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Heft Nr. 45

Prof. Dr. Denis Jabaudon

«Fate and freedom in the developing neocortex»

Prof. Dr. Markus G. Manz

«Hematopoiesis – A paradigmatic stem cell supported organ system»

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VORWORT

Prof. Dr. med. Adriano Fontana

Mit **Prof. Dr. Denis Jabaudon** würdigt die Stiftung Professor Dr. Max Cloetta einen Neurowissenschaftler, welcher im Neurozentrum der Universität Genf die Mechanismen der Entwicklung neuronaler Netzwerke im Hirn untersucht. Insbesondere haben seine bahnbrechenden Studien zur Identifikation von Genen geführt, welche für die funktionelle Verknüpfung von Neuronen in der Hirnrinde und im Thalamus verantwortlich sind.

Der zweite Preisträger ist **Prof. Dr. Markus Manz,** welchem es in der Klinik für Hämatologie im Universitätsspital Zürich erstmals gelang, von Blutstammzellen ausgehend die Entwicklung von dendritischen Zellen des Immunsystems aufzuzeigen. Darüber hinaus hat er ein weltweit verwendetes Verfahren entwickelt, welches es in Mäusen erlaubt, die Entwicklung und Funktion des Immunsystems des Menschen zu untersuchen.

Wie bereits anlässlich der Verleihung des Cloetta-Preises 2016 hervorgehoben wurde, werden erneut zwei Wissenschaftler ausgezeichnet, deren hervorragende wissenschaftliche Beiträge mitunter durch von ihnen entwickelte technische Durchbrüche gelungen sind. Technik zum einen, Ideenreichtum, Scharfsinn, freudiges Beobachten und Experimentieren zum andern. Welche Kontraste zur immer mehr um sich greifenden postfaktischen Gesinnung und populistischen Meinungsäusserung, mit welcher die Wissensgesellschaft heute konfrontiert ist!

Mit der Verleihung des Cloëtta Preises wird die Leistung von Prof. Dr. Denis Jabaudon und Prof. Dr. Markus Manz gewürdigt. Die Cloëtta Stiftung freut sich, die Preisträger am 3. November 2017 in Zürich zu feiern.

Brigitt Küttel
Geschäftsführerin

Stiftungsrat

«Regierungsräte, Ständeräte und Richter dürfen im Kanton Glarus nicht älter als 65 sein. Jetzt soll diese Altersbeschränkung auf ihre Richtigkeit überprüft werden» (Quelle: Südostschweiz, 2.12.2016).

Nicht nur Gesetze, sondern auch die Statuten zahlreicher Stiftungen und anderer juristischer Personen sehen eine sog. «Altersguillotine» – welch schreckliches Wort! – und damit den zwingenden Rücktritt aus einem Gremium oder von einer Funktion bei Erreichen eines gewissen Alters vor. Wie sinnvoll eine solche Regelung ist, wird immer wieder diskutiert, verfügen doch Menschen in der dritten Lebensphase über einen prall gefüllten Rucksack an Know-how und Erfahrungen, mehr Zeit als während des aktiven Berufslebens und zudem häufig über die viel gerühmte Altersweisheit. Nun, auch die Stiftung Prof. Dr. Max Cloëtta hat eine solche Klausel in ihren Statuten, wobei wir uns zur Höhe der festgelegten Altersgrenze hier nicht äussern.

Dr. Peter Weibel, der seit 2012 sein profundes Wissen im Bereich Finanzen und Vermögensverwaltung der Stiftung zur Verfügung gestellt hatte, ist 2017 aus ebendiesem Grund aus dem Stiftungsrat zurückgetreten. Wir danken ihm herzlich für sein grosses Engagement und wünschen ihm ein paar erholsame zusätzliche Momente. Die UZH Foundation, die Dr. Weibel seit ihrer Gründung präsidiert, wird dankbar sein für die zusätzlich zur Verfügung stehende Zeit!

Mit Peter Ochsner konnte die Stiftung ein neues Mitglied gewinnen, das in über 30 Jahren bei PriceWaterhouseCoopers, als Finanzverantwortlicher der Zürcher Festspielstiftung und Verwaltungsrat der Banque Cantonale Vaudoise über ein enorm breites Wissen verfügt. Wir heissen ihn sehr herzlich willkommen und freuen uns auf die kommende Zusammenarbeit!

Cloëtta-Preis

Stiftungsrat und Geschäftsstelle freuen sich, auch dieses Jahr zwei herausragende Forscher mit dem Cloëtta-Preis auszeichnen zu können: Prof. Denis Jabaudon aus Genf und Prof. Markus G. Manz aus Zürich. Letzterer kann die verdiente Auszeichnung «zu Hause» entgegennehmen, denn wir dürfen wieder am UniversitätsSpital Zürich zu Gast sein. An dieser Stelle bedanken wir uns herzlich bei den Verantwortlichen der Universität und ihrem Vertreter in unserem Stiftungsrat, Prof. Dr. Fritjof Helmchen, für ihre Unterstützung.

Die Geschichte zeigt übrigens, dass unsere Stiftung immer wieder Forschende auszeichnet, die später auch zu noch höheren Weihen als dem Cloëtta-Preis kommen. Mit den Professoren Susumu Tonegawa (1978) und Rolf Zinkernagel (1981) erhielten zwei Cloëtta-Preisträger später den Nobel-Preis für Medizin. Dieses Jahr erhielt Professor Michael Hall, unser Preisträger 2003, den Preis der in New York ansässigen Albert and Mary Lasker Foundation. Der Lasker-Preis gilt als eine der höchsten Auszeichnungen in der biomedizinischen Forschung.

Herzlichen Glückwunsch allen Preisträgern!

Forschungsstellen

Die Research Positions 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 selbstständig arbeitende Forscherinnen und Forscher bis max. 40 Jahre. Mit diesem Programm will die Stiftung einem Mangel an Forschernachwuchs in der Schweiz entgegenwirken und den Stelleninhabern helfen, die manchmal nicht einfache Phase bis zur Berufung auf eine ordentliche Professur zu überbrücken. Die Stipendien werden alle zwei Jahre vergeben, das nächste Mal wieder 2018.

2017 finanzierte die Stiftung Prof. Dr. Max Cloëtta folgende Forscher an Schweizer Universitäten mit fünfjähriger Unterstützungsperiode:

Dr. Mathias Hauri-Hohl, 1975, Universitäts-Kinderspital Zürich, Abteilung Stammzelltransplantation. Projekt: «Improving T-Cell Reconstitution and Enhancing Central Tolerance Mechanism in Hematopoietic Stem Cell Transplantation». Unterstützungsdauer: 1.1.2016–31.12.2020

Dr. Alexandre Theocharides, 1975, Universitätsspital Zürich, Klinik für Hämatologie. Projekt: «The Role of Cell-Extrinsic Factors in Hematopoietic Stem Cell Malignancies». Unterstützungsdauer: 1.6.2015–31.5.2020

Dr. Wei Lynn Wong, 1976, Universität Zürich, Institut für experimentelle Immunologie. Projekt: «The Role of IAPs and RIPKs in Hematopoiesis and Disease, Specifically in Tumor Formation and Metastasis». Unterstützungsdauer: 1.1.2016–31.12.2020

Mit dreieinhalbjähriger Unterstützungsdauer:

Dr. Grégory Verdeil, 1976, Universität Lausanne, Abteilung für fundamentale Onkologie und Ludwig Cancer Centre. Projekt: «Finding and characterizing new targets to overcome T-cell exhaustion for immunotherapy of cancer». Unterstützungsdauer: 1.8.2017–31.1.2021

Dr. Francesca Siclari, 1980, Universitätsspital Lausanne, Zentrum für Schlafforschung (CIRS). Projekt: «The Neural Correlates of Consciousness in Sleep Disorders». Unterstützungsdauer: 1.11.2017–30.4.2021

Dr. Britta Maurer, 1976, UniversitätsSpital Zürich, Klinik für Rheumatologie und Zentrum für eperimentelle Rheumatologie. Projekt: «Early diagnosis in disease monitoring of systemic autoimmune disorders with molecular targeted imaging». Unterstützungsdauer: 1.11.2017–30.4.2021

Klinische Medizin Plus

Seit 2010 vergibt die Stiftung Prof. Dr. Max Cloëtta in Zusammenarbeit mit der Uniscientia Stiftung, Vaduz, die Stipendien «Klinische Medizin Plus». Medizinerinnen und Mediziner 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. Die Uniscientia Stiftung finanziert das Programm, der Stiftung Prof. Dr. Max Cloëtta obliegt die wissenschaftliche Verantwortung. Ende 2015 wurde der Vertrag über diese erfolgreiche Zusammenarbeit um weitere drei Jahre bis und mit 2018 verlängert.

2017 kommen folgende Medizinerinnen und Mediziner in den Genuss eines Stipendiums (Unterstützung läuft oder wurde 2017 zugesprochen):

Dr. med. Bigna Buddeberg Bichsel, 1981, Honorary Fellow, Dept. of Cardiology, Barts Health Trust, London. Combined clinical and research fellowship in Obstetric Anaesthesia. Guest Institution: St. George's University Hospital, London. 1.4.16–31.3.17.

Dr. med. Anna Hirschmann, 1978, Section Head Musculoskeletal Radiology, Universitätsspital Basel. Dynamic ankle and knee joint MR imaging using LiveView sequence. Guest Institution: New York University, New York 1.12.16–31.3.17.

Dr. med. Flurina Saner, 1984, Registrar, Unispital Basel. Analysis of Clincal and genetical characteristics in longterm survivors with ovarian cancer. Guest Institution : Peter MacCallum Cancer Centre, Melbourne, 1.1.17–31.12.17.

Dr. med. Arseny Sokolov, 1986, Clinical and research fellow (chef de clinique), Universitätsspital Lausanne. Technology-based therapeutic approaches for cognitive neurology. Guest Institution: University of California, San Francisco, USA 1.9.17–31.8.18.

Zusammen mit dem Team der Geschäftsstelle freue ich mich, die Stiftung Prof. Dr. Max Cloëtta auch weiterhin in eine aktive Zukunft für die Förderung der medizinischen Forschung in der Schweiz begleiten zu dürfen. Dem Stiftungsrat, der Uniscientia Stiftung, unseren Stipendiatinnen und Stipendiaten und den medizinischen Fakultäten danken wir herzlich für die jederzeit sehr angenehme Zusammenarbeit.

