudinal observation of single cells, fundamentally important aspects in the context of adult hippocampal NSC biology remained controversial for a long time. For example, it was controversial whether NSCs exist in the DG that possess long-term self-renewal potential (i.e., renewing through cell division while giving rise to differentiated progeny) or if activation of NSCs leads to their rapid depletion from the stem cell pool via terminal differentiation (Bonaguidi et al., 2011; Encinas et al., 2011; Kempermann, 2011; Urban et al., 2016; Pilz et al., 2018). For a long time, it seemed not possible to follow individual NSCs and their daughter cells over time given the deep localization of the DG within the mouse brain. However, the advent of long wavelength two photon (2P) lasers and advanced surgery opened a possible

avenue to use light-microscopy to reach the DG in living mice. Indeed, we first established the required technology together with Fritjof Helmchen's group, benefitting from his group's pioneering experience in multiphoton microscopy (Pilz et al., 2016). After establishing an approach to reach the DG with 2P microscopy, we used transgenic approaches to genetically label individual NSCs and followed their behaviour, cellular output and subsequent steps of neuronal maturation over time within the living DG of adult mice. Thus, we were able to establish a chronic *in vivo* imaging approach using 2P microscopy and followed single NSCs and their progeny in the mouse hippocampus for several months (Figure 2) (Pilz et al., 2018).

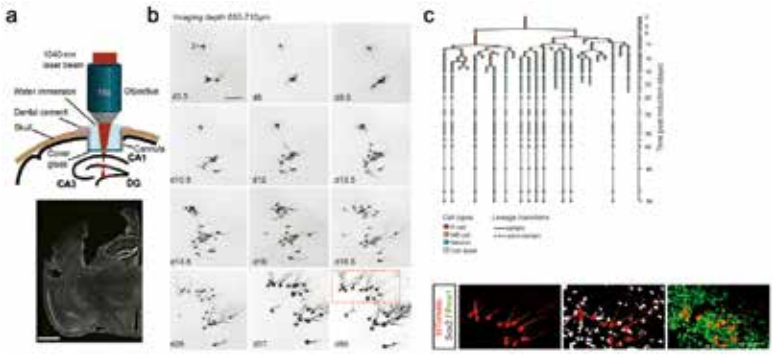


Figure 2. a. *Schematic illustrating the experimental approach allowing for chronic in vivo imaging of NSCs in the adult DG.* ***b.*** *Selected imaging time points of two NSCs (depicted with open and closed arrowhead) over the course of two months resulting in two neuronal clones. Note the clonal expansion of individual NSCs and their progeny and subsequent neuronal maturation. Colored panels show post hoc immunhistochemical analyses of the clone shown in b (boxed area at day 59) confirm neuronal progeny with newborn cells positive for PROX1 (green) and negative for SOX2 (white).* ***c.*** *Lineage tree deduced from tracking one NSC (closed arrowhead in D) and its progeny. Figure adapted from Pilz et al., 2018 and Pilz et a., 2016.*

First, we used an approach to genetically target individual NSCs by using Cre-mediated expression through the regulatory elements of the Achaete-scute homolog 1 (Ascl1) gene that is active in hippocampal NSCs (Kim et al., 2011). This allowed us to provide direct evidence for asymmetric, self-renewing, yet temporally limited cell divisions of Ascl1-expressing, radial glia-like NSCs (Pilz et al., 2018). In addition, we could reveal unexpected asymmetric divisions of non-radial glia-like NSCs. Using a computational, modelling-based approach, we could show that the cell fate behaviour of Ascl1-labeled lineages appeared to be compatible with a developmental-like program involving the sequential transition from a proliferative to a neurogenic phase. Thus, we could follow individual NSCs and their daughter cells for the very first time in their endogenous niche and were able to reveal the cellular dynamics of NSC divisions allowing for life-long hippocampal neurogenesis (Gotz, 2018; Pilz et al., 2018).

However, in this initial study we only used one genetic approach to target hippocampal NSCs. Would it be possible that another population may show indeed more long-term self-renewing behaviors as had been suggested using static approaches? To probe for this, we used again 2P microscopy but labelled now NSCs through conditional recombination driven by the regulatory elements of the stem cell-expressed genes GLI Family Zinc Finger 1 (Gli1) (Ahn and Joyner, 2005). Indeed, we could observe that a subset of Gli1-targeted NSCs showed extended self-renewal (>100 days), providing direct evidence within the adult hippocampus that neurogenic cells exist that show bona fide stem cell properties (Bottes et al., 2021). How could the distinct behavior of Ascl1- vs. Gli1-targeted cells be explained? Are these two distinct populations or do they rather represent distinct behavioural states within the same lineage? Answering this question is not trivial but one approach to get closer to an answer is to use RNA expression analyses of Ascl1- vs. Gli1-targeted cells. Thus, we used single-cell RNA sequencing (scRNA-seq), to show that Gli1- and Ascl1-targeted cells had highly similar yet distinct transcriptional profiles, supporting the existence of heterogeneous NSC populations with diverse behavioral properties (Figure 3) (Bottes et al., 2021). Currently, we do speculate that the distinct behaviors of Ascl1- vs. Gli1-targeted cells represent a continuum of stem cell states rather

than two completely distinct stem cell populations. Establishing the technology to follow individual stem cells and their daughter cells over time fundamentally changed our knowledge how new neurons are generated throughout life in the mammalian hippocampus. Further, we used the 2P approach we established to study other processes in the brain, for example, the expansion of myelinating oligodendrocytes to repair the lesioned corpus callosum (Bottes and Jessberger, 2021).

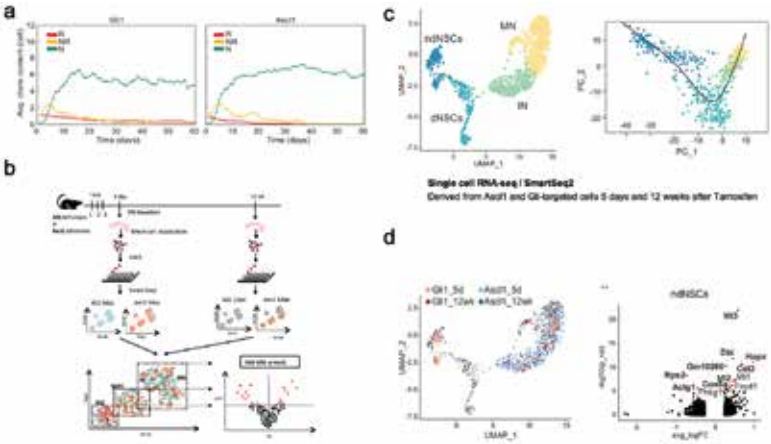


Figure 3. a. *Gli1-targeted NSCs show long-term self-renewal (shown is relative presence of NSCs, red, progenitors, yellow, and neuronal daughters, blue). In contrast, Ascl1-targeted cells rather enter a neurogenic burst upon activation.* ***b.*** *Schematic of scRNA-seq experiments to reveal single cell trancriptomes of distinct NSC populations.* ***c.*** *UMAP representation (and pseudotime trajectory) of single cells, detecting non-dividing NSCs (ndNSCs), dividing NSCs (dNSCs), immature (IN) and mature neurons (MN).* ***d.*** *UMAP reveals substantial overlap of Ascl1- and Gli1-targeted populations. Volcano plot to the right shows differentially expressed genes between non-dividing (nd) NSCs between Ascl1- and Gli1-targeted cells. Figure adapted from Bottes et al., 2021.*

Consequences of age on stem cell behavior

Whereas Kant and Kierkegaard may disagree what «time» describes or means, it is clear that elapsing time causes organismal aging, commonly defined as progressive cellular change that leads to organismal dysfunction. No matter what species or animal: time will cause aging. Notably, gradual, time-dependent deterioration results in an increased incidence of age-associated diseases, among others neurodegeneration, cardiovascular disease, and cancer (Niccoli and Partridge, 2012). Previously, common aging hallmarks, revealing key molecular pathways causally linked to the aging process, have been identified (Lopez-Otin et al., 2013). Aging hallmarks include epigenetic changes, cellular senescence, mitochondrial dysfunction, genomic instability, telomere attrition, loss of proteostasis, altered intercellular interactions, and dysregulated nutrient sensing. However, accumulating evidence argues against the existence of a single, universal aging rate (Elliott et al., 2021; Rando and Wyss-Coray, 2021). From interindividual differences in aging kinetics, to divergent aging trajectories between single cells and tissues, the temporal progression of the aging process appears to be highly variable: heterogeneous aging rates have been reported among tissues and between single cells within the same tissue (Ahadi et al., 2020; Schaum et al., 2020). Thus, biological aging appears to depend not only on time but seems to be influenced by previous cellular experiences (e.g., prior cell divisions for proliferative cells, cellular stress and damage, or exposure to inflammatory signals) that determine the individual cell's aging trajectory (Lopez-Otin et al., 2013; Rando and Wyss-Coray, 2021). Aging also strongly affects behavior and properties of somatic stem cells, including stem cells in the brain.

How stem cells age and how cellular age is propagated to their daughter cells has been a core interest of my laboratory. First, we asked a fundamentally important but very simple question: how is age segregated when a stem cell divides? Asking this question was inspired by seminal work in the budding yeast field where it had been shown that certain aging factor (i.e., factors that contribute to cellular aging) are retained in the mother cells, thus allowing the newly generated daughter cells a full replicative lifespan. In other words: The mother sacrifices itself (by retaining the «damaged goods») to rejuvenate her daughters (Henderson and

Gottschling, 2008). How is this achieved? One mechanism, identified by our long-term collaborator Yves Barral in Zurich, is the emergence of a lateral diffusion barrier in the endoplasmic reticulum (ER) that prevents segregation of «damage» to the daughter cell during cell division (Shcheprova et al., 2008). Could a similar mechanism exist in mammalian cells (that have fundamentally distinct mechanisms of cell division)?

