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:

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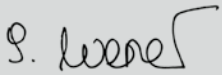

SEBASTIAN JESSBERGER

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).

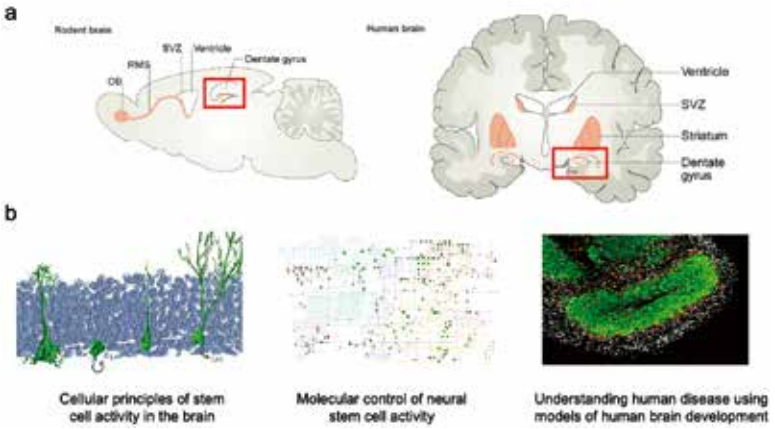

Figure 1. a. *Schematized view of a sagittal section through the mouse brain shows the two main neurogenic areas of the adult rodent brain. The focus of our work is on neurogenesis in the DG of the hippocampus (boxed). The schematic on the right side shows a coronal view of a human brain highlighting 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).

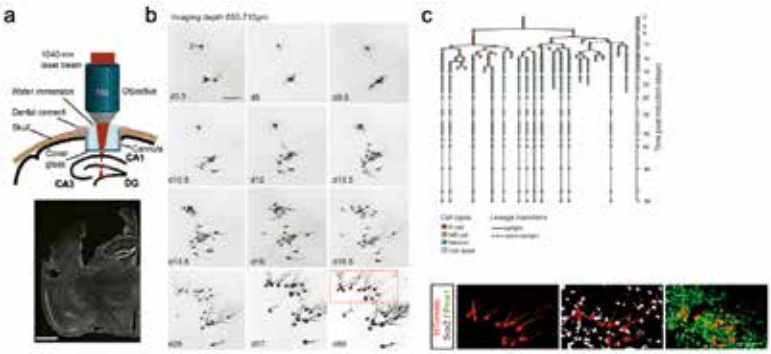

Figure 2. a. *Schematic illustrating the experimental approach allowing for chronic in vivo imaging of NSCs in the adult DG.* ***b.*** *Selected imaging time points of two NSCs (depicted with open and closed arrowhead) over the course of two months resulting in two neuronal clones. Note the clonal expansion 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).

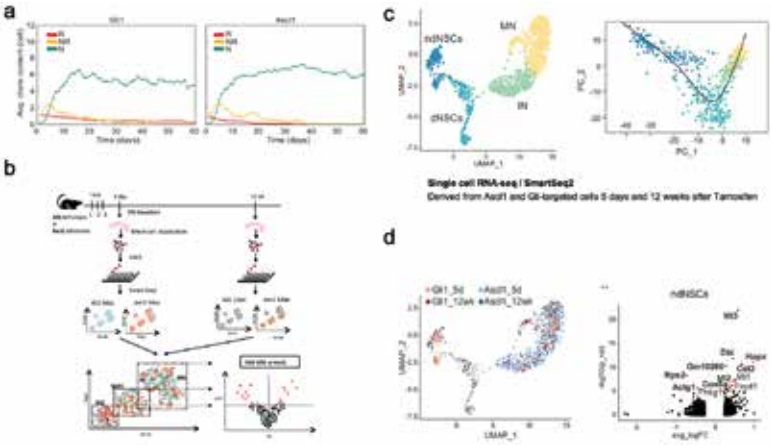

Figure 3. a. *Gli1-targeted NSCs show long-term self-renewal (shown is relative presence of NSCs, red, progenitors, yellow, and neuronal daughters, blue). In contrast, Ascl1-targeted cells rather enter a neurogenic burst upon activation.* ***b.*** *Schematic of scRNA-seq experiments to reveal single 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).