THE CLOËTTA PRIZE 2017
IS AWARDED TO

PROFESSOR

DENIS JABAUDON

BORN IN 1971 IN VEVEY, SWITZERLAND
DIRECTOR OF THE NEUROCENTER OF THE UNIVERSITY
OF GENEVA

FOR HIS GROUND BREAKING FINDINGS ABOUT GENETIC
MECHANISMS GOVERNING ASSEMBLY AND
FUNCTIONAL INTEGRATION OF CORTICAL AND THALAMIC
NEURONS INTO NEURONAL CIRCUITS

Zürich, 3rd November 2017

IN THE NAME OF THE FOUNDATION BOARD:

THE PRESIDENT

THE VICE PRESIDENT

MEMBER

Denis Jabaudon

BIOGRAPHY

Name: Jahuadon, Denis
Date of Birth: 30th January 1971
Place of Birth: Vevey, Switzerland

Education

1989–1995	Medical School	University of Lausanne
1996–1999	MD-PhD Scholar	Brain Research Institute University of Zürich

Positions

1999–2004	Neurology Residency	Lausanne and Geneva University Hospitals
2004–2008	Postdoctoral Fellow	Harvard Medical School Boston, Massachusetts, USA
2008–2009	Junior Research Fellow (Chef de Clinique Scientifique)	Dept. of Basic Neurosciences University of Geneva
2008–	Attending Physician	Clinic of Neurology Geneva University Hospital
2009–2015	SNSF Assistant Professor	Dept. of Basic Neurosciences University of Geneva
2015–	Full Professor	Dept. of Basic Neurosciences University of Geneva

Denis Jabaudon obtained his MD-PhD degree at the Universities of Lausanne and Zurich in Switzerland, where he studied mechanisms controlling synaptic transmission in the laboratory of Prof. Beat Gähwiler. After a neurology residency at Geneva University Hospital, he completed a postdoctoral fellowship at Harvard University, in the laboratory of Prof. J. Macklis, where he began investigating the genetic mechanisms controlling cortical development.

He is currently a professor at the University of Geneva, Switzerland, since 2009, where he has his independent research group, and also practices as a clinical neurologist at Geneva University Hospital.

His work on the genetics of neuronal circuit assembly during cortical development has earned him several prestigious prizes, including the Freedman Prize for Exceptional Basic Research from the Brain and Behavior Research Foundation (NARSAD), the Pfizer Research Prize, and the Bing Prize from the Swiss Academy of Medical Science. Prof. Jabaudon is currently the Director of the Geneva University Neurocenter; he is a member of the FENS Kavli Network of Excellence and his work is funded by the Swiss National Science Foundation (Project and Consolidator Grants) and the Brain and Behavior Research Foundation.

Work in the Jabaudon laboratory is aimed at understanding how genetic and input-dependent mechanisms interact to control neuronal circuit assembly during development. The approaches his team uses to address these questions include the isolation and genetic characterization of single forebrain neurons subtypes, in vivo genetic manipulations during development and optogenetic interrogation of developing circuits.

The long-term aim of his research is to understand how altered environmental conditions and abnormal gene expression interact to lead to circuit miswiring and behavioral changes in neurodevelopmental and psychiatric disorders.

SELECTED PUBLICATIONS

1. Jabaudon D. Fate and freedom in developing neocortical circuits. Nature Communications 2017. doi: 10.1038/ncomms16042. Review.

2. Frangeul* L, Pouchelon* G, Telley* L, Lefort S, Luscher C, Jabaudon D. A cross-modal genetic framework for the development and plasticity of sensory pathways. Nature 2016, 538: 96-98. doi: 10.1038/nature19770. *equal contributors.

3. Telley* L, Govindan* S, Stevant I, Prados J, Dermitzakis E, Nef S, Dayer A, Jabaudon D. Sequential transcriptional waves direct early neuronal differentiation in the mouse neocortex. Science 2016; 351(6280):1443–6. doi: 10.1126/science.aad8361. *equal contributors.

4. Pouchelon G, Golding B, Bellone C, Gambino F, Lüscher C, Holtmaat A, Jabaudon D. Modality-specific thalamocortical inputs instruct the identity of postsynaptic L4 neurons. Nature 2014; 511(7510): 471–474. doi: 10.1038/nature13390

5. Golding B, Pouchelon G, Bellone C, Di Nardo A, Lüscher C, Shimogori T, Dayer A, Jabaudon D. Retinal activity directs the recruitment of inhibitory interneurons into thalamic visual circuits. Neuron 2014; 81(5): 1057–69. doi: 10.1016/j.neuron.2014.01.032

6. De La Rossa A, Bellone C, Golding B, Moss J, Toni N, Lüscher C, Jabaudon D. In vivo reprogramming of circuit connectivity in postmitotic neocortical neurons. Nature Neuroscience 2013; 16(2): 193–200. doi: 10.1038/nn.3299

FATE AND FREEDOM IN THE DEVELOPING NEOCORTEX

Denis Jabaudon

Summary

The activity of neuronal circuits of the neocortex underlies our ability to perceive the world and interact with our environment. During development, these circuits emerge from dynamic interactions between cell-intrinsic, genetically determined programs, and input/activity-dependent signals, which together shape these circuits into adulthood. Over the past decade or so, technological developments have progressively allowed us to interrogate these nature-nurture interactions with single gene / single input / single cell resolution. In this review, I will discuss some of the genetic and input-dependent mechanisms controlling how individual cortical neurons differentiate into specialized cells to form neuronal circuits and highlight, when appropriate, the contributions we made to this global effort. This monograph is closely adapted from a review I recently published on this topic (Jabaudon 2017).

Introduction

The neuronal circuits of the neocortex underlie our ability to perceive the world and conduct meaningful interactions with our surroundings. Neocortical circuits, through their activity, account for processes such as sensory perception and integration, sensory-motor transformation, motor planning and execution, long-term memory, and attention. These circuits are formed by a diversity of specialized neuronal subtypes, which can be distinguished from each other by anatomical, morphological, physiological, hodological (i.e. relating to connectivity) and genetic features.

Neocortical circuits are both robust and flexible: they reliably carry out complex repetitive tasks, yet are also able to modify the execution of these tasks in response to context and previous experience. To accommodate the seemingly opposing constraints of reliability and plasticity, at least two main driving forces are at play during development: (1) *genetically determined processes*, which act within single cells and allow the generation and differentiation of a core set of specialized neuronal cell types, and (2) non cell-autonomous, *input/activity dependent processes*, which act during critical periods of development to refine these neurons into further subtypes, allowing neural circuit diversification and context-dependent expansion of the behavioral repertoire. Balance between these intrinsic developmental programs and external signals is essential for the proper differentiation and assembly of neurons into circuits, yet the dynamic contribution of these two types of processes to cortical development remains unclear.

Over the past decade or so, my laboratory has been interested in teasing out how genetic and circuit-derived factors bidirectionally interact during development to give rise to the neuronal and circuit diversity found in the adult neocortex. In the current monograph, which is closely transcribed and adapted from a review I recently published on this topic (Jabaudon 2017), I will first provide an introduction on the cerebral cortex and its cellular diversity, then introduce how different types of input modulate cortical neuron differentiation. Throughout this narrative, as per the tradition of the Max Cloëtta Series, I will highlight some contributions of my laboratory to the understanding of these processes.

The neocortex is organized in layers and areas

The neocortex consists in a thick sheet of neurons which covers the surface of both hemispheres in mammals (**Fig. 1**). As introduced above, this structure is the place where sensory inputs converge to generate our conscious perception of the outside world, and where voluntary motor actions are planned and initiated. The neocortex is radially organized into layers, which each are enriched in specialized subtypes of neurons, and tangentially organized into areas, which specialize in diverse sensory, motor, and associative functions (**Fig. 1**). There are six main layers in the neocortex, which have historically been defined by distinct densities of neuronal somas, dendrites and axons. These laminae are not only anatomical landmarks, but actually consist of developmentally and functionally distinct subtypes of glutamatergic neurons (**Fig. 1**) (Jabaudon 2017; Molyneaux et al. 2007; Harris and Shepherd 2015).

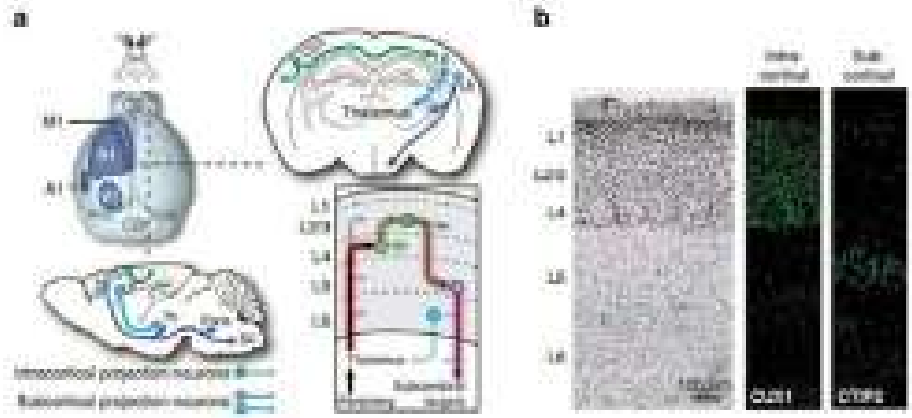

Figure 1: Areal and laminar organization of the neocortex. *(a) Schematic representation of the distinct primary cortical areas in the mouse, and cell-type specific connectivity of cortical projection neurons. A1: primary auditory cortex, CB: Cerebellum, M1 primary motor cortex, S1: primary somatosensory cortex, SC: spinal cord, Th: Thalamus, V1: primary visual cortex. (b) Laminar organization of the neocortex (S1). CUX1 specifically labels intracortical projection neurons while CTIP2 labels corticospinal neurons in layer (L) 5. Taken from Jabaudon, 2017.*

The deepest cortical layers contain neurons whose axons target subcortical structures such as the thalamus (corticothalamic neurons, layer (L) 6) and the tectum, hindbrain and spinal cord ("corticospinal" neurons, L5). In contrast, neurons located more superficially in layers 2 and 3

(L2/3), and 4 (L4) have intracortical axonal targets. Neurons in L4 (also called the "granular layer") differ from the neurons present in other layers in that they are locally-projecting glutamatergic interneurons, i.e. they do not send long-range projections. They are the main targets of neurons in exteroceptive sensory thalamic nuclei (i.e. which receive input from the sense organs) (Petreanu et al. 2009; Erzurumlu, Murakami, and Rijli 2010; Vitali and Jabaudon 2014), and, as such, form the principal sensory gateway to the neocortex. L4 neurons are particularly sensitive to impairments of the sensory organs or their input pathways; as will be discussed in detail later, this is particularly striking in the rodent somatosensory cortex. Within this cortical area, whisker-input receiving L4 neurons are clustered into distinct cellular assemblies called "barrels", which each receive input from a single principal whisker, and are somatotopically distributed such that neighboring barrels receive input from neighboring whiskers (Vitali and Jabaudon 2014; Erzurumlu, Murakami, and Rijli 2010; Pouchelon and Jabaudon 2014). As will be discussed below, in several of my laboratory's research projects, we are taking advantage of the exquisite sensitivity of L4 neurons to input to study the role of activity-dependent signals in neuronal differentiation and circuit formation (see e.g. Pouchelon et al. 2014; Frangeul et al. 2014; Rossa et al. 2013).