We used an approach called fluorescent loss in photobleaching (FLIP) that allowed us to study diffusion barriers in the ER during mammalian stem cell divisions. Indeed, we could identify that, in analogy to yeast cells, also mammalian NSCs established a diffusion barrier in the ER during cell division (Moore et al., 2015). Strikingly, this diffusion barrier allows for the asymmetric segregation of, for example, damaged proteins. Thus, we could show that cellular age is asymmetrically inherited when a stem cell divides. But is this process affected in the aging brain? And could we target the barrier to rejuvenate cells in the aged DG?

We screened for genes that may affect the barrier and that are altered in their expression patterns with advancing age. One of the pathways we identified was the nuclear lamina protein Lamin B1 (LB1) that we found to be downregulated with age in mouse hippocampal NSCs whereas protein levels of Sun-domain containing protein 1 (SUN1, previously implicated in Hutchinson-Gilford progeria syndrome, HGPS), increased (Bin Imtiaz et al., 2021). Balancing the levels of LB1 and SUN1 in aged NSCs was sufficient to restore the strength of the ER diffusion barrier and enhanced stem cell activity *in vitro* and *in vivo*. Thus, we were able to identify a novel mechanism associated with the age-related decline of neurogenesis in the mammalian hippocampus that appears to be mediated by regulating the strength of the ER diffusion barrier (Bin Imtiaz et al., 2021). Notably, not only mouse NSCs establish a diffusion barrier in the ER: we could also demonstrate that human NSCs show a very similar phenomenon when they divide (Bin Imtiaz et al., 2022).

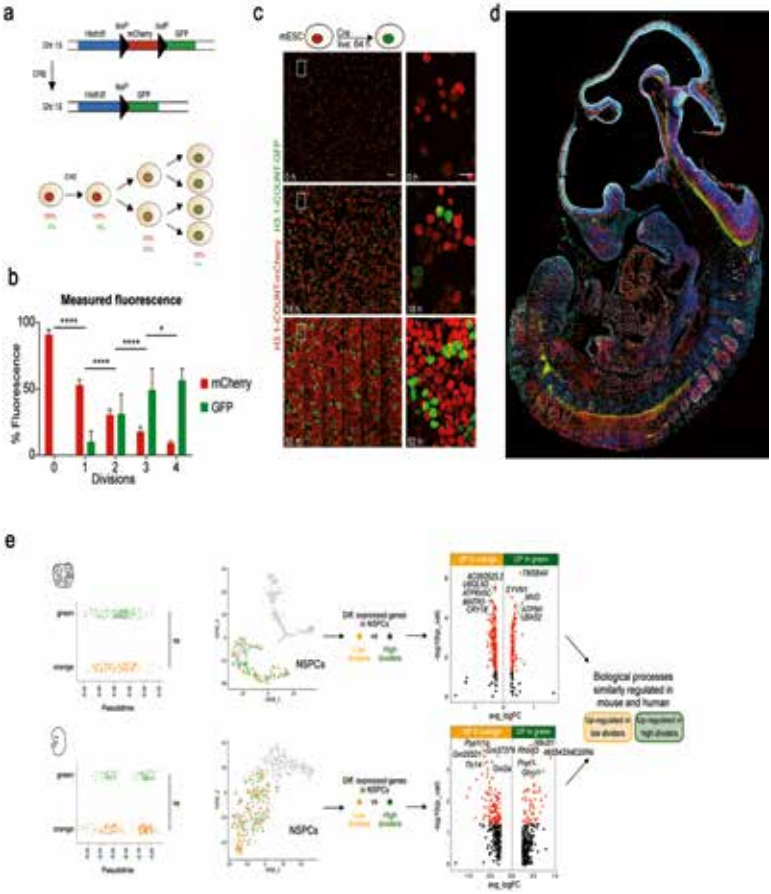


Figure 4. a. *Schematic of the iCOUNT approach (for details please refer to Denoth-Lippuner et al., 2021).* ***b-c.*** *Time-lapse imaging of proliferating mouse ESCs reveals accuracy of iCOUNT system. Not the switch from red to green-labeled histones upon Cre-based recombination.* ***d.*** *iCOUNT embryo at embryonic day 11.5. Note the presence of red/green labelled cells throughout the developing embryo.* ***e.*** *iCOUNT system was used to identify the molecular differences between «high-dividing» and «low-dividing» cells in the cortex of mouse embryos and human ESC-derived forebrain organoids. Figure adapted from Denoth-Lippuner et al., 2021.*

These findings suggested that cell divisions are a key cellular event that contributes to the determination of the biological age of a stem cell. Thus, despite increasing knowledge about lineage relationships of somatic stem cells, based on advances in cellular barcoding and imaging (Fuentealba et al., 2015; Mayer et al., 2015; McKenna et al., 2016; Park et al., 2016; Kalhor et al., 2018), the consequences of previous cellular experiences, such as cell division events, remained largely unknown (Royall and Jessberger, 2021). Thus, we aimed to identify the cell division history of individual cells in complex tissues and generated a novel genetic tool to achieve this aim. We designed an inducible cell division counter (iCOUNT). The iCOUNT approach is based on the recombination induced tag exchange (RITE) of endogenously tagged cell cycle-dependent proteins, such as histone variant H3.1 and Nup155, allowing for a Cre-dependent switch from a red to a green fluorescent-tagged protein, as shown for a switch from H3.1-mCherry to H3.1-GFP (Verzijlbergen et al., 2010; Toyama et al., 2013). Our approach was based on the hypothesis that, after addition of Cre recombinase, subsequent cell divisions reduce the amount of pre-existing red histones by one half and refill the pool of histones with newly synthesized green histones, thus allowing the number of previous cell divisions to be inferred from the changes in red/green ratios (Figure 4) (Denoth-Lippuner et al., 2021).

Indeed, the approach worked as hypothesized, the iCOUNT showed robust recording of cell division events (Denoth-Lippuner et al., 2021). We used scRNA-seq of iCOUNT-labelled progenitor cells and their progenies from the developing mouse cortex and forebrain-regionalized human organoids to identify functionally relevant molecular pathways that are commonly regulated between mouse and human cells, depending on the individual cell division history (Denoth-Lippuner et al., 2021). Thus, we developed a tool to characterize the molecular consequences of repeated cell divisions of stem cells that allows for an analysis of the cellular principles underlying tissue formation, homeostasis, and repair. At this time, we combine the iCOUNT technology with intravital imaging technology to probe how previous experiences (i.e., cell division) affect the individual cell's behaviour *in vivo.*

Further, we used the 2P-based approach to study how aging affects distinct developmental steps in the course of neurogenesis (Wu et al., 2023). We could show that aging affects multiple steps from cell cycle-entry of quiescent NSCs to the number of surviving cells, ultimately causing reduced clonal output of individual NSCs. Our data were able to define the developmental stages that may be targeted to enhance neurogenesis with the aim to maintain hippocampal plasticity with advancing age (Wu et al., 2023). In addition, we used iterative immunostaining approaches to characterize cellular changes with advancing age in the mouse DG (Cole et al., 2022). These data are the foundation for ongoing and future studies (as outlined in the *Perspectives*) to eventually harness the endogenous potential of the mammalian brain for regenerative repair.

Molecular control of neural stem cell activity

Each step, from the maintenance and subsequent activation of a quiescent NSC to fate determination and subsequent cellular differentiation of daughter cells, requires delicate molecular control to achieve successful integration of newborn neurons in the adult brain. Our previous work had identified several pathways/genes that are critically involved in distinct developmental steps in the course of neurogenesis (e.g., Karalay et al., 2011; Bracko et al., 2012; Vadodaria et al., 2013). Many questions remain open at this time (Olpe and Jessberger, 2023). But an important contribution of our work was that we pioneered experiments to characterize a critical role for lipid metabolism in the context of NSC behavior in the adult brain. We could show that adult NSCs require for cell proliferation high activity of an enzyme called fatty acid synthase (FASN), the key enzyme of de novo lipogenesis, that is converting glucose into fatty acids (Knobloch et al., 2013). In contrast to proliferating cells that produce lipids *de novo,* we found that quiescent NSCs rely on the oxidation of fatty acids to produce energy and to fulfill their metabolic demands (Knobloch et al., 2017). Thus, our work identified distinct metabolic shifts that govern the behavior of NSCs in the adult brain (Knobloch and Jessberger, 2017). These findings substantially contributed to our understanding of how cellular metabolism regulates adult stem cell activity.

Further, we aimed to understand the fate of newly synthesized lipids. The product of FASN results in the generation of palmitate, the building block of complex fatty acids. In addition, palmitate is used as the substrate for lipidation of proteins. Many proteins are modified by the attachment of lipid moieties such as myristoylation, prenylation and palmitoylation (also referred to as S-acylation) that modulate protein function (Chen et al., 2018). Among all known lipid modifications, S-acylation represents the only known reversible form of lipid modification that has been shown to play a pivotal role in protein trafficking, stability, and function (Chamberlain and Shipston, 2015; Chen et al., 2018). Using an unbiased screening approach, we identified proteins that are S-acylated in mouse NSCs and were able to show that the bone morphogenic protein receptor 1a (BMPR1a), a core mediator of BMP signaling (Bond et al., 2012; Bach et al., 2018), is palmitoylated (Wegleiter et al., 2019). Using targeted genetic manipulation of S-acylated sites within the BMPR1a, we could show that this affects the localization and trafficking of BMPR1a and leads to altered BMP signaling (Wegleiter et al., 2019). Strikingly, defective palmitoylation of BMPR1a modulated NSC function within the mouse brain, resulting in enhanced oligodendrogenesis. Thus, this work identified a novel mechanism regulating the behavior of NSCs and provided the framework to characterize dynamic post-translational lipid modifications of proteins in the context of NSC biology (Wegleiter et al., 2019). Indeed, these findings led the foundation for later work using embryonic stem cell-derived models of human brain development (Gonzalez-Bohorquez et al., 2022).