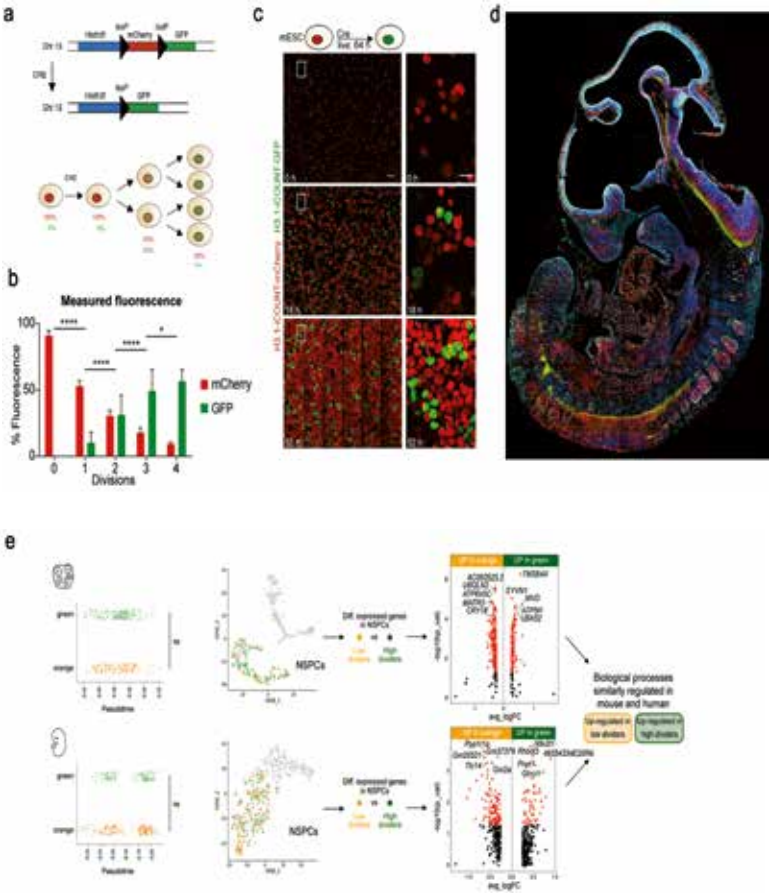

Figure 4. a. *Schematic of the iCOUNT approach (for details please refer to Denoth-Lippuner et al., 2021).* ***b-c.*** *Time-lapse imaging of proliferating mouse ESCs reveals accuracy of iCOUNT system. Not the switch from red to green-labeled histones upon Cre-based recombination.* ***d.*** *iCOUNT embryo 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.

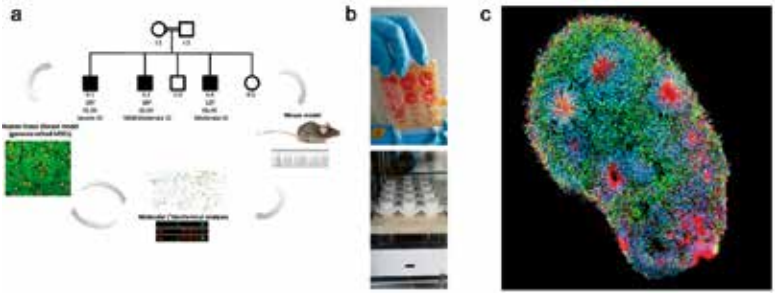

Figure 5. a. *Schematic of the comprehensive disease modeling approach we used to test the consequences of a human variant in the gene encoding for FASN, based on mouse genetics and genome-edited hESCs that were differentiated into forebrain organoids.* ***b.*** *Depiction of organoid technology used 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?

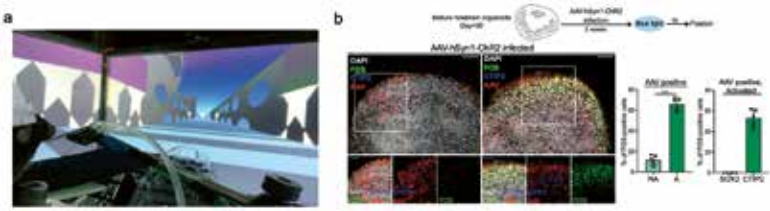

Figure 6. a. *Example of a mouse learning a hippocampus-dependent, virtual reality-based task while the activity of hippocampal neurons is measured using 2P microscopy.* ***b.*** *Cerebral organoids where optogenetic stimulation (mediated by viral infections with viruses (red) expressing Channelrhodopsin-2 (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.

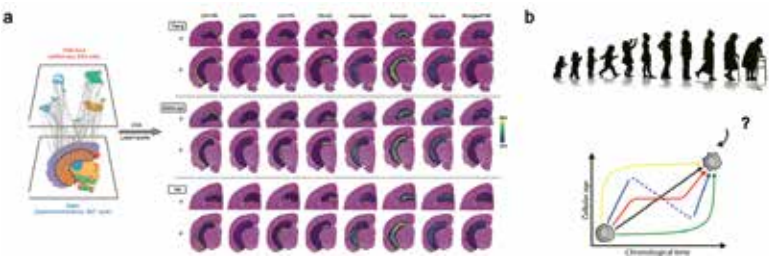

Figure 7. a. *scRNA-seq and spatially resolved transcriptomics aim to identify molecular changes in hippocampal gene expression across adult lifespan.* ***b.*** *Advancing time inevitably leads to a decline in organ and tissue function, resulting in a loss of physiological integrity and aging. However, 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.*

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