In addition to excitatory glutamatergic neurons, the neocortex contains another population of neurons, which are inhibitory, use another transmitter, GABA, and are born from distinct germinal zones (i.e. proliferative regions where progenitor are located) than excitatory neurons (see below). The diverse populations of GABAergic interneurons play a pivotal role in the gating and spread of cortical signals through processes such as feedforward inhibition, dis-inhibition and feedback inhibition.

Cortical areas

Layers are not homogenous across the rostro-caudal and latero-medial extent of the neocortex. Instead, local cytoarchitecture varies in an often discontinuous way across the tangential surface of the cortex, defining distinct cortical areas. Histological discontinuities are particularly striking in species with large cortices, and form the basis of the classical Brodmann classification of cortical areas (Zilles and Amunts 2010).

Each cortical area is reciprocally connected with a defined subset of inputs from the thalamus, a structure which relays inputs from the different sense organs (e.g. skin mechanoreceptors, retinal photoreceptors, auditory cells in the cochlea, Fig. 2a). Frontally-located cortical areas are connected with frontally-located thalamic nuclei, including those involved in motor planning and execution, while parieto-occipital and temporal cortical areas are interconnected with more posterior thalamic nuclei, and are involved in sensory perception and integration (López-Bendito and Molnár 2003; Clascá, Rubio-Garrido, and Jabaudon 2012). Delineations between individual cortical areas are particularly sharp in areas receiving input from exteroceptive thalamic nuclei, such as the primary somatosensory, visual, and auditory cortices. Because of their characteristic cytoarchitectural features, these primary sensory areas, and particularly the primary somatosensory (S1) and visual (V1) areas have been extensively used as model systems to study the role of input on cortical differentiation. As a consequence, our understanding of thalamocortical organization and information flow is largely based on the connectivity of primary sensory areas, and particularly somatosensory and visual areas, (Frangeul et al. 2016; Kral 2013). However, these areas only represent a small fraction of the total cortical surface, and different connectivities and information flow exist in other cortical areas and thalamic nuclei, as will be detailed in the next section. A significant part of the work in my laboratory has focused on trying to better characterize the relationship between primary exteroceptive regions and secondary, associative regions, and on trying to understand how input acts to shape secondary regions into primary ones, as discussed later in the text (see e.g. Pouchelon et al. 2014; Frangeul et al. 2016).

Cortical information flow

Sensation starts with detection of stimulus through activation of peripheral receptors, such as skin mechanoreceptors or retinal photoreceptors. Input from these receptors reaches neurons located in exteroceptive, "first order" thalamic nuclei such as the ventrobasalis nucleus (VB, for tactile stimuli), the dorsolateral geniculate nucleus (LG, for visual stimuli), and the ventral medial geniculate nucleus (vMG, for auditory stimuli). Sensory information then reaches primary sensory areas of the neocortex,

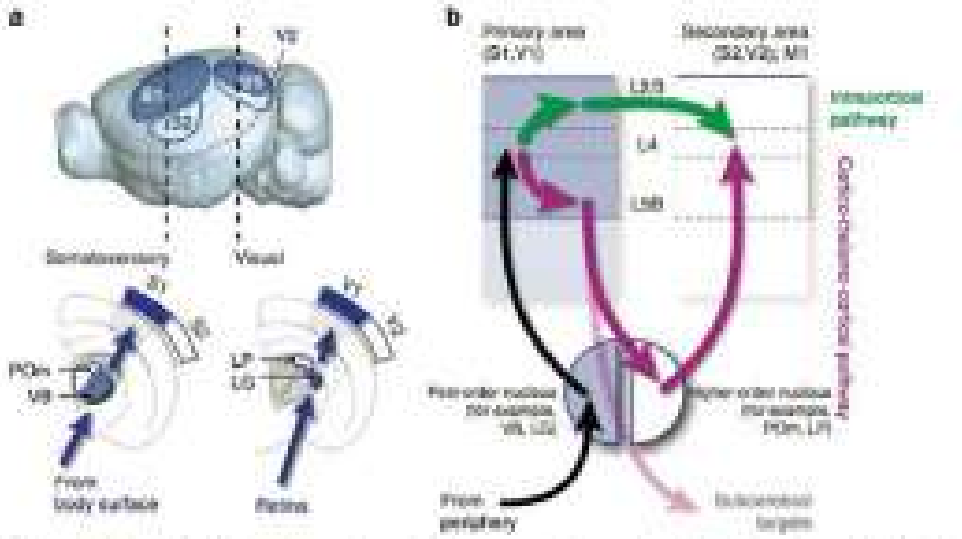

Figure 2: Cortical information flow. *(a) Extroceptive, first-order thalamic nuclei VB, LG (filled in blue) project to primary cortical areas (S1, V1). Higher order thalamic nuclei and secondary cortical areas are outlined in blue. POm: posteromedial thalamic nucleus; LG: dorsolateral geniculate nucleus; LP: lateroposterior nucleus; VB: ventrobasalis nucleus. (b) Two distinct pathways allow inter-areal communications: an intracortical pathway (green) and a cortico-thalamo-cortical pathway (purple), originating from L5B cortico-pinal neurons and which transits through higher-order thalamic nuclei. Taken from Jabaudon, 2017.*

where core stimulus properties are perceived, and is then forwarded to secondary sensory (e.g. S2 and V2) and associational areas where stimulus features are dynamically and multi-modally processed **(Fig. 2a)**.

Within primary sensory areas, first order nuclei project particularly strongly onto L4 neurons, which act as the main entry point of extracortical input (Vitali and Jabaudon 2014). From L4 neurons, information is then split into two parallel streams **(Fig. 2b)**: a "classical", intracortical stream, and a more recently characterized extracortical stream. In the intracortical stream, signals are sent to distinct subtypes of L2/3 intracortical neurons, which project to specific sets of cortical areas, including S2, V2, and M1; in the other, cortico-thalamo-cortical stream, L4 signals are sent to infragranular L5B neurons, which send top-down projections to non-exteroceptive, "higher-order" thalamic nuclei (posteromedial nucleus (POm), from S1; lateroposterior nucleus or pulvinar (LP) from V1), and dorsal medial geniculate nucleus (dMG), from A1). Higher-order

thalamic nuclei in turn project to L4 neurons of secondary sensory (i.e. S2, V2) areas, thus closing a cortico-thalamo-cortical loop (Theyel, Llano, and Sherman 2010; Guillery and Sherman 2002). Higher-order thalamic nuclei do not project exclusively to secondary sensory areas but instead have diffuse connections across many cortical areas (Clascá, Rubio-Garrido, and Jabaudon 2012). As such, they may be involved in the coordination of activity across motor and somatosensory cortices during active sensing, as occurs when mice sweep their whiskers back and forth to generate a tactile representation of their environment.

Interestingly, these two main inter-areal communication pathways have distinct evolutionary histories, since supragranular intracortical projection neurons are a novel acquisition of mammals. In the absence of such intracortical projections, diffuse cortico-thalamo-cortical circuits may have been the main pathway allowing different cortical regions to communicate with one another, as might still be the case in reptiles. Based on results to be discussed below (Pouchelon et al. 2014; Frangeul et al. 2016; Frangeul et al. 2014), we have proposed that by providing a novel pathway to direct information to specific brain areas, supragranular intracortical projection neurons in mammals may have allowed the untethering of cortical function from input-output thalamocortical loops, and emergence of stimulus-dissociated, integrative neocortical functions.

Development of the neocortex

The processes allowing the emergence and functional specialization of cortical circuits start with the genesis of neurons from progenitors and extend into adulthood through experience-dependent developmental processes. Genetic, cell-intrinsic processes, and input/activity-dependent processes thus both play a role in shaping cortical circuits. While input-dependent processes classically occur at later developmental stages, activity and environment are likely to play important roles even early during differentiation, as suggested by recent, unpublished data from our laboratory showing that the bioelectric properties of neuronal progenitors affect their division modes and the type of neurons that they produce. This finding would support earlier findings in which input-dependent controls over progenitor proliferation via thalamocortical afferents oc-

curs, which could in principle contribute to area-specific differences in cytoarchitectures and cell types (Dehay et al. 2001; Rakic, Sußer, and Williams 1991; Zechel, Nakagawa, and Ibáñez 2016).

During embryogenesis, the diverse subtypes of neurons that form cortical circuits are born from a pool of progenitors located deep within the brain, underneath the developing cortex. The neurons that form the distinct layers of the neocortex are sequentially born within two main germinal zones between E10.5 and E18.5 in the mouse: the ventricular zone (VZ) of the dorsal pallium, which gives rise to excitatory glutamatergic neurons (Molyneaux et al. 2007), and a parcellated ventral pallial VZ, including the medial and caudal ganglionic eminences and pre-optic area, which gives rise to distinct subtypes of cortical inhibitory GABAergic interneurons.