Understanding human disease using models of human brain development

Until a few years ago our work largely relied on mouse genetics and the interrogation of mechanisms in cultured NSCs obtained from the mouse brain. Mice and humans share >90% of genetic information and in principle the brains between mice and humans follow the same general architecture. Nevertheless, there is no doubt that the human and the mouse brain also largely differ, not only in size but also in function. However, it has been notoriously difficult to study healthy brain development and neural function using human tissues. In contrast to many other disciplines in the life sciences, the neurosciences have rather little access to healthy tissues

and largely rely on surgical specimen (where the threshold to perform surgery or to obtain biopsies is obviously higher compared to other organs, such as skin, liver, or intestines) or post-mortem samples. Thus, the field got all of a sudden, a completely new tool at hand with the invention of brain organoids, also referred to as mini-brains (Lancaster et al., 2013). Starting from pluripotent stem cells (either induced pluripotent stem cells, iPSCs, or embryonic stem cells, ESCs) it became possible to instruct cells to form self-organized, organoid-like structures that resemble many features of the developing human brain (Di Lullo and Kriegstein, 2017).

The advent of organoid technology opened the exciting possibility to probe the relevance of genes/pathways for human brain development and to investigate how human genetic variants contribute to disease phenotypes. Guided by our work in the mouse brain, we focused initial projects on the role of lipid metabolism. These experiments aimed to investigate a link between NSC-associated lipid metabolism and cognition. To this end, we generated transgenic mice and human embryonic stem cells (hESCs) mimicking a genetic variant in FASN that had been previously identified in humans with intellectual disability (Najmabadi et al., 2011). Strikingly, mice homozygous for the FASN R1812W variant showed impaired hippocampal NSC activity associated with cognitive impairment due to presumed toxic accumulation of lipids in NSCs (Bowers et al., 2020). Moreover, human NSCs homozygous for the FASN R1819W variant showed reduced rates of proliferation in 2D cultures and 3D forebrain regionalized brain organoids, revealing that the functional significance of lipid metabolism for NSC activity is conserved between rodents and humans (Bowers et al., 2020). Thus, our data revealed, by taking a comprehensive disease modeling approach, the first genetic evidence for a link between altered lipid metabolism, NSC activity and brain function in humans (Figure 5). Indeed, the combination of mouse genetics and human ESC-derived organoids represents a powerful tool to study mechanisms underlying lifelong brain development.

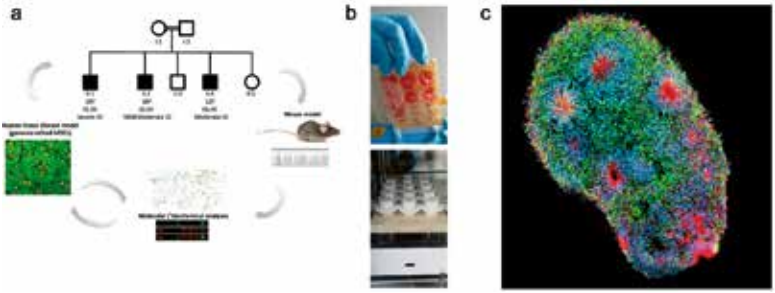


Figure 5. a. *Schematic of the comprehensive disease modeling approach we used to test the consequences of a human variant in the gene encoding for FASN, based on mouse genetics and genome-edited hESCs that were differentiated into forebrain organoids.* ***b.*** *Depiction of organoid technology used in the Jessberger lab that is based on spinning bioreactors (for details refer to Bowers et al., 2020).* ***c.*** *Example of a forebrain organoid comprised of several «cortical units.» These units mimic the structure of a developing human brain. The regions surrounding the ventricles are radial-glia like progenitors with their processes labeled with the intermediate filament Nestin (green). The radial-glia scaffold is essential for proper brain development and depends on FASN-dependent lipid metabolism, which may be involved in regulating palmiotylation-mediated modification of proteins enriched in inner ventricular zones (visualized using the palmitate analogue 17-ODYA, in red). Nuclei are counterstained with DAPI (blue). For details refer to Gonzalez-Bohorquez et al., 2022.*

Similar to the knock-in study mimicking a human FASN variant, we also took a genetic approach to probe the relevance of FASN for physiological mouse and human brain development. We could show that loss of FASN in the developing mouse brain causes severe microcephaly, largely due to altered polarity of apical, radial glia progenitors and reduced progenitor proliferation (Gonzalez-Bohorquez et al., 2022). Further, genetic deletion and pharmacological inhibition of FASN in human ESC-derived forebrain organoids identified a conserved role of FASN-dependent lipogenesis for radial glia cell polarity in human brain organoids. Thus, our data established a role of *de novo* lipogenesis for mouse and human brain development and identified a link between progenitor cell polarity and lipid metabolism. Indeed, we found that cell polarity alterations upon FASN inhibition were – at least partially – due

to the changes in protein s-acylation, a mechanism that we continue to study in more detail (Wegleiter et al., 2019; Gonzalez-Bohorquez et al., 2022).

Perspectives

Where do we go from here? As in the past, our research depends on the highly interdisciplinary expertise of group members trained in biology, medicine, physics, and computer sciences. Striving to bring these different backgrounds and skills together and to unite them on their quest to understand how the brain develops and how it generates new neurons throughout life, will be foundation for future discoveries.

We currently characterize the functional consequences of the addition of new neurons to hippocampal circuits using functional imaging approaches (Figure 6). Of special interest are changes we will observe in the course of aging. How do new neurons shape dentate connectivity in aged mice? What happens if we experimentally manipulate the addition of newborn nerve cells?

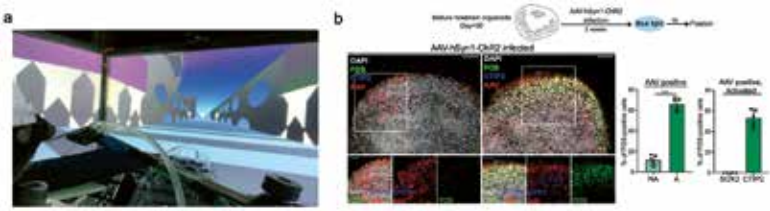


Figure 6. a. *Example of a mouse learning a hippocampus-dependent, virtual reality-based task while the activity of hippocampal neurons is measured using 2P microscopy.* ***b.*** *Cerebral organoids where optogenetic stimulation (mediated by viral infections with viruses (red) expressing Channelrhodopsin-2 (ChR2) under the regulatory elements of the human synapsin 1 (hSyn1) promoter) causes activation and expression of the immediate early gene FOS (green) in neurons expressing CTIP2 (blue). We use this approach to characterize the responses of human neuronal networks to exogenous (i.e., through optogenetic stimulation) or endogenous network activity.*

We have also expanded our interest with the aim to understand what happens in mouse and human neurons when circuits are exposed to novel experiences, when they learn (Figure 6). Which genes are upregulated? What is shared between activated mouse and human neurons? Very unexpectedly we found that the centromeric histone CENP-A is dynamically regulated with synaptic activity on the RNA and protein level, causing non-centromeric deposition of CENP-A at gene promoters, including those of plasticity-associated genes. Indeed, we found that conditional downregulation of CENP-A perturbed activity-dependent gene expression and impaired hippocampus-dependent learning and memory. Furthermore, we found that CENP-A is required for activation-induced IEG expression in human neurons of ESC-derived forebrain organoids. Thus, these new results revealed a mitosis-independent, conserved role of CENP-A for activity-dependent gene expression in mammalian neurons and identified a novel, chromatin-based mechanism regulating learning and memory. The mechanistic details of this novel finding are currently explored in our laboratory.

Importantly, we also use novel technology to reach even deeper into the living brain: for example, we have recently established a 3-photon microscopy system – to our knowledge one of the first ones successfully operating in Switzerland – that will allow to image the DG without invasive surgical procedures.

Furthermore, we have generated exciting data to characterize the molecular consequences of aging in the mouse hippocampus using multimodal transcriptomic approaches (Figure 7). Which genes are dysregulated with advancing age? Can we enhance neurogenesis by manipulating gene expression to rejuvenate the aging DG? These data will provide a rich data resource for the field to truly understand the mechanisms underlying hippocampal aging.

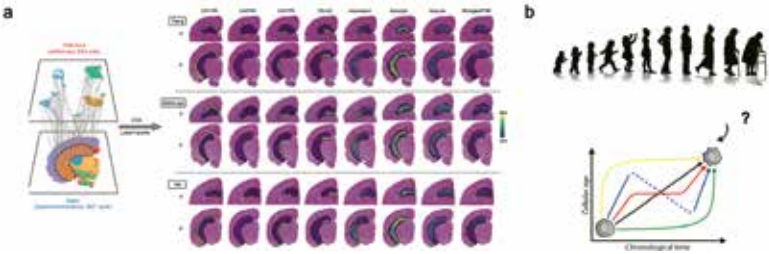


Figure 7. a. *scRNA-seq and spatially resolved transcriptomics aim to identify molecular changes in hippocampal gene expression across adult lifespan.* ***b.*** *Advancing time inevitably leads to a decline in organ and tissue function, resulting in a loss of physiological integrity and aging. However, the course of single cell aging remains poorly understood. The timepoint of initiation, rate, direction and constancy of single cell aging are largely unclear: cellular aging may progress linearly or exponentially with phases of stagnation. In future work, we aim to further our understanding of age-related changes in neural stem cell behavior and aging kinetics within the mammalian brain.*

Of particular interest are ongoing efforts to visualize and to record previous cellular experiences. For example, we generated a modified iCOUNT mouse (the miCOUNT, Denoth-Lippuner et al., 2021) that allows for much more detailed analyses of previous cell division events. Furthermore, we currently aim to develop sensors that will allow us to directly determine biological age or at least correlates of it directly in live tissues. Why is this important? Currently, it is not known whether cellular aging advances linearly or whether the progression fluctuates over time, with stages of stagnation or even rejuvenation events (Figure 7). Furthermore, it remains only poorly understood if individual cellular aging trajectories differ among different tissues within organisms. In the future, we will use a combinatorial approach of intravital imaging, single cell and spatial transcriptomics followed by genetic manipulations, and the development of novel live aging sensors, to determine the characteristics and trajectories of cellular aging in the brain.

The long-term goal of our research is to bridge the gap between the basic sciences and human disease, and to eventually use this knowledge to truly affect the diagnosis, prediction, or treatment of neuropsychiatric disease.

Without a doubt: the road to achieve this aim is long and winding. Translation from the bench to the bedside has been exceptionally hard and often disappointing in the neurosciences over the last decades. Thus, we are convinced that we still need to understand more of the fundamental principles underlying the life-long activity of stem cells and the processes regulating neurogenesis in the mammalian brain before we can successfully translate results to human disease.

Members of the laboratory *in June 2023 with MSc students, PhD students, and postdoctoral fellows from Switzerland, France, Italy, the Netherlands, Serbia, China, Ukraine, Colombia, Portugal, Canada, and Japan.*

Acknowledgments

I am very thankful and honored for receiving this prestigious award given by the Prof. Dr. Max Cloëtta Foundation. Since starting my own research group in Zurich in 2007 I have been blessed by outstanding students and postdocs – they did all the work. They not only spent long hours in the lab but their intellectual aptitude to ask questions, their ambition and curiosity, and their ideas are the driving force for the findings and discoveries we have made. I am very proud that most of my former lab members went on with the next steps in their scientific careers as postdocs and principal investigators in world-leading research institutions. Students and postdocs coming to Zurich from >15 countries certainly taught me more than I could teach them. I am extremely thankful for this wonderful group of current and former lab members.

I also want to thank my mentors Rusty Gage and Gerd Kempermann for years of advice, guidance, and friendship (even though I still blame them for the fact that I left the clinic to do full time research).

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THE CLOËTTA PRIZE 2023
IS AWARDED TO

PROFESSOR

CHRISTOPH HESS

BORN IN 1970 IN ZURICH, SWITZERLAND

PROFESSOR AND HEAD OF INTERNAL MEDICINE OF THE MEDICAL OUTPATIENT DIVISION, CLINICAL IMMUNOLOGY SERVICE, UNIVERSITY HOSPITAL BASEL, IMMUNOBIOLOGY LABORATORY AT THE DEPARTMENT OF BIOMEDICINE, UNIVERSITY OF BASEL AND SENIOR FACULTY AND PRINCIPAL INVESTIGATOR, ACADEMIC HEAD CLINICAL IMMUNOLOGY IN THE DEPARTMENT OF MEDICINE AT THE UNIVERSITY OF CAMBRIDGE

FOR HIS OUTSTANDING CONTRIBUTIONS TO BIOMEDICAL RESEARCH, ESPECIALLY IN THE FIELD OF IMMUNOMETABOLISM, AND FOR HIS INTEGRATION OF BASIC FINDINGS WITH CLINICAL HUMAN IMMUNOLOGY

BASEL, 24TH NOVEMBER 2023

IN THE NAME OF THE FOUNDATION BOARD:

THE PRESIDENT

THE VICE PRESIDENT

A MEMBER

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Education and employment history

1990–1996	Medical school Zurich and Lausanne & USMLE 1&2
1997–1999	MD PhD training, University of Basel
2000–2001	Clinical training: Internal Medicine, University Hospital Basel, BS
2001–2001	Clinical training: Imperial College, Hammersmith Hospital, London, UK
2002–2004	Fellowship, Massachusetts General Hospital/Harvard Medical School, USA
2004–2007	SCORE Fellow and specialist Registrar, University Hospital BS
2005	Junior faculty position, University of Basel
2007–6/2009	SNSF Professorship grant, University Hospital BS
2006	Diploma *Internal Medicine* (FMH)
2006	Diploma *Consultant Immunologist* (DGfI)

2007–2009	Consultant, Internal Medicine, University Hospital BS
Since 7/2009	Senior Faculty and Head, Internal Medicine, Outpatients, University Hospital BS
Since 2012	Lead – Clinical Immunology (primary immunodeficiency and autoimmunity)
Since 4/2019	Senior Faculty and Principal Investigator, Academic Head Clinical Immunology, University of Cambridge, Department of Medicine, UK (dual affiliation with University of Basel).

Approved research projects

Current only (PI unless stated otherwise)		
Wellcome Trust, 2020 (4 Co-PIs)	GBP	4.041.000
SNSF project grant, 2021	CHF	1.224.000
BBSRC PhD studentship grant, 2019	GBP	102.000
SNSF project grant, 2022	CHF	904.000
Uniscientia Foundation grant, 2021	CHF	298.000
Milner Consortium grant, 2022	GBP	950.000
NSMBF Project grant, 2023	CHF	80.000
BSI/CRUK Prime Funding, 2023	GBP	25.000

Teaching activities

Internal Medicine; Immunology – Faculty of Medicine, Basel University
Translational Medicine and Immunology – Faculty of Science, Basel University
Supervision of Masters-, MD-, MD-PhD- and PhD-students

Clinical activities

Outpatient: evaluation/treatment of patients with complex systemic autoimmune disorders and primary immune dysregulation and -deficiencies.

Inpatient: evaluation/treatment of patients across the spectrum of general internal medicine. *University Center for Immunology (initiated and established jointly with Alex Navarini):* Weekly interdisciplinary patient discussions.

Panels/boards/review activity
Head, Euro-Exchange Program for Residents (2010–2018)
Swiss Transplant Cohort Study – Scientific Board, since 2006
Novartis Foundation for Medical-Biological Research, since 2015
Goldschmidt-Jacobson Foundation, University of Basel (2014–2018)
University of Basel Research Board (2015-2018)
SNSF Research Council – Division 3, since 2018
Board of Reviewing Editors, Science, since 2021
Ad hoc reviewer activity for journals (selection): Science; Cell; Nature Immunology; Nature Cell Biology; Nature Communications; Immunity; Cell Metabolism; Cell Reports; Journal of Experimental Medicine; Journal of Clinical Investigation; European Journal of Immunology; EMBO Journal; FEBS journal; Trends in Immunology
Ad hoc reviewer for granting bodies: MRC, UK; Wellcome Trust, UK; Science Foundation Ireland; German-Israel Foundation for Scientific Research and Development; Kay Kendall Leukaemia Fund, UK; Tenovus Cancer Charity, UK

Memberships
Swiss Society of Internal Medicine (FMH) – full license to practice
General Medical Council, UK (Specialist Register) – full license to practice
Swiss Society of Allergy and Immunology
Swiss Transplantation Society
German Society of Immunology
Royal College of Physicians, UK
European Society of Immunodeficiency (ESID)
American Association of Immunologists
Fellow of the Royal College of Physicians (UK)
Member of the Swiss Academy of Medical Sciences

Fellowships, prizes/awards

Fellowships
SNSF MD PhD stipend (1997–99)
SNSF Advanced Postdoc mobility fellowship (2002–2004)
SNSF SCORE fellowship (2004–2006)
SNSF Professor fellowship (2007–2011)

Research
Faculty award 2001, MD-thesis, University of Basel
Pfizer Young Investigator award 2001
Swiss Transplant award 2006, 1st Prize
Dep. of Biomedicine 2013; best publication of the year
Cloëtta price 2023

Teaching
Since 2009: 7x *excellent teacher award* (selection by medical students)

Patents
IRP-mediated improvement of cell therapy (EP19192299.6)
LFA-1 signaling mediator for use in cancer therapy (EP20/191392.8)
Compositions for the Treatment of EBV Associated Diseases
or Conditions (EP 21161105.8 and PCT/EP2022/055647)
Non-canonical PHGDH-mediated improvement of cell therapy
(EP22163501.4)

SELECTED PUBLICATIONS

Ruffieux H., A. L. Hanson, S. Lodge, N.G. Lawler, L. Whiley, N. Gray, T.H. Nolan, L. Bergamaschi, F. Mescia, L. Turner, A. de Sa, V.S. Pelly; CITIID-NIHR BioResource COVID-19 Collaboration; P. Kotagiri, N. Kingston, J.R. Bradley, E. Holmes, J. Wist, J.K. Nicholson, P.A. Lyons, K.G.C. Smith, S. Richardson, G.R. Bantug, **C. Hess.** A patient-centric characterization of systemic recovery from SARS-CoV-2 infection. Nature Immunology 2023. 24:349–358.

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Balmer M. L., R. Epple, E. H. Ma, A. Egli, L. Bubendorf, K. Rentsch, A.-K. Woischnig, N. KhannaJ. Loeliger, J. Loetscher, P. Dehio, G. Perrin, J. D. Warncke, O. P. Schären, C. M. Schürch, G. Unterstab, A. Thompson, S. Hapfelmeier, R. G. Jones, **C. Hess.** Memory $CD8^+$ T cells balance pro- and anti-inflammatory activity by reprogramming cellular acetate handling at sites of infection. Cell Metabolism 2020. 32: 457–467.

Dimeloe S., P. Gubser, J. Loeliger, C. Frick, L. Develioglu, M. Fischer, F. Marquardsen, G. R. Bantug, D. Thommen, Y. Lecoultre, A. Zippelius, A. Langenkamp, **C. Hess.** Tumor-derived TGF-⊠ inhibits mitochondrial respiration to suppress IFN-⊠ production by human CD4+ T cells. Science Signaling 2019. 12, 599: eaav3334.

Burgener A.-V., G. R. Bantug, B. Meyer, R. Higgins, A. Ghosh, O. Bignucolo, E. H. Ma, J. Löliger, G. Unterstab, M. Geigges, R. Steiner, M. Enamorado, R. Ivanek, D. Hunziker, A. Schmidt, B. Müller-Durovic, J. Grählert, R. Epple, S. Dimeloe, J. Lötscher, U. Sauder, M. Ebnöther, B. Burger, I. Heijnen, S. Martínez-Cano, N. Cantoni, R. Brücker, C. R. Kahlert, D. Sancho, R. G. Jones, A. Navarini, M. Recher, **C. Hess.** SDHA gain-of-function engages inflammatory mitochondrial retrograde signaling via KEAP1–Nrf2. Nature Immunology 2019. 20, 1311–1321.