Glutamatergic neurons migrate radially into the cortex from the pallial VZ, which they populate in an inside-out manner **(Fig. 3)**. During early corticogenesis (until about E10.5 in mice), VZ progenitors initially self-amplify (at this stage, they are called neuroepithelial cells), and then begin giving rise directly to neurons (at this stage they are referred to as "radial glia"). As corticogenesis proceeds, "direct" neurogenesis decreases; instead, VZ progenitors increasingly generate intermediate progenitors (transit amplifying cells, also called basal intermediate progenitors), which accumulate between the VZ and the developing cortical plate to form an additional germinal zone, the subventricular zone (SVZ), from which most L2/3 neurons are thought to be born (Lui, Hansen, and Kriegstein 2011; Pontious et al. 2008) **(Fig. 3)**.

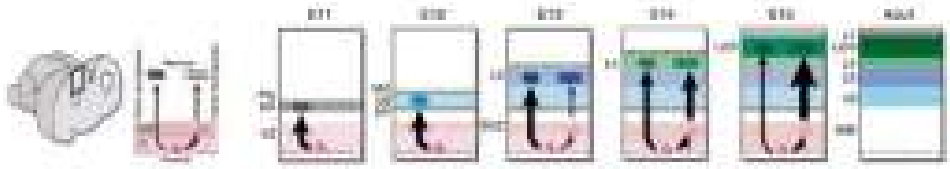

Figure 3: Neurogenic sequence during corticogenesis. *The neocortex is built in an inside-out manner in which neurons born from deeply located germinal zone migrate past earlier-born neurons to reside in more superficial layers. Note that initially, the preplate (PP) is split into a subplate (SP) and superficially located marginal zone (MZ) by incoming L6 neurons, such that early-born neurons are later found in L1. Direct neurogenesis from the ventricular zone (VZ) predominates at early developmental stages, while indirect neurogenesis from the subventricular zone (SVZ) progressively increases during corticogenesis. MZ: marginal zone; PP: preplate; SP: subplate. Taken from Jabaudon, 2017.*

Cortical size depends on the net balance between amplifying divisions, which give rise to new progenitors, and differentiative divisions, which give rise to postmitotic neurons (Florio and Huttner 2014; Dehay and Kennedy 2007). Indirect neurogenesis increases the final number of neurons by amplifying the progenitor pool. This is thought to be a critical step in gyrification, the process through which the neocortex becomes folded in some mammals. This process allows an increase in cortical surface and neuron number within the confined volume of the cranium. The increase in cortical size is particularly striking in supragranular layers (i.e. L2/3), suggesting that cortico-cortical connections increase disproportionately compared to subcortical connections in gyrencephalic species.

An area of intense research is whether fate-restricted VZ progenitors exist (i.e. progenitors which can only give rise to a subset of cortical neurons, as is seen in subpallial proliferative zones), or whether there is a single progenitor type whose competence progresses throughout development (Franco et al. 2012; Eckler et al. 2015). This question has been difficult to investigate because it requires assessing the progeny of single progenitors with clonal resolution in vivo. Progenitors can sequentially give rise to distinct molecularly-defined neuronal cell types in vitro (Gaspard et al. 2008; Shen et al. 2006), and classical transplantation experiments in ferrets support the notion that progenitors can acquire the competence to generate normally later-born, but not earlier-born neurons (McConnell and Kaznowski 1991). Interestingly, this question of the neurogenic plasticity of cortical progenitors has not been reassessed with modern molecular tools and has only been examined in the ferret. The extent to which this principle is generalizable, and the mechanisms at play, remain thus largely unexplored.

The presence of DNA mosaicism in postmitotic neurons, likely resulting from DNA rearrangements immediately following mitosis, represents an additional potential source of neuronal functional diversity (Lodato et al. 2015). Such mosaicism may contribute to inter individual differences in cell types, circuits and behavior, and may be relevant to the broad spectrum of psychiatric disorders. If clinically relevant, diagnosis of such conditions will be challenging since causal mutations are only present in affected neurons and would not be detected by classical methods of DNA

collection, such as buccal swabs or blood samples. In a recent study to be described below, we have identified an increase in an enzyme which repairs DNA damage shortly after cell division, providing additional support for a substantial amount of mosaicism in the developing neocortex (Telley et al. 2016).

Neocortical neuron specification and migration

Once neurons are born, they still have to migrate and mature (i.e. develop their characteristic morphological, molecular and synaptic features). Several transcription factors control the differentiation and function of specific neuronal subpopulations of cortical neurons (Molyneaux et al. 2007), some of which I have contributed to characterize during my postdoctoral fellowship (Lai et al. 2008; Jabaudon et al. 2011). These include FEZF2 (Molyneaux et al. 2005; Chen et al. 2005) and CTIP2 (Arlotta et al. 2005) for L5B corticospinal neurons, and SATB2 for intracortical projection neurons (Alcamo et al. 2008; Britanova et al. 2008). While the initial events that control acquisition of neuron-type specific features following mitosis remain poorly characterized, we have recently shown that early neuronal differentiation is directed by a series of transcriptional waves whose sequence is critical for normal progression through development, as will now be detailed (Telley et al. 2016).

The distinct types of neurons that compose the neocortex have different connectivities but also different transcriptional signatures. While all excitatory neurons are born from progenitor cells located in the ventricular zone, below the cortex, the mechanisms that control the generation and differentiation of distinct neuronal cell types from progenitors are overall poorly understood. A main limitation in understanding these processes has been the inability to identify and isolate pure progenitor / early postmitotic cells, since the ventricular zone is a highly heterogeneous and dynamic region. To circumvent these limitations, we have developed a technology we called FlashTag that enables the isolation and visualization of neurons at the very moment they are born. Using this approach, we have identified transcriptional programs controlling neuronal differentiation (Telley et al. 2016). Upon FlashTag injections into the ventricular space, dividing progenitors are tagged with a fluorescent marker that persists in

their progeny, based on the fact that they undergo mitosis in contact with the ventricular wall (**Fig. 4**). Thus, nascent cohorts of simultaneously-born neurons can be labeled and isolated for transcriptional analysis using single-cell RNA sequencing (Telley et al. 2016) (**Fig. 5**). Using this approach, we identified and functionally characterized neuron-specific primordial transcriptional programs as they dynamically unfolded (**Fig. 6**). Our results revealed early transcriptional waves that instruct the sequence and pace of neuronal differentiation events, guiding newborn neurons toward their final fate. Beyond its contribution to the understanding of early neuronal differentiation events, this work potentially provides a genetic road map to be used for the reverse engineering of specific classes of cortical neurons from undifferentiated cells.

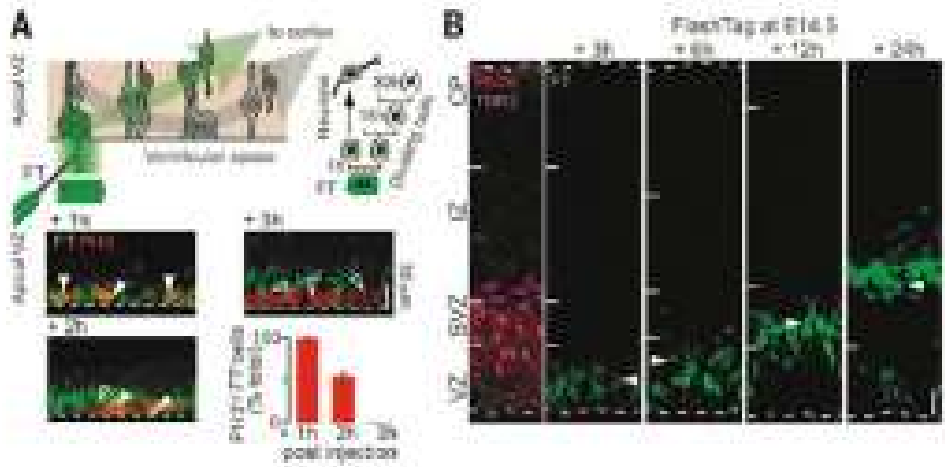

Figure 4: FlashTag (FT) labels time-locked cohorts of newborn cells during corticogenesis. *(A) (Top) Schematic representation of the labeling principle. (Bottom) Pulse-labeling of isochronic mitotic cells using FT at E14.5. PH3, phospho-histone 3, an M-phase marker. (B) Isochronic cohorts of FT positive cells radially migrate from the VZ to the cortex. PAX6 and TBR2 delineate the VZ and SVZ. CP: cortical plate; Cx, cortex; IZ, intermediate zone. Taken from Telley et al., 2016.*

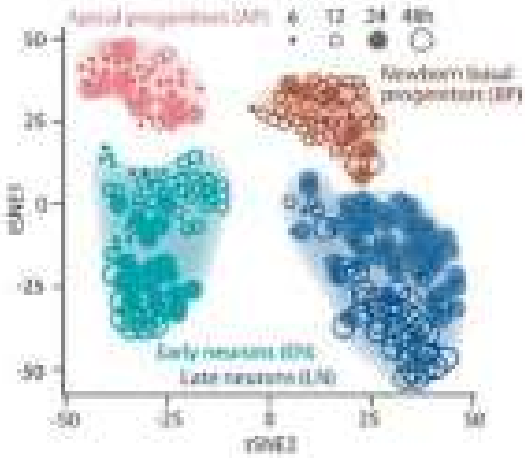

Figure 5: Identification of newborn cortical neurons. *Apical progenitors, daughter basal progenitors, and newborn neurons can be distinguished by unbiased clustering using their transcriptional signatures, obtained through single-cell RNA sequencing. Taken from Telley et al., 2016.*

Figure 6: Real-time functional transcriptomics of early postmitotic neurons in vivo. *(A) Genetically-identified neurons are staggered by age along a pseudotime axis, based on their transcriptional similarities. (B) Gene expression dynamics for classical proliferative (Sox2), neurogenic (Neurog2), and neuronal (Tbr1) genes can be identified using this pseudotime alignment. Note for example that Neurod2 is expressed more strongly and earlier than Tbr1, which enables newborn neurons to be identified at earlier time points than previously possible. QR code, http://genebrowser.unige.ch/telley2016, for access to dynamics of all transcripts. Taken from Telley et al., 2016.*