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METABOLIC REGULATION OF T CELL FUNCTION

Christoph Hess

Introduction

T cells are a key component of the adaptive immune system, acting as both coordinators and effectors of immunity. As such, T cells are instrumental in protecting the host from invading pathogens. The different stages of T cell activation, expansion and contraction are integrated with systemic inflammation and the control of microbial growth. However, when activated inappropriately – due to cell-intrinsic or cell-extrinsic factors – T cells contribute to a wide spectrum of diseases (1–5).

T cell metabolic reprogramming is crucial for the differentiation, proliferation and acquisition of effector functions. A key change in cellular metabolism in activated T cells is the upregulation of aerobic glycolysis (that is, the conversion of glucose-derived pyruvate into lactate under normoxic conditions). Although this is an energetically inefficient process, the engagement of aerobic glycolysis promotes the build-up of biochemical intermediates that are necessary for nucleotide, amino acid and fatty acid synthesis. Glycolytic metabolites and interlinked pathways, such as the pentose phosphate pathway and glycerol and amino acid synthesis pathways, as well as pyruvate usage, are essential for the proper functioning of activated T cells. Concomitant with changes in glucose metabolism, T cell activation also enhances mitochondrial biogenesis and oxidative phosphorylation (OXPHOS) and drives mitochondrial membrane hyper-polarization, amino acid uptake and glutaminolysis. Mitochondria, in addition to their primary role in generating ATP, play further key metabolic roles, such as in calcium buffering, the generation of reactive oxygen species (ROS), nitrogen metabolism or the fueling of cytoplasmic acetyl-CoA synthesis and lipogenesis. Each of these mitochondrial pro-

cesses is known – or is likely – to have links to T cell function. Metabolic pathway usage is subject to regulation on multiple levels, both intrinsic (for example, allosteric regulation of enzymes in a given pathway, such as inhibition of phosphofructokinase by ATP), and extrinsic in nature (for example, upregulation of glycolytic enzymes in proliferating cells receiving activating signals via stimulatory receptors). Key metabolic checkpoint kinases, such as mechanistic target of rapamycin (mTOR) and 5'-AMP-activated kinase (AMPK), integrate extrinsic signals and intracellular nutrient and energy abundance to initiate appropriate metabolic reprogramming (**Figure 1,** from (6)):

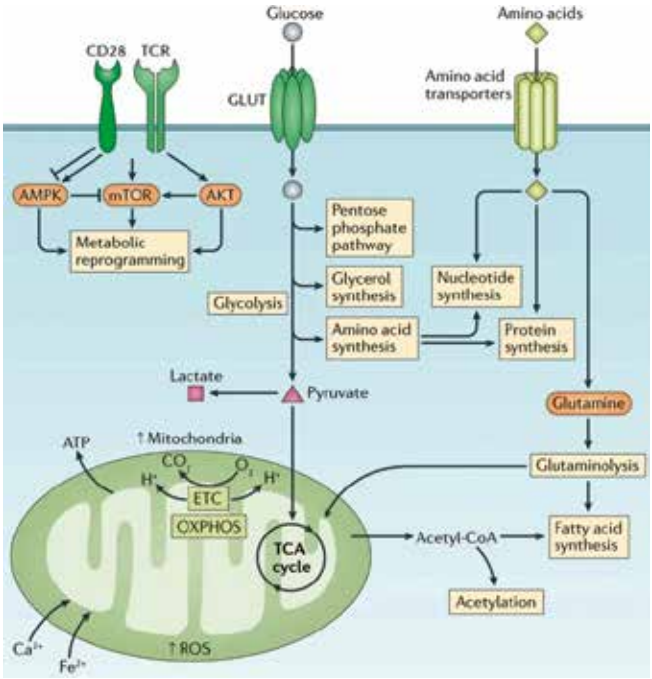


Figure 1. Metabolic changes that accompany effector T cell maturation. *Abbreviations: ETC, electron transport chain; GLUT, glucose transporter; TCA, tricarboxylic acid; TCR, T cell receptor.*

The metabolic requirements that support the pivotal rapid memory functionality have been a focus of our work. Here, I will summarize a few contributions we made over the years to the now burgeoning field of immunometabolism, covering basic, translational and clinical aspects.

Fundamental research into the metabolic regulation of T cells

Glucose and mitochondrial metabolism orchestrate effector T cell function

During acute viral infection, pathogen-specific naive $CD8^+$ T cells become activated, followed by clonal expansion and differentiation into cytotoxic effector cells (7). Resolution of infection triggers the contraction of effector cell populations, accompanied by the formation of a long-lived memory pool (8). In a highly coordinated process, memory $CD8^+$ T cells subsequently enhance host protection after secondary infection (recall response) (8).

Naive and memory $CD8^+$ T cells are metabolically quiescent cells, which depend mainly on OXPHOS as their energy source (9–11). Ligation of the T cell antigen receptor (TCR) and subsequent costimulation of quiescent cells initiates substantial changes in cellular metabolic pathway use (12). Upregulation of aerobic glycolysis (the Warburg effect) is an important feature of this metabolic adaptation and is a prerequisite for the growth and population expansion of $CD8^+$ T cells (13–15). Augmented glycolysis by proliferating cells is linked to enhanced glucose uptake and increased expression and activity of glycolytic enzymes, whereas glucose use via OXPHOS is decreased (16, 17). This 'metabolic switch' satiates higher energy demands and provides biochemical intermediates used in the biosynthesis of macromolecules (18).

The early recall phase of an immune response relies on antigen-experienced T cells that are able to acquire effector function with rapid kinetics (19). Effector memory (EM) $CD8^+$ T cells are specialized antigen-experienced lymphocytes that traffic between blood and non-lymphoid tissues (20–23). EM $CD8^+$ T cells are ideally positioned to rapidly respond and execute effector functions at sites of infection. We

found that EM CD8⁺ T cells have an immediate-early ability to take up and metabolize glucose in a sustained manner. Additionally, we demonstrated that co-stimulation via CD28 signaling was critical for sustaining the immediate-early glycolytic switch of EM CD8⁺ T cells (**Figure 2**).

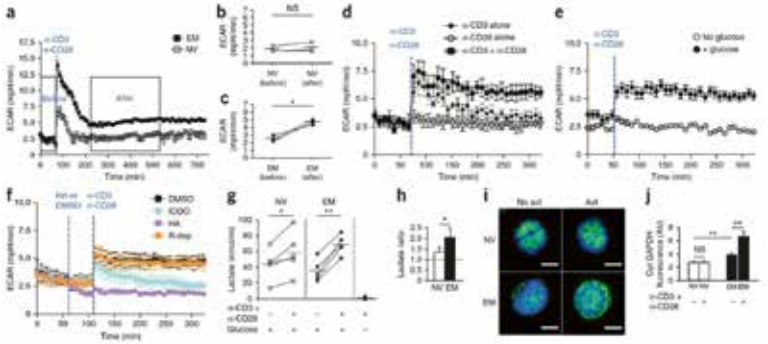


Figure 2. Memory CD8⁺ T cells are equipped with a preformed capacity to rapidly engage glycolytic activity. ***(a)*** *Extracellular acidification rate (ECAR; a measure of glycolysis) of naive and EM CD8⁺ T cells before and after 'in-Seahorse' activation with anti-CD3 (α-CD3) and anti-CD28 (α-CD28); boxes outline ECAR values used for calculation of means before and after injection.* ***(b,c)*** *Mean ECAR values before and after injection of anti-CD3 plus anti-CD28 onto plated naive CD8⁺ T cells* ***(b)*** *or EM CD8⁺ T cells* ***(c).*** ***(d)*** *ECAR of EM CD8⁺ T cells activated with anti-CD3 or anti-CD28 alone or the mAbs together (key).* ***(e)*** *ECAR of bulk CD8⁺ T cells activated with anti-CD3 and anti-CD28 in the presence of 10 mM glucose (+ glucose) or glucose-free medium (No glucose).* ***(f)*** *ECAR of bulk CD8⁺ T cells pretreated with dimethyl sulfoxide (DMSO) or the inhibitor (Inh) iodoacetate (IODO; inhibitor of the glycolytic enzyme Glyceraldehyde 3-phosphate dehydrogenase; GAPDH), heptelidic acid (HA; GAPDH inhibitor) or R-(−)-deprenyl hydrochloride (R-dep; MAO inhibitor, used as a control) before activation as in* ***e.*** ***(g)*** *Quantification of lactate in the medium of naive and EM CD8⁺ T cells (n = 5 donors) left nonactivated (−) or activated (+) with anti-CD3 plus anti-CD28 with or without glucose (bottom row).* ***(h)*** *Linear-regression analysis of the lactate concentrations in (g), presented as lactate in activated cells/lactate in nonactivated cells.* ***(i)*** *Microscopy of naive and EM CD8⁺ T cells left non-activated (No act) or activated (Act) for 2 h with anti-CD3 and anti-CD28: green, GAPDH; blue, DAPI. Scale bars, 3 μm.* ***(j)*** *Fluorescence intensity of cytoplasmic GAPDH in naive*

and EM CD8⁺ T cells left nonactivated (−) or stimulated (+) for 2 h with anti-CD3 plus anti-CD28; total cells: n = 30 (nonactivated naive), 43 (activated naive), 47 (nonactivated EM) or 70 (activated EM). Each symbol ***(b,c,g)*** *represents an individual donor; small horizontal lines indicate the mean. *P < 0.05 and **P < 0.001 (paired two-tailed Student's t-test* ***(b,c,g),*** *linear-regression analysis* ***(h)*** *or Mann-Whitney U-test* ***(j)****). Data are representative of three experiments* ***(a-d,i,j),*** *one experiment* ***(e),*** *four experiments* ***(f)*** *or five experiments* ***(g,h;*** *all one experiment per donor; mean and s.e.m. in* ***a,d-f,h,j).***