Reprogramming postmitotic neurons

Manipulating gene expression in cortical progenitors can modify their competence to generate specific subtypes of neurons (Molyneaux et al. 2007), but whether neurons can be post-mitotically reprogrammed remained, until recently, unknown. To address this question, in a study published a few years ago (De la Rossa et al. 2013), we sought to reprogram L4 neurons of the mouse neocortex, which receive input connections from the thalamus, into L5B cortical output neurons. For this purpose, we used a gene delivery technique developed in the laboratory (De la Rossa and Jabaudon 2015), which enables rapid expression of select transgenes in postmitotic neurons *in vivo*, to ectopically express a transcription factor specific to layer 5B output neurons, *Fezf2*, into postnatal L4 neurons. *Fezf2* was an ideal candidate to act as an identity switch, because it is both necessary and sufficient to generate L5B neurons during development. Using a combination of *in vivo* and *ex vivo* approaches, including optogenetic interrogation of the reprogrammed circuits, we demonstrated that *Fezf2*-expressing L4 neurons acquire the cardinal molecular, morphological, physiological, and input/output circuit properties of L5B output neurons. A remarkable feature of the reprogrammed cells was that they integrated existing circuits at the correct location (i.e. as expected for normal, naturally *Fezf2*-expressing cells), which we could demonstrate using cell-type specific optogenetic circuit interrogation (**Fig. 7**). These findings are interesting because they provided a proof-of-principle for the postnatal re-engineering of neuronal circuits *in vivo*, demonstrating for the first time that gene expression dynamically controls the circuit identity of cortical neurons. Furthermore, they revealed a previously unsuspected level of plasticity in postmitotic neurons, which has also been found in other cortical cell types (Roumax and Arlotta 2013). Thus, following mitosis, neuronal fate becomes progressively restricted rather than irreversibly switched.

The cellular and molecular mechanisms controlling neuron migration from the VZ to the cortex have been well described, in particular with regard to the migration along radial glia processes and the critical role of extracellular Reelin (Tissir and Goffinet 2003). However, the cell-type specific processes controlling final laminar location remain poorly understood. From mid-corticogenesis on, there appears to be a tight rela-

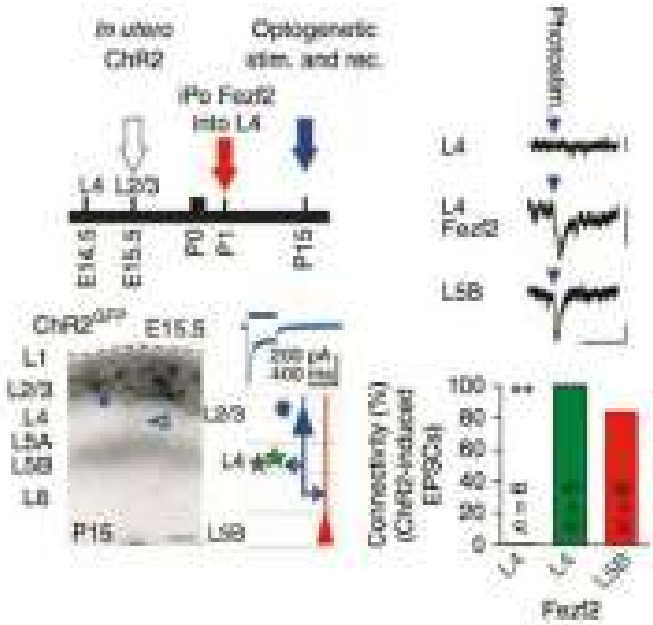

Figure 7: In vivo interrogation of the circuit integration of reprogrammed neurons. *L2/3 neurons are born after L4 neurons, and normally receive unidirectional projections from these cells (i.e. they do not project back to L4 neurons). In contrast, L5B neurons receive input from L2/3 cells. Using optogenetic stimulation of L2/3 cells (through in utero electroporation of channelrhodopsin, ChR2, into L2/3 cells at the time of their birth), the connectivity between L2/3 cells and L4 cells, Fezf2-expressing L4 cells, and L5B cells, can be interrogated. Results show that reprogrammed Fezf2-expressing L4 cells receive L2/3 input, as L5B cells normally do. Taken from De la Rossa et al, 2007.*

tionship between date of birth and laminar position, since VZ-born isochronic neurons align along a narrow sublamina in L4 and L2/3, but at earlier stages, we recently obtained data suggesting that the relationship between date of birth and precise laminar location is less strictly determined (Telley et al. 2016). The mechanisms underlying a more stringent control over laminar location (and perhaps cell type identity) are unknown, and may relate to non-cell autonomous, input-dependent factors, including arrival of thalamocortical afferents, which may act to synchronize progenitor cell behavior (Dehay et al. 2001).

In addition to cell-intrinsic genetic programs and extracellular molecular gradients, activity-dependent processes also control neuronal migration. This has been demonstrated for the tangential migration and differen-

tiation of specific populations of GABAergic interneurons (De Marco García, Karayannis, and Fishell 2011). These cells can be recruited to specific target regions in an input-dependent manner, as shown both in the neocortex (De Marco García et al. 2015) and in the thalamus (Golding et al. 2014), providing an input-dependent mechanism for homeostatic regulation of circuit excitability. In the visual thalamus (i.e. dLGN), we showed that input from the retina is critical for GABAergic interneurons to migrate to their proper location and integrate into circuits (Golding et al. 2014). In this absence of this input, or upon disruption of retinal waves, which are critical for circuit assembly, interneurons mismigrate, resulting in an overall hyperexcitable circuit. This process may represent a homeostatic mechanism to compensate for decreased external inputs. Interestingly, a similar process seems to be at play in the neocortex, where we found that S1 becomes hyperexcitable upon loss of VB input (Pouchelon et al. 2014).

Compared with GABAergic interneurons, early stages of differentiation of glutamatergic excitatory neurons appear to be less dramatically affected by activity. Interestingly, cortical lamination appears to proceed largely normally in the absence of vesicular neurotransmitter release (Washbourne et al. 2002), or in the absence of input/output neocortical connectivity (Zhou et al. 2010), although the morphology and connectivity of neocortical neurons is likely to be affected. Supporting this possibility, chronic hyperpolarization of intracortical projection neurons and thalamic neurons affects axonal elongation and arborization (Mire et al. 2012; Mizuno, Hirano, and Tagawa 2010; Rodríguez-Tornos et al. 2016), and sensory input affects interhemispheric connectivity (Suárez et al. 2014).

Role of input in cortical neuron differentiation

Since the entry point of specific types of thalamic inputs into the cortex coincides with the presence of distinctive cytoarchitectural features (e.g. barrels in S1), a lot of effort has gone into understanding the cellular and molecular mechanisms through which input affects cortical neuron differentiation. This is a topic of particular interest in the laboratory (**Fig. 8**), and this question has been particularly well studied in S1 and

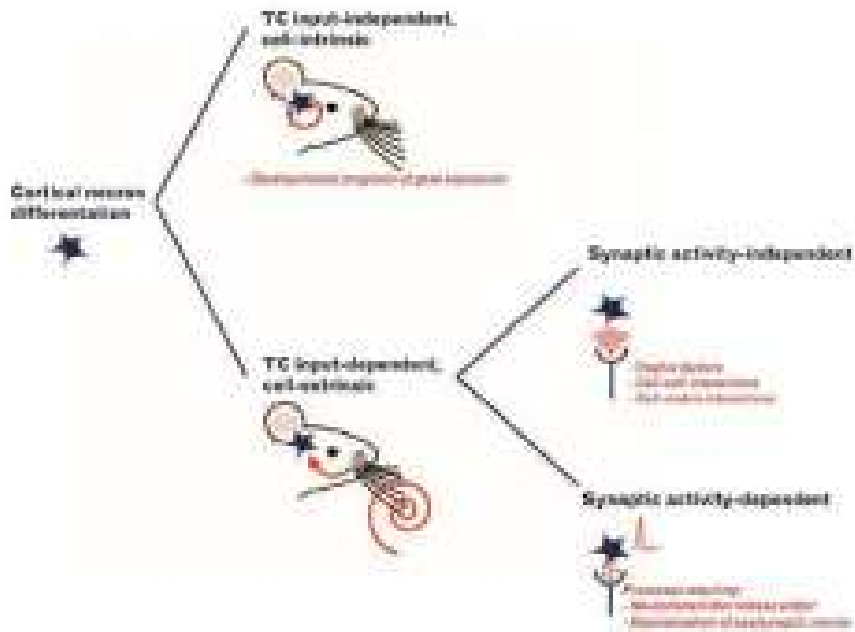

Figure 8: Potential controls over cortical neuron differentiation.

V1. Within these sensory areas, there is a topographical representation of the sensory periphery on the cortical surface, whereby neighbouring neurons respond to activation of neighbouring peripheral receptors, and where densely innervated regions occupy proportionally large regions of the cortical representation. This topographical layout is called somatotopy in S1, retinotopy in V1 and tonotopy in A1.

In S1, the input dependence of these maps was originally studied by lesioning sensory input pathways, such as by section of the infraorbital nerve, which conveys input from the whiskers, or by follicle cautery. These approaches consistently lead to impaired barrel pattering, with shrinkage/disappearance of injured whisker representations and expansion of remaining ones (Fox and Wong 2005; Van der Loos and Woolsey 1973).

These results, however, cannot unambiguously be ascribed to purely developmental mechanisms, since injury-related processes such as axonal sprouting or neuronal death may be at play. To circumvent these limitations, pharmacological attempts have been made to manipulate sensory input, but dose-dependent effects and lack of specificity limit the inter-

pretation of these studies. More recently, manipulations of neuronal activity with cell-subtype specificity together with transcriptional analysis have enabled a better understanding of the molecular and cellular mechanisms that control the assembly of neuronal maps. These studies have shown that synaptic release of glutamate from the thalamocortical axons is required for the assembly of L4 neurons into barrels and dendritic polarisation towards these axons, in particular via activation of NMDA receptors and metabotropic glutamate receptors (López-Bendito and Molnár 2003). In addition, several transcription factors, which we have contributed to identify and include Npas4, Zbtb20 function to polarize L4 dendrites towards incoming VB axons in S1(Pouchelon et al. 2014; Wang et al. 2017; Shetty et al. 2013), and Btbd3 has a similar role in V1- (Matsui et al. 2013).