The rapid production of IFN-γ by EM naive CD8⁺ T cells but not by naive CD8⁺ T cells suggested differences in epigenetic regulation of the *IFNG* promoter. Increased glycolytic activity in proliferating cells decreases the cellular ratio of NAD^+ to NADH, which can affect epigenetic modifications, such as deacetylation mediated by NAD^+-sensitive class III histone deacetylases (17, 24). To determine the effect of immediate-early glycolysis on NAD^+/NADH, we assessed the concentration of NAD^+ and NADH in unstimulated EM CD8⁺ T cells and those activated with anti-CD3 plus anti-CD28. At 6 h after activation, there was only a small yet significant increase in NAD^+ concentration in EM CD8⁺ T cells **(Figure 2a).** Notably, NADH concentrations were very low or undetectable under nonactivating and immediate-early–activating conditions **(Figure 3a).** We detected substantial changes in the total NADH concentration and in NAD^+/NADH only in actively proliferating CD8⁺ T cells **(Figure 2a)** and in proliferating Jurkat human T lymphocytes (data not shown). Despite the small increase in NAD^+ early after activation, EM CD8⁺ T cells rapidly produced IFN-γ in a glycolysis-dependent manner (data not shown). Hence, the small increase in NAD^+ did not seem to have a functionally relevant effect on *IFNG* transcription. These findings also demonstrated that NAD^+/NADH in resting and nascently activated EM CD8⁺ T cells favored NAD^+, which emphasized a difference in the bioenergetic status of immediate-early activated CD8⁺ T cells and that of proliferating CD8⁺ T cells.

Histones are modified differently in the *IFNG* promoter in naive versus memory CD8⁺ T cells (25). Specifically, hyperacetylation of histone H3 Lys9 (H3K9) in the *IFNG* promoter of memory CD8⁺ T cells reflects an active chromatin conformation state (25). Additionally, in mouse CD8⁺ T cells, substantial chromatin remodeling (i.e., histone loss) takes place

in the promoters of *Gzmb* (which encodes granzyme B) and *Ifng* after activation, which facilitates binding of RNA polymerase II and gene expression (26, 27). It is well established that glycolysis provides substrates for histone acetylation (28); however, its effect on chromatin remodeling remains undefined. To determine the effect of immediate-early glycolysis on histone loss and modification in the *IFNG* promoter of nascently activated memory $CD8^+$ T cells, we assessed total histone H3 and acetylated H3K9 in proximal and distal regions of the promoter (positions -7, -382 and -4179 relative to the transcription start site) after activation. We observed a substantial loss of histone H3, indicative of rapid chromatin remodeling, in all three regions of the *IFNG* promoter in both naive and EM $CD8^+$ T cells after 6 h of stimulation with anti-CD3 plus anti-CD28 **(Figure 3b).** In the presence of 2-DG, loss of histone H3 at the *IFNG* promoter was abrogated in activated EM $CD8^+$ T cells **(Figure 3b),** which indicated a role for immediate-early glycolysis in chromatin remodeling. Under non-activating conditions, there was a greater abundance of acetylated H3K9 in all three *IFNG* promoter regions in EM $CD8^+$ T cells than in naive $CD8^+$ T cells **(Figure 3b),** reflective of the active state of *IFNG* promoters in memory $CD8^+$ T cells (25).

After activation, there was a marked decrease in detectable acetylated H3K9 in the *IFNG* promoter of both subpopulations **(Figure 3b).** The observed loss of acetylated histone H3 was in agreement with the lower total histone H3 content at the *IFNG* promoter of activated $CD8^+$ T cells. Notably, the abundance of acetylated H3K9 remained higher in activated EM $CD8^+$ T cells than in their activated naive counterparts **(Figure 2b),** which indicated that the IFNG promoter of activated EM $CD8^+$ T cells maintained an active chromatin conformation state. Finally, similar to the effect of 2-DG on histone H3 content, the abundance of acetylated H3K9 in EM $CD8^+$ T cells activated in the presence of 2-DG was similar to that of nonactivated control cells **(Figure 3b),** which again indicated the importance of immediate-early glycolysis in regulating the positioning of histone H3 in the *IFNG* promoter of activated memory $CD8^+$ T cells. Together these findings established that the diminished IFN-γ synthesis in EM $CD8^+$ T cells after blockade of immediate-early glycolysis was linked to the abrogation of chromatin remodeling in the *IFNG* promoter region and not to lower abundance of acetylated H3K9.

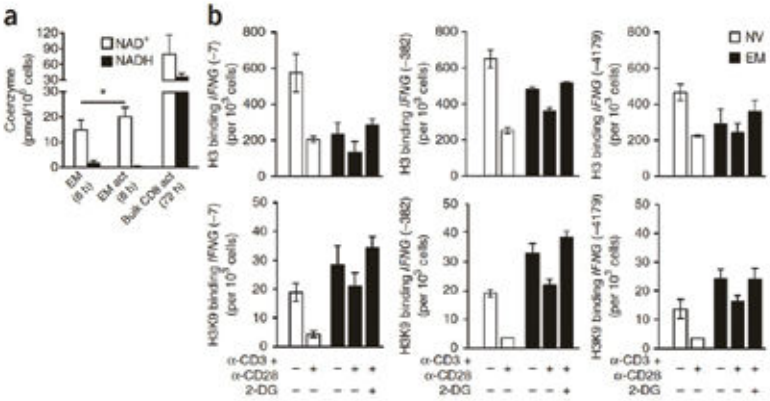


Figure 3. Metabolism interlinks with epigenetic remodeling in activated memory CD8⁺ T cells. ***(a)*** *NAD⁺ and NADH in EM CD8⁺ T cells (n = 5 donors) cultured for 6 h under nonstimulating conditions (left) or stimulated with anti-CD3 plus anti-CD28 (middle) or in bulk CD8⁺ T cells activated for 72 h (right). *P < 0.05 (paired two-tailed Student's t-test).* ***(b)*** *Chromatin-immunoprecipitation analysis of naive and EM CD8⁺ T cells left unstimulated or activated for 6 h with anti-CD3 plus anti-CD28 in the presence or absence of 2-DG, assessing the binding of histone H3 (top) or acetylated H3K9 (bottom) to the various regions of the IFNG promoter (vertical axes). Data are representative of five experiments (**a;** one donor per experiment; error bars, s.e.m.) or one experiment with cells pooled from three donors (**b;** error bars, s.d.).*

Together these data identified CD8⁺ memory T cells to have an 'imprinted' glycolytic potential required for efficient immediate-early IFN-γ recall responses. Conceptually the report was the first to link environmental signals, metabolic reprogramming and epigenetic adaptation in T cells (29).

We then interrogated the molecular and subcellular structural elements enabling enhanced glucose metabolism in nascent activated memory CD8⁺ T cells, and the molecular metabolic link between glycolysis and epigenetic remodeling. Glucose metabolism is tightly interlinked with mitochondrial function. How mitochondrial respiration in memory CD8⁺ T cells is altered early following activation remained largely un-

explored. Thus, we first examined respiration in non-activated versus nascent activated naive and EM human $CD8^+$ T cells, *in vitro*. As previously demonstrated, both maximal and spare respiratory capacities were greater in EM than in naive $CD8^+$ T cells under non-activated conditions **(Figure 4a)** Following activation, a noticeable increase in mitochondrial respiration was observed in activated EM $CD8^+$ T cells but not in naive counterparts **(Figure 4a).** Glycolysis was elevated in both activated $CD8^+$ T cell subsets, with EM cells displaying, as expected, a more prominent increase than naive cells (29).

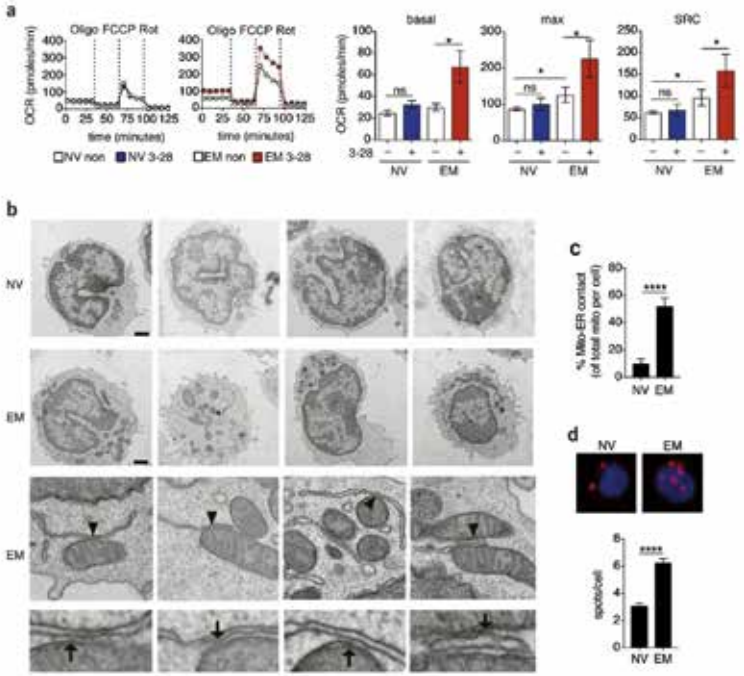
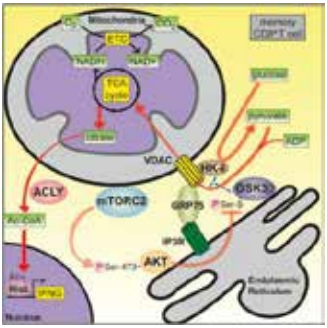