To study the role of input in cortical neuron differentiation, we developed a genetic mouse model in which VB thalamic neurons, which normally innervate L4 neurons in S1, degenerate shortly after birth, such that the latter cells do not receive their normal thalamic input (Pouchelon et al. 2014) **(Fig. 9)**. Under these circumstances, S1L4 neurons acquired the molecular properties of L4 neurons in associative regions, i.e. in this case S2. A similar process occurs in the visual system (Chou et al. 2013; Vue et al. 2013; Pouchelon et al. 2014). Interestingly, in the case of the somatosensory cortex, deprived S1 circuits acquire S2-like features (i.e. an increase in excitatory/inhibitory ratio), suggesting that thalamic input not only affects L4 neurons but also determines downstream circuit assembly (Pouchelon et al. 2014). As already introduced in a previous chapter, these findings suggest that associative cortical identity is a ground-state feature, and that acquisition of primary cortical area circuit properties is imparted by first-order thalamic input.

Taking a step back, while our early work on the reprogramming of post-mitotic neurons described above (De la Rossa et al. 2013), in which we addressed gene-circuit relationships in the gene-to-circuit direction, here instead we manipulated neuronal circuits and assessed how this affects the genetic identity of post-synaptic target neurons. In both cases, the identity of neurons was congruently reassigned on the genetic, morphological and input-output circuit level. The Pouchelon et al. study showed that the identity of cortical neurons and the circuits they form is signi-

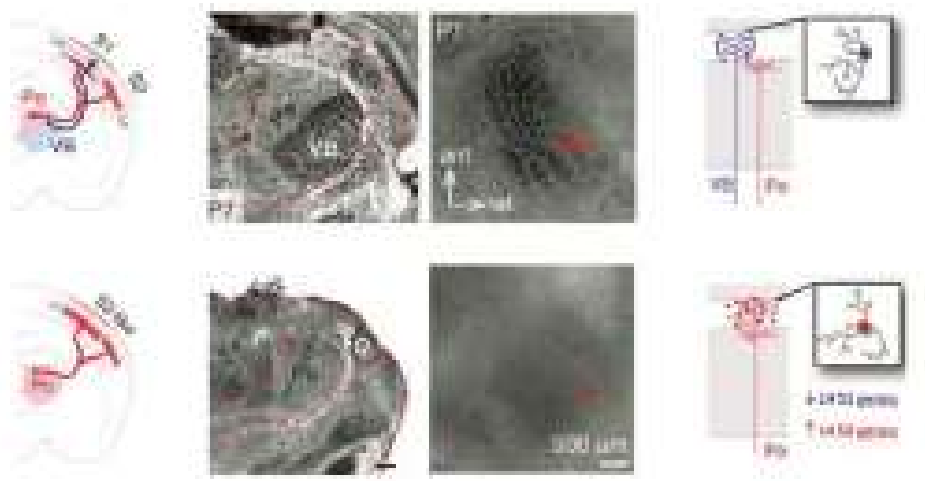

Figure 9: Loss of exteroceptive input leads to a respecification of L4 neurons in S1, which acquire the characteristics of L4 neurons in S2. *A. Under normal conditions, L4 neurons in S1 receive VB input and L4 neurons in S2 receive Po input. Upon genetic ablation of the VB (bottom), Po input is rewired onto S1. (B) Photomicrographs showing loss of VB following genetic ablation (left, compare top and bottom), and loss of barrel patterning in S1 (right). (C) Upon acquisition of Po input, the genetic identity of L4 neurons in S1 resembles that of L4S2 neurons. Photomicrographs from Pouchelon et al., 2014.*

ficantly determined by sensory input, and identified the molecular mechanisms underlying this effect. Therefore, environmental factors strongly influence neuronal gene expression and circuit formation during development, providing a path through which adverse environmental conditions could lead to abnormal gene expression and secondary circuit miswiring in neurodevelopmental disorders.

More recently, we showed that a similar process is at play within sensory thalamic nuclei, where input ablation experiments support the idea that higher-order genetic identity is a default feature, and that first-order identity is acquired in an input-dependent manner (Frangeul et al. 2016). We and others showed that in the absence of input from the retina, exteroceptive visual nucleus LGN receives input from L5B (Frangeul et al. 2016; Grant, Hoerder-Suabedissen, and Molnar 2016), a normally higher-order nucleus-destined afferent, and develops a corresponding higher-order transcriptional identity (Frangeul et al. 2016). This finding is interesting because it suggests that ascending exteroceptive and descend-

ing corticofugal inputs may thus compete to innervate thalamic nuclei **(Fig. 10)**.

From an evolutionary perspective, the findings above support the view that neurons in primary areas and first-order nuclei/areas may have emerged from ancestral secondary/higher-order-type neurons(Slutsky, Manger, and Krubitzer 2000; Sanides 1969). We have thus proposed that first-order neurons may have been co-opted from a ground-state pool of higher-order type neurons based on their ability to convey signals generated by high-resolution body receptors because of specific metabolic, electrophysiological and connectivity features (Frangeul et al. 2016).

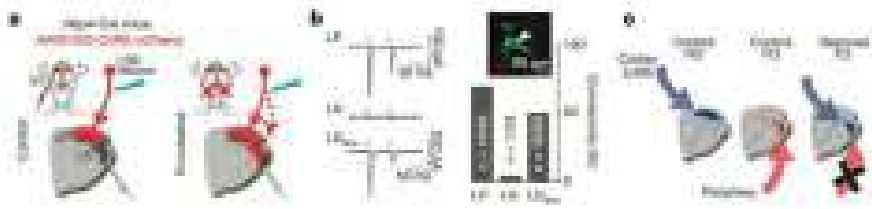

Figure 10: Rewiring of descending cortical input onto de-afferented thalamic nuclei. *(a) Schematic of the experimental setup: Optogenetic stimulation of L5B neurons in the cortex normally activates only LP neurons, while LG neurons are not targeted. In the absence of retinal input, descending inputs now invade the LG. (b) Experimental results (c) Summary of the findings. FO: first order nucleus, HO: higher order nucleus.*

Conclusion and outlook

The level of coordination the assembly of distinct subtypes of neurons into specialized functional circuits across space and time is staggering and raises a number of questions. What is the level of cellular diversity necessary to sustain the functions of the neocortex, and which are the features that delineate these core cell types? How do these features emerge during development and how do they vary across individuals, or in interaction with the environment? To which extent are they involved in the emergence of neurodevelopmental and neuropsychiatric disorders?

I believe that studies involving "non-clonal" model animals might contribute to better define the normal spectrum of variability in cell positioning and circuit assembly, while raising animals in more natural environments could be used to gauge the impact of experience of this process.

While these protocols will introduce natural "noise" in the system, the increase in the resolution of the tools we use to manipulate and assess neurons and circuits, including single-cell RNA sequencing, single-cell optogenetics, and targeted gene editing, will contribute to refine the read-out of these studies and provide a more truthful picture of the degrees of freedom in cortical assembly, and on the limits between normal and abnormal development.

Finally, understanding the number and nature of the independent parameters that define the configuration of the neocortex will be critical in attempts to reverse engineer developmental processes. Understanding these parameters will be important not only to define the relationship between developmental gene expression and mature neuronal function, but also to account for inter-individual variability in brain circuits and behavior in both normal and pathological settings.

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THE CLOËTTA PRIZE 2017
IS AWARDED TO

PROFESSOR

MARKUS G. MANZ

BORN IN 1967 IN STUTTGART, GERMANY
DIRECTOR OF THE DEPARTMENT OF
HAEMATOLOGY AND ONCOLOGY OF THE UNIVERSITY
HOSPITAL OF ZURICH

FOR HIS GROUND-BREAKING CONTRIBUTIONS TO
UNDERSTANDING THE DEVELOPMENT OF DENDRITIC
CELLS ON THE BASIS OF BLOOD STEM CELLS

ZÜRICH, 3RD NOVEMBER 2017

IN THE NAME OF THE FOUNDATION BOARD:

THE PRESIDENT

THE VICE PRESIDENT

MEMBER

Markus G. Manz, M.D.

CURRICULUM VITAE & PUBLICATIONS

Position and Work Address

– Professor/Ordinarius of Hematology University of Zürich (UZH)
– Director Hematology University Hospital Zurich (USZ)
– Director a.i. Oncology USZ
– Director Department of Hematology and Oncology USZ
– Chairman Leukemia-, Lymphoma-, Myeloma-Center USZ

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Personal DOB 03.09.1967, married, 6 children

Education

1974–1987	Freie Waldorfschule, Stuttgart Uhlandshoehe, Germany
1989–1995	University of Tuebingen Medical School, Germany
1994	US Medical Licensing Examination Step II

Public Service

1987–1989	Civil service (alternative to mandatory military service) Karl-Olga-Krankenhaus, Stuttgart, Germany

Clinical Training

1995–1999	Resident Physician, Department of Medicine, and Department of Hematology/Oncology/Immunology University of Tuebingen Medical School, Germany
2004–2006	Clinical Fellow, Department of Hematology/Oncology/Immunology University of Tuebingen Medical School, Germany

Licensure and Board Qualification

2006	Internal Medicine, Germany/European Union
2007	Hematology and Oncology, Germany/European Union
2009	Internal Medicine license recognition Switzerland (FMH)
2009	Hematology license recognition Switzerland (FMH)

Research Training

1992–1996	Thesis (Dissertation): «Tumornecrosis factor ß Gen-Polymorphisms in myasthenia gravis» Department for Hematology/Transplantation Immunology, University of Tuebingen Medical School, Germany Advisor: Prof. Dr. Claudia A. Müller
1999–2002	Postdoctoral Research Fellow Department of Pathology and Developmental Biology Stanford University Medical School, USA Advisor: Prof. Dr. Irving L. Weissman

02/2007	Habilitation (Venia Legendi in Internal Medicine) University of Tuebingen Medical School, Germany