Figure 4. Effector memory CD8⁺ T cells selectively increase respiration upon activation and possess abundant mitochondria-associated ER membranes. ***(a)*** *Left, representative mitochondrial perturbation assays of naive (NV) and EM human CD8⁺ T cells left non-activated (non) or activated for 12 h with plate-bound α-CD3 and soluble α-CD28 mAb (3–28). Mitochondrial perturbation was performed by sequential treatment with oligomycin (Oligo), FCCP, and rotenone (Rot). Oxygen consumption rate (OCR) was measured by metabolic flux analysis. Right, summary bar graphs showing calculated basal respiration, maximal respiration (max), and spare respiratory capacity (SRC) in non-activated (–) or activated (+) NV and EM human CD8⁺ T cells.* ***(b)*** *Transmission electron microscopy images of NV (top) and EM (middle and bottom) human CD8⁺ T cells. Arrowheads mark mitochondria and ER contact sites that were digitally magnified in the bottom panel. Arrows show electron-dense regions of mitochondria-ER junctions. Scale bars, 1,000 nm.* ***(c)*** *Percentage of mitochondria-ER contact sites per cell in NV and EM human CD8⁺ T cells.* ***(d)*** *Top, representative proximity ligation assay (PLA) images of freshly sorted NV (left) and EM (right) human CD8⁺ T cells probed with*

*α-IP3R1 and α-VDAC1 antibodies. Red spots indicate contact sites between mitochondria (α-VDAC) and ER (α-IP3R). Cells were counterstained with DAPI (blue). Bottom, quantitative analysis of PLA from 3 donors. Data are presented as mean ± s.e.m. Two-tailed paired Wilcoxon signed rank tests (a) and two-tailed unpaired Student's t test (c and d) were used to compare groups. *P < 0.05, ****P < 0.0001, ns, not significant.*

Mitochondria-ER interactions have been shown to modulate mitochondrial respiration and bioenergetics in non-immune cells (30), although the molecular composition of mitochondria-ER tethering complexes in metazoans is not fully defined (31). In search of additional ultra-structural features that may offer a biologic basis for the contrasting activation-induced respiration phenotypes of naive versus EM $CD8^+$ T cells, we evaluated the abundance of mitochondria-ER contact sites in both subsets. We observed that in naive cells, mitochondria in close association to the ER were sparse (**Figure 4b,** top panel, and **Figure 4c**). In EM cells, by contrast, the frequency of mitochondria-ER contacts per cell was higher (**Figure 4b,** middle panels, and **Figure 4c**). The average distance between apposed ER and mitochondrial membranes in EM $CD8^+$ T cells was 21 nm (data not shown). Electron-dense zones between the mitochondrial outer membrane and ER at contact sites indicated that these organellar appositions were distinct subcellular structures (**Figure 4b,** bottom panel). To further elaborate on these findings, we performed proximity ligation assays (PLA) to quantify the abundance of mitochondria-ER junctions in naive and EM $CD8^+$ T cell subsets. Mitochondria-ER contacts were detected and enumerated by using α-VDAC1 (mitochondria) and α-IP3R1 (inositol triphosphate receptor 1, ER) antibodies as probes (32). Once again, the abundance of mitochondria-ER contact sites was found to be lower in naive cells compared to EM $CD8^+$ T cells **(Figure 4d).** In all, these data identified (a) a rapid increase in mitochondrial respiration as a distinct functional feature of EM $CD8^+$ T cells and (b) increased abundance of mitochondrial-ER contacts as a defining structural characteristic of EM $CD8^+$ T cells.

Downstream interrogation of the functional relevance and molecular composition of mitochondrial-ER contacts demonstrated that:



(i) mitochondrial respiration in newly activated memory T cells was intricately tied to their physical association with the ER
(ii) stable mitochondria-ER contacts support mTORC2-Akt-GSK3β signaling, which in turn allows recruitment of HK-I to mitochondria.
(iii) HK-I binding to VDAC in memory CD8⁺ T cells altered VDAC conductance, enabling metabolism of glucose-derived pyruvate in the mitochondria
(iv) pyruvate-derived citrate was key for generating acetyl-CoA by ACLY and subsequent histone acetylation ***(Figure 5)*** *from (33).*

Figure 5. Graphical summary of the structural and molecular underpinnings enabling rapid CD8+ T cell effector function.

Integration of organismal- and T cell intrinsic metabolism

Whether acutely altered organismal metabolism during acute infections impacts immune cell function by altering cell-intrinsic metabolism has not been explored. Systemic acetate release occurs in catabolic and metabolic stress conditions (34). Pathogen invasion triggers a series of defined innate defensive mechanisms and concurrent systemic catabolic metabolism (35). The hypothesis that catabolism *per se,* and the consequent availability of free acetate, might serve a specific function for host resistance to infection has not been experimentally explored. We found that acetate accumulates in the serum within hours of systemic bacterial infections **(Figure 6).**

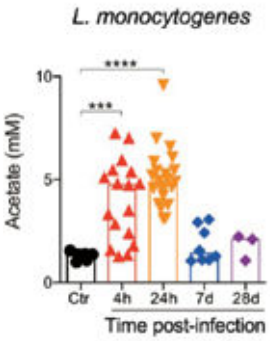


Figure 6. Acetate is an acute-phase metabolite. *Serum acetate concentrations following i.v. infection with 5,000 CFU Listeria monocytogenes. Each dot represents one mouse, bars indicate means of pooled data. One-way ANOVA was used to compare groups. ***P < 0.001, ****P < 0.0001.*

We thus went on and tested how raising acetate-levels from homeostatic to stress levels affected production of IFN-γ and interlinked glycolytic capacity in memory $CD8^+$ T cells. A notable increase in both glycolytic reserve and production of IFN-γ was observed in these experiments **(Figure 7).**

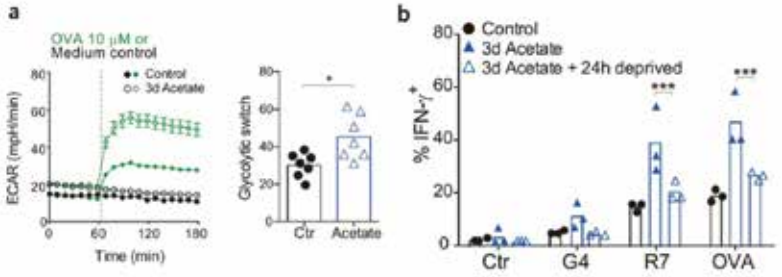


Figure 7. Acetate regulates glycolysis and interlinked effector function of memory CD8⁺ T cells. (a) *Left panel: Representative ECAR-measurements of control (filled symbols) and 3-day acetate-exposed (open-symbols) OT-I memory T cells, after injection of medium control (black) or OVA peptide (green) directly into metabolic flux analyzer (dashed line). Right panel: Glycolytic switch (mpH/min) was calculated by subtracting maximal ECAR from baseline ECAR-measurements in control (black dots) and 3 day acetate-exposed (blue triangles) OT-I memory T cells.* ***(b)*** *Percentage of IFN-γ positive OT-I memory T cells 4 h after re-stimulation with medium control (Ctr), or the APLs G4 and R7, or OVA peptide, determined by ICS. Cells were cultured in control medium (black dots) or acetate medium (5 mM) (filled blue triangles) for 3 days, and then switched back to control medium (open blue triangles) for 24 h. Each dot represents data obtained from cells isolated from one mouse, and bars indicate means of pooled data. Unpaired t test (a) and two-way ANOVA (b) were used to compare groups. *P < 0.05, ***P < 0.001.*

To gain a more detailed understanding of acetate metabolism in OT-I memory T cells, we performed tracing studies. These experiments showed that acetate contributed substantially to citrate and acetyl-CoA production and suggested the conversion of citrate to acetyl-CoA by ATP citrate lyase (ACLY). Inhibiting ACLY in OT-I memory T cells during acetate exposure using two different inhibitors blocked the acetate-mediated augmentation of IFN-γ production. In line with this, knockdown of *Acly* also reduced the capacity of OT-I cells to produce IFN-γ. Together these data indicated that acetyl-CoA, derived from the enzymatic conversion of citrate by ACLY, was key in mediating acetate-induced enhancement of memory T cell function (data not shown). In addition to co-regulating gene transcription via acetylation of histones, acetylation of most of the enzymes of the glycolytic pathway and the TCA cycle has been shown to occur, influencing enzymatic

activities via several proposed mechanisms (36). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is among the most abundantly expressed glycolytic enzymes across multiple tissues and a rate-limiting step of aerobic glycolysis (37, 38). In memory T cells, GAPDH regulates rapid IFN-γ production – as discussed above (29). We therefore aimed to assess whether GAPDH played a role in linking the increased cellular acetyl-CoA pool and IFN-γ production after acetate exposure. First, expression of GAPDH was re-assessed both at the mRNA and the protein level in OT-I memory T cells cultured for 3 days in acetate versus controls and confirmed to be similar **(Figure 8a).** Next we explored the possibility that exogenous acetate exerted a regulatory function on OT-I memory T cells by acetylation of GAPDH, thus increasing its catalytic activity (36, 39) Indeed, GAPDH functional activity was significantly increased in acetate-exposed cells **(Figure 8b).** This gain of function was not observed when garcinol, an inhibitor of acetyltransferases (40), was added to the cell culture during acetate exposure **(Figure 8b).** Lysates of acetate-exposed and acetate-deprived OT-I memory T cells were next probed by Western blot, using an acetylated-lysine-specific antibody. The most prominent band detected in OT-I memory T cells after 3 days of exposure to acetate was at the size of GAPDH (37 kDa) **(Figure 8c).** To formally test whether exposure of OT-I memory T cells to acetate resulted in acetylation of GAPDH, we analyzed immunoprecipitated GAPDH by mass-spectrometry. GAPDH was acetylated at lysine K217, a previously described acetylation site of murine GAPDH (41), in acetate-exposed OT-I memory T cells, but not in control cells **(Figure 8d).** In order to directly define the functional importance of acetylation at K217 for GAPDH function, we investigated enzymatic activity of GAPDH mutated at K217 (K→A). Despite providing non-limiting amounts of glucose and acetate, GAPDH functional activity was significantly lower in fibroblasts transfected with the GAPDH K217 mutant **(Figure 8e).** This reduced activity was also recapitulated in metabolic flux studies (data not shown). The requirement for acetylation to support GAPDH enzymatic activity was confirmed by deacetylation assays, using the bacterial de-acetylase CobB **(Figure 8e).**