Academic and Hospital Appointments

2002–2004	Research Group Leader Institute for Research in Biomedicine (IRB) Bellinzona, Switzerland
04/2004–09/2006	Associate research group leader Institute for Research in Biomedicine (IRB) Bellinzona, Switzerland
3–9/2006	Physician, Department of Hematology/Oncology/ Immunology University of Tuebingen Medical School, Germany Chairman: Prof. Dr. Lothar Kanz
08/2006	Elected «primo loco» as Director (W3) of the «Department of Cellular Therapeutics and Research» at the Essen University Medical School, Germany (refused 10/2006)
10/2006–08/2009	Research Group Leader Institute for Research in Biomedicine (IRB) Bellinzona, Switzerland
11/2006–08/2009	Attending Department of Hematology, Oncology Institute of Southern Switzerland, Bellinzona Chairman: Prof. Dr. Franco Cavalli
02/2007–08/2009	Privatdozent/PD Medical Faculty, Eberhard-Karls-University Tuebingen, Germany
07/2008–08/2009	Vice-Director IRB, Bellinzona, Switzerland
09/2009–12/2011	Associate research group leader IRB, Bellinzona, Switzerland

09/2009–ongoing	Professor/Ordinarius of Hematology at the Medical Faculty and Director Hematology at the University and University Hospital of Zürich, Switzerland
11/2010–ongoing	Professor with «Promotionsrecht» at the Mathematical and Natural Sciences Faculty at the University of Zürich
01/2012–05/2017	Chairman Steering Committee Cancer Network Zürich (UZH/ETHZ)
06-2017–ongoing	Steering Committee Cancer Network Zürich (UZH/ETHZ)
08/2013–ongoing	Lead Clinical Research Priority Program UZH («Human Hemato-Lymph. Diseases»)
01/2014–ongoing	Director Leukemia-, Lymphoma-, Myeloma-Center USZ
02/2014–ongoing	Cancer Biology PhD Program Steering Committee Member (Life Sciences UZH/ETHZ)
2016–ongoing	Secretary Swiss Society of Hematology
06/2016	Elected "primo loco" as Director (W3) Hematology and Oncology at Charite University Medicine Berlin, Germany (declined 12/2016)
07/2016–ongoing	Director Department of Hematology and Oncology USZ
01/2017–ongoing	Director a.i. Oncology USZ

Honors and Awards

1999 Postdoctoral Research Fellowship, Deutsche Krebshilfe (https://www.krebshilfe.de/)

2002 Swissbridge Award (http://www.swissbridge.ch)

2004 Artur-Pappenheim-Award, German Society of Hematology and Oncology (DGHO; https://www.dgho.de)

2008 San Salvatore Foundation Award (http://www.fondazionesansalvatore.ch/)

2010 Ellermann Award Hematology 2009, Swiss Society of Hematology (SGH; http://www.sgh-ssh.ch/)

2016 Otto Naegeli Award (http://www.otto-naegeli-preis.ch/)

2017 Cloëtta Award (http://www.cloetta-foundation.ch/de/cloetta-preis/)

Professional Organizations and Societies

Swiss Society of Hematology (SGH, Secretary 2016–ongoing), Swiss Medical Association (FMH), Swiss Society for Allergology and Immunology (SSAI), German Society of Hematology and Oncology (DGHO), German Society of Internal Medicine (DGIM), European Society of Hematology (EHA, Sci Committee 2010–2013), European School of Hematology (Scientific Committee 2013–2015), American Society of Hematology (ASH), International Society of Experimental Hematology (ISEH), Henry Kunkel Society (HKS), Swiss Society of the Friends of the Weizmann Institute of Science (Board member), Charles Rodolphe Brupbacher Foundation (Sci Board), Swiss Stem Cell Network (SSCN), Cancer Network Zürich (CNZ)

Scientific Board Member

Swiss Stem Cell Network (SSCN, 2013–ongoing)
Charles Rodolphe Brupbacher Foundation (2011–ongoing)
Justus Müller Stiftung (2015–ongoing)
Swiss Soc. Friends of the Weizmann Institute of Science (2011–ongoing)
International Society of Experimental Hematology (ISEH, 2015–ongoing)
American Society of Hematology (ASH, 2015–ongoing)
Swiss Society of Hematology (SGH, 2016–ongoing)

Editorial Board Member

Blood Editorial Board (2013–2017)
Blood Advances Associate Editor (2016–ongoing)

Ad hoc Editorial Referee

Blood, Cell Stem Cell, European Journal of Immunology, Hematologica–The Hematology Journal, Immunity, Nature, Nature Immunology, Nature Medicine, Nature Biotechnology, PLoS Biology, Proceedings of the National Academy of Sciences, The Journal of Experimental Medicine, The Journal of Immunology

10 MOST IMPORTANT PUBLICATIONS

1. Takizawa H, Fritsch K, Kovtonyuk LV, Saito Y, Yakkala C, Jacobs K, Ahuja AK, Lopes M, Hausmann A, Hardt WD, Gomariz A, Nombela-Arrieta C, *Manz MG*. Pathogen-Induced TLR4-TRIF Innate Immune Signaling in Hematopoietic Stem Cells Promotes Proliferation but Reduces Competitive Fitness.
Cell Stem Cell. 2017 Jul 19. pii: S1934-5909(17)30239-4. doi: 10.1016/j.stem.2017.06.013. [Epub ahead of print]

2. Boettcher S, Gerosa R, Radpour R, Bauer J, Ampenberger F, Heikenwalder M, Kopf M, *Manz MG*.
Endothelial cells translate pathogen signals into G-CSF-driven emergency granulopoiesis.
Blood. 2014 Jul 2. pii: blood-2014-04-570762. [Epub ahead of print]

3. *Manz MG* and Boettcher S.
Emergency Granulopoiesis.
Nature Rev Immunol. 2014 May;14(5):302-14. doi: 10.1038/nri3660. Epub 2014 Apr 22. Review.

4. Rongvaux A, Takizawa H, Strowig T, Willinger T,Eynon EE, Flavell RA, *Manz MG*.
Human Hemato-Lymphoid System Mice: Current Use and Future Potential for Medicine
Annu Rev Immunol. 2013 Jan 16. [Epub ahead of print]

5. Takizawa H, Regoes RR, Boddupalli CS, Bonhoeffer S, *Manz MG*.
Dynamic variation in cycling of hematopoietic stem cells in steady state and inflammation.
J Exp Med. 2011 Feb 14;208(2):273–84. Epub 2011 Feb 7.

6. Onai N, Obata-Onai A, Schmid MA, Ohteki T, Jarrossay D, *Manz MG*.
Identification of clonogenic common Flt3(+)M-CSFR(+) plasmacytoid and conventional dendritic cell progenitors in mouse bone marrow.
Nat Immunol. 2007 Nov;8(11):1207–16. Epub 2007 Oct 7.

7. Onai N, Obata-Onai A, Tussiwand R, Lanzavecchia A, *Manz MG*.
Activation of the Flt3 signal-transduction cascade rescues and enhances type I interferon-producing and dendritic cell development.
J Exp Med. 2006 Jan 23;203(1):227–38. Epub 2006 Jan 17.

8. Traggiai E, Chicha L, Mazzucchelli L, Bronz L, Piffaretti J-C, Lanzavecchia A, *Manz MG*.
Development of a Human Adaptive Immune System in Cord Blood Cell Transplanted mice
Science. 2004 Apr 2;304:104–107

9. *Manz MG**, Miyamoto T*, Akashi K, Weissman IL.
Prospective isolation of human clonogenic common myeloid progenitors.
Proc Natl Acad Sci U S A. 2002 Sep 3;99(18):11872–7. *equal contribution

10. Traver D*, Akashi K*, *Manz M**, Merad M, Miyamoto T, Engleman EG, Weissman IL.
Development of CD8alpha-positive dendritic cells from a common myeloid progenitor.
Science. 2000 Dec 15;290(5499):2152–4. *equal contribution

HEMATOPOIESIS – A PARADIGMATIC STEM CELL SUPPORTED ORGAN SYSTEM

Markus G. Manz

Summary

The hematopoietic system constitutes one of the largest organs in mammalian bodies. In adults, hematopoiesis is mostly confined to the bone marrow (BM) where red blood cells, platelets and white blood cells are continuously produced from rare, self-renewing hematopoietic stem cells (HSCs) and HSC-derived, highly-proliferative, increasingly lineage-restricted hematopoietic progenitor cells (HPCs). This system was shaped by evolution in a highly regulated and versatile manner, such as it is capable to respond to hemato-immunological stress by increasing its output to circulation from steady state to demand-adapted production of mature hematopoietic effector cells. Adaptability, however, implies risk for instability. Indeed, with ageing, hematopoiesis becomes increasingly frail, oligo- or monoclonal hematopoiesis develops in a substantial fraction of elderly humans, and clinically relevant hematopoietic alterations may occur, which are in worst cases hematopoietic insufficiency or development of HSC-derived leukemia. Hematopoiesis stands as a paradigmatic somatic stem cell-supported organ system, which is, due to its fluid character, highly accessible and scientifically testable. Understanding intrinsic and extrinsic regulation of hematopoiesis in physiology, during hemato-immunologic challenge, and during the process of ageing and malignant transformation will allow to better treat hematopoietic stem and progenitor cell (HSPC) diseases, the ultimate goal in our translational research efforts. In this review, I will focus on our own scientific contributions over the last one and a half decades to understand structure and regulation of mouse and human hematopoiesis in health and disease. These, naturally, are inspired by and connected to many prior and concurrent basic and clinical research achievements from colleagues all over the world.

Introduction

Blood as a renewable and fluid organ is fascinating. This fascination finds its expression in religion, philosophy, art and medicine alike. Since the introduction of blood donation and banking, blood is the only broadly shared, cellular product or "organ", saving millions of lives. Moreover, HSC donation and transplantation for inherited or malignant disease has become routine organ-donation practice. Remarkably, this organ-transplant does not require a scalpel to be successful as HSCs can mobilize from BM to circulation and find their way "home" to bone marrow upon infusion in circulation due to selective adhesion molecule interactions. Moreover, donors re-grow HSCs upon donation, and, likely due to these facts, more volunteer donors have registered than there are recipients in need. Blood is thus connecting humans. However, it also carries critical elements of immune distinction, i.e. the white blood cells that are able to dissect self from non-self.

In this brief piece, I will focus on describing and summarizing our own work (and my fascination) on blood and bone marrow as well as immunology research and thus will mostly cite our own primary and review articles. For a broader and more balanced view on this fast evolving field, I would like to refer to the reference sections of the here cited published work.