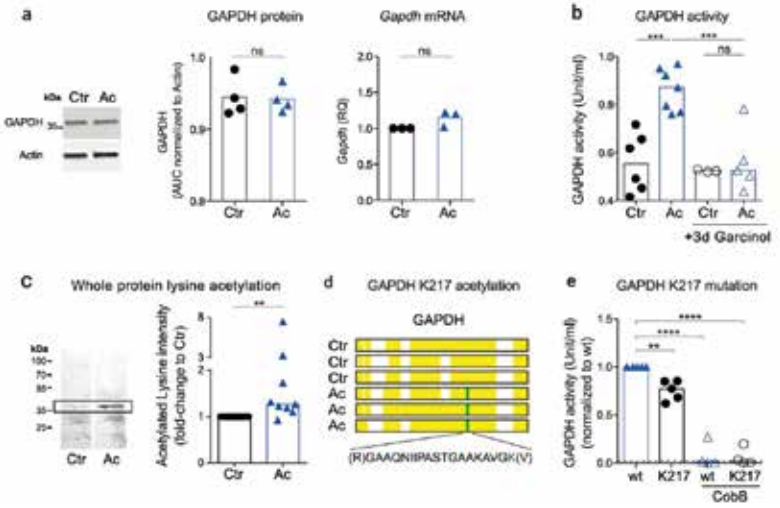


Figure 8. Acetylation of GAPDH regulates the enzymatic activity. ***(a)*** *Representative Western blot from whole-protein extracts of control (Ctr, black dots) and 3 day acetate-exposed (Ac, blue triangles) OT-I memory T cells, probed for GAPDH and Actin. GAPDH protein concentration was quantified and normalized to Actin (middle). Gapdh mRNA normalized to 18S and control memory cells, determined by RT PCR, are shown in the right panel.* ***(b)*** *GAPDH activity measured in cell lysates of control (Ctr, black dots) and 3-day acetate-exposed (Ac, blue triangles) OT-I memory T cells in the presence (open symbols) or absence (filled symbols) of 5 μM garcinol for 3 days.* ***(c)*** *Western blot analysis of whole-protein extracts of control and 3 day acetate-exposed OT-I memory T cells probed for acetylated-lysine. Left panel: representative blot; right panel: pooled data (Ctr, black dots; Ac, blue triangles). Bands were quantified and normalized to Actin and fold-change over control OT-I memory T cells determined.* ***(d)*** *GAPDH was immunoprecipitated in control and OT-I memory T cells exposed to acetate for 3 d, each. The figure represents detection of an acetylated peptide (K217) (green) in GAPDH among acetate-exposed but not control OT-I memory T cells. Yellow indicates coverage.* ***(e)*** *GAPDH activity in mouse fibroblasts transfected with wild-type (blue triangles) or K→A 217 mutated (black dots) GAPDH for 48–96 h. To test for overall acetylation-dependency of GAPDH activity, we treated cell lysates with the bacterial de-acetylase CobB (open symbols) or buffer control (filled symbols) for 1 h. Each dot represents data obtained from cells isolated from one mouse, bars indicate means of pooled data. One-way ANOVA (b) and (e), unpaired t test (a, protein), and Wilcoxon matched-pairs signed rank test (a, mRNA) and (c) were used to compare groups. **P < 0.01, ****P < 0.0001, ns = not significant.*

Lastly, building on these detailed molecular data we also investigated how T cell memory function related to the acetate-driven augmentation of GAPDH and the overall glycolytic activity in these cells. Both *in vitro* and *in vivo* acetate-augmented memory T cells were functionally superior to acetate-deprived counterparts (data not shown). A summary of the findings in this report are provided below **(Figure 9)** (42).

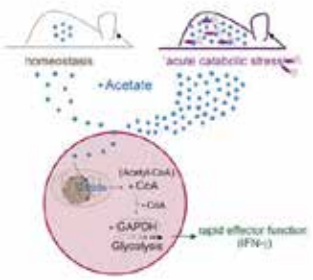


Figure 9. Graphical summary of how the organismal acute-phase acetate response is integrated at the cellular level in memory CD8⁺ T cells (from (42).

A path to clinical translation

Similar to acetate, also magnesium (Mg^{2+}) is an understudied component of the extracellular environment. Low dietary Mg^{2+} intake and hypomagnesemia have been implicated in the pathophysiology of various diseases, including infection and cancer (43–46). Only limited experimental data are available exploring how organismal Mg^{2+} abundance may affect the immune system. We recently found that the co-stimulatory cell-surface molecule LFA-1 requires Mg^{2+} to adopt its active conformation on $CD8^+$ T cells, thereby augmenting calcium flux, signal transduction, metabolic reprogramming, immune synapse formation and, as a consequence, specific cytotoxicity. Accordingly, magnesium-sufficiency sensed via LFA-1 translated to the superior performance of pathogen- and tumor-specific T cells and improved CAR T cell function (47) **(Figure 10):**

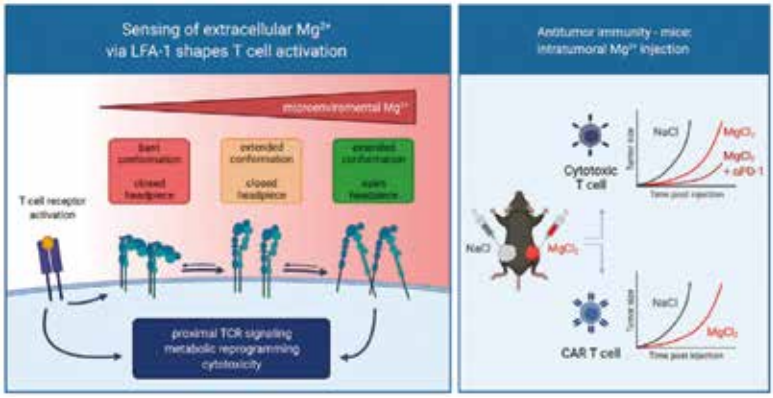


Figure 10. Graphical summary: mechanism of Mg^{2+} sensing by $CD8^+$ T cells and functional relevance of Mg^{2+} sufficiency (from (47).

This prompted us to retrospectively assess the relationship between serum Mg^{2+} levels and clinical outcomes in a CAR T cell trial and in an immune checkpoint inhibitor study. The CAR trial included a cohort of 100 patients with refractory B cell lymphoma treated with CD19-directed CAR T cells (Axicabtagene Ciloleucel), of which four had to be excluded from the retrospective analysis due to incomplete Mg^{2+}-serum testing. Patients were classified into two strata according to the mean Mg^{2+} level between days −5 and +3 of treatment (n = 5 measurements available for each patient). An arbitrary cut-off was set at 1.7 mg dl−1 for assigning patients into normo- versus hypomagnesemia groups **(Figure 11a,** *left panel*). Baseline characteristics of these retrospectively assigned study populations were similar, including age, ECOG performance status, and disease stage (data not shown). Although the number of patients with a mean Mg^{2+} level of <1.7 mg dl−1 was low, overall survival and median progression-free survival for these patients were reduced as compared with patients with normal serum Mg^{2+} levels **(Figure 11a,** *right panel*). We next explored how organismal Mg^{2+} abundance was associated with outcome in a cohort of non-small cell lung cancer (NSCLC) patients enrolled in an immune checkpoint inhibitor trial (SAKK16/14) (48). From a total of 67 initially

enrolled patients, two had to be excluded, leaving 65 that were treated with an anti-PD-L1 mAb (Durvalumab) in addition to neoadjuvant chemotherapy. Any detection of hypomagnesemia during the course of the trial assigned an individual to the hypomagnesemia group. This stratification strategy well discriminated the mean Mg^{2+} levels across all available measurements **(Figure 11b,** *left panel*). Also in this clinical trial, baseline characteristics were similar between the two retrospectively assigned groups (data not shown). Pathological complete response and overall survival **(Figure 11b,** *middle and right panels*), as well as radiographic response and event-free survival (data not shown) were all reduced in patients with hypomagnesemia. While these retrospective analyses have many limitations, in the context of our experimental data, the findings aligned with the concept that Mg^{2+}, by increasing LFA-1 outside-in signaling activity, may contribute to the clinical efficacy of CAR T cells and endogenous cancer-directed T cells in human patients. A prospective clinical trial is now being conducted.

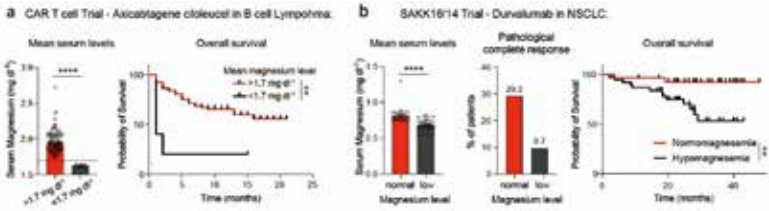


Figure 11. Serum magnesium levels and outcome in patients with cancer. (a) *Stratification of patients according to mean serum magnesium levels > 1.7 mg dl^{-1} versus <1.7 mg dl^{-1} between day −5 and day +3 of adoptive cell therapy, n = 5 measurements per patient (left panel). Each symbol represents one individual. Overall survival of patients stratified according to normal and low Mg^{2+} levels (right panel).* ***(b)*** *Comparison of mean serum magnesium levels after stratification according to occurrence of ≥1 hypomagnesemia-measurement during the trial (left panel). Complete pathological response (middle panel), and overall survival (right panel) according to this stratification. NSCLC, non-small cell lung cancer. Data are presented as median ± 95% CI left panel of (L and M). Statistical significance was assessed by unpaired Student's t test left panel of (a) and (b), and log-rank Mantel-Cox test in right panels of (a) and (b). **P < 0.01, **** P < 0.0001.*

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