Metrics and structural organization of bone marrow

Bone marrow (BM) accounts for 4–5 % of body weight and thus exceeds other organs as brain (2 %), liver (2–3 %) or heart (0.5 %) and lymphoid tissue (1.5 %). BM generates the highest number of cells per day (4–5x10E11 cells in humans, 0.5–1.5x10E6 in mice), outnumbering cellular production of intestinal epithelium or testis. In fact, BM produces about half of its own cellular content per day and, at any given time, about 90 % of total cell numbers in the organism originates from or resides in BM, although only a fraction of these cells are nucleated. In sharp contrast, HSCs only account for a very small fraction of bone marrow hematopoietic cells, i.e. 0.001–0.2 % (about 28–112x10E6 in humans and 11 2000–22 400 in mice) and HSPCs together account for less than 2 % of BM nucleated cells, indicating impressively their replicative and burst forming potential. Table 1 and 2 summarize representative parameters of

BM function and cellularity in humans and mice (Nombela-Arrieta and Manz, 2017; Sender et al., 2016).

Table 1. Representative parameters of BM function in humans and mice

Parameters		Humans	Mice
Total weight of BM (relative to body mass)		4–5 %	1.5–2 %
Weight in standard individual		3 kg	0.4–0.5 g
Total volume BM		1100 cm^3–2000 cm^3	0.35–0.4 cm^3
Total volume blood		70–80 ml/kg	85–95 ml/kg
Blood volume in the BM (% of tissue volume)		N.D	15–30 %
Ratio cortical/ trabecular bone		80:20	65:35
Nucleated BM cells/kg body weight		1.1–2.1 x 10^{8}	1.1–1.8 x 10^{8}
Total nucleated BM cells		0.8–1.5 x 10^{11}	2.8–5.2 x 10^{8}
Cell production/ day	Total	4–5 x 10^{11} (5–7 x 10^{8} cells/kg)	0.5–1.5 x 10^{8} (2–6 x 10^{8} cells/kg)
	RBCs	2.2 x10^{11}	0.45–0.85 x10^{8} **
	Platelets	1–1.75 x 10^{11}	0.16–0.7 10^{8} **
	Neutrophils	0.45–1.2 x10^{11}	0.7–1.9 x10^{7}
Major BM cavities (% of total BM content)		Lower Limbs 26–38 % Vertebrae 14–28 % Pelvis 16 %	Vertebrae 32–52 % Lower Limbs 14–20 % Pelvis 25 %
BM adipogenesis (% of BM volume)		30–70 %	1–2 % in 12 week old 18–20 % in 56 week old (measured in proximal tibial metaphysis)
Number of HSCs (functional definition)		28–112 x 10^{4}	11200–22400
Myeloid:erythroid ratio		3:1	1.7:1–2.3:1

*Values depicted have been in most cases obtained for, or adjusted to a reference standard individual of 70 kg for humans and 25 g for mice. *Reliable estimations of total HSC numbers in humans are lacking to date. As depicted, for most parameters presented, including weight and blood cell production, the ratio of values between mouse and human species approximately falls with a range of 2500–5000. The theoretical number of HSCs for the human system provided in this table has been estimated assuming that similar ratios would apply for proportional scaling of HSC content between species.*
Table adapted from: Nombela-Arrieta and Manz: Blood Advances, Feb 2017, Volume 1, Number 6

Table 2. Cellular content of the BM as determined by flow cytometry

	Humans		Mice	
Populations	**Phenotype**	**Freq. of BMMNC (%)**	**Phenotype**	**Freq. of BMMNC (%)**
HSCs	Lin⁻CD34⁺CD38⁻ CD90⁺CD45RA⁻	0.01–0.2	Lin⁻c-kit+Sca-1+(LSK) CD48⁻CD150⁺	0.004–0.007
Common Myeloid progenitors	Lin⁻CD34⁺CD38⁺ CD123⁺CD45RA⁻	0.2–0.8	Lin⁻c-kit+ CD34⁺CD16/32lo	0.4
Common lymphoid progenitors	Lin⁻CD34⁺CD38⁻ CD127⁺	0.02–0.18	Lin⁻c-kit+CD127⁺	0.02
Erythroid progenitors	CD235⁺CD71⁺	4–16	Ter119⁺	5–15
Granulocytes	CD66⁺	57–86	Gr-1⁺	30-50
Megakaryocytes	*	0.05	CD41⁺	0.29
Monocytes	CD14⁺	2–5.8	CD115⁺ C⁻11b⁺Ly6C⁺	5–7
B cell lineage (including progenitors)	CD19⁺	1–7	B220	35–45
T lymphocytes	CD45⁺CD66⁻ CD34⁻CD14⁻	8–20	CD3⁺ CD8⁺	4–5 2
Endothelial cells	CD45⁻ Ter119⁻CD31⁺	N.D	CD45⁻Ter119⁻ CD31⁺	0.03–0.4
Fibroblastic reticular stromal cells	CD146⁺ CD271⁺ CD146⁻CD51⁺ CD140a⁺	0.02–0.08 0.03 0.1	CD45⁻Ter119⁻CXCL12GFP⁺ CD45⁻Ter119⁻ CD140⁺LepR⁺	0.02–0.04 0.3

Estimated ranges of frequencies of different hematopoietic and non-hematopoietic populations in human and mouse BM expressed as percentages of nucleated BM cells.
** Estimation based on microscopic examination of BM, not flow cytometry.*
Table adapted from: Nombela-Arrieta and Manz; Blood Advances, Feb 2017, Volume 1, Number 6

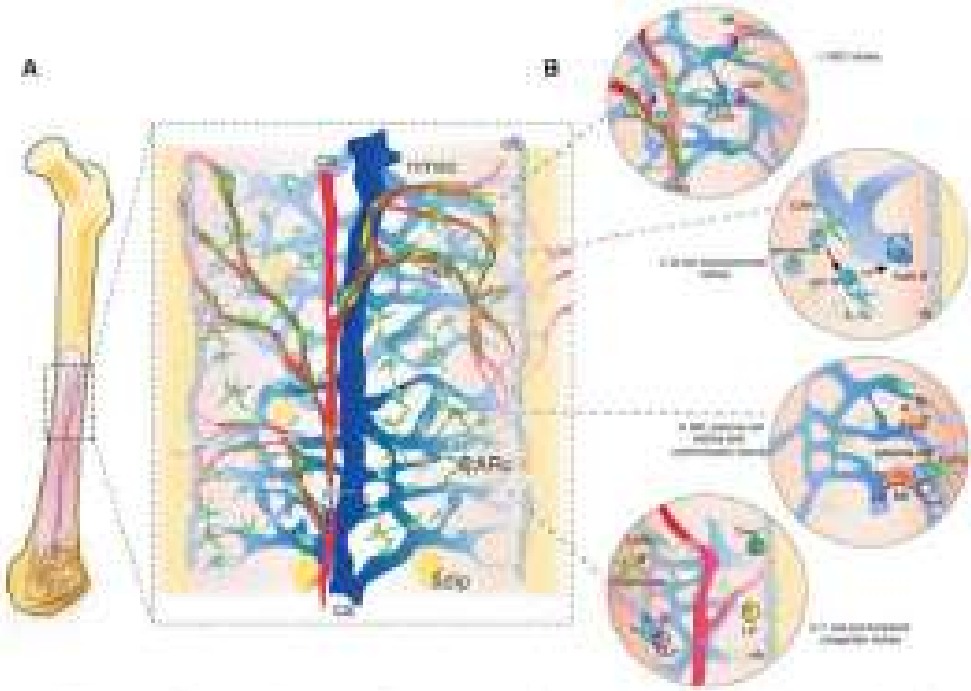
In contrast to other organs, spacial organization of BM tissues and relation of this to confined domains of blood formation is only being explored in recent years with the availability of three-dimensional tissue imaging. While mapping of BM is an ongoing effort, it already became clear that there are no clear macro-domains identifiable, but rather the BM is organized in microdomains where few hematopoietic and stromal cells (as vasculature and other mesenchymal cells) built "niches", as HSC-niches, erythroblastic-niches or plasmacell-niches that nurture the respective cell types. Figure 1 shows a resolution of mouse BM and Figure 2 gives a schematic insight of various BM niche organizations.

Figure 1. Three-dimensional imaging of BM

(A) Representative stages of murine femoral bones during processing for 3D imaging. From left to right: sectioned, sliced unprocessed and optically cleared BM slices. The last 2 images to the right correspond to an example of 3D reconstruction of the entire BM microvascular system of the femur (arteries and sinusoids) using multidimensional confocal imaging of a cleared BM slice. A detailed view of the central sinus running along the longitudinal axis of the marrow is provided. (B) High-resolution 3D imaging of a reduced field of view showing sinusoidal vessels (red) and the network of perivascular bodies of CAR cells (green), forming a dense matrix through the emission of abundant cytoplasmic projections.

Figure adapted from: Nombela-Arrieta and Manz; Blood Advances, Feb 2017, Volume 1, Number 6.

Figure 2. Structural organization of BM tissues


A
B
CXCL12-abundant reticular cells
Arteriole
Sinusoid
Adipocyte
Osteoblast
Megakaryocyte
Nestin-GFP+ cell
NG2+ cell
Osteoprogenitor
Osteoblast
Osteocyte
Adipocyte
Megakaryocyte
Sympathetic nerve fibers
Schwann cell
Endosteum
Bone marrow cavity
Bone matrix
Blood vessels
Nerve fibers
Cell types
Cell lineages
Bone marrow stroma
Hematopoietic cells
Osteolineage cells
Endothelial cells
Perivascular cells
Neural cells
Adipocytes
Osteoblastic lineage cells
Osteoclasts
Osteocytes
Osteoprogenitors
Osteoblasts
Osteoclast
Osteocyte
Osteoprogenitor
Osteoblast

minor fraction enriched in quiescent HSCs has been reported to localize in a protective niche adjacent to nonpermeable arterioles, under the regulatory influence of neighboring Nestin-GFPhi, NG2 mesenchymal cells (mes) and nonmyelinating Schwann cells (in yellow). (ii) B-cell progenitors have been suggested to sequentially migrate along different niches as they progress through maturation. Early stage pre-pro B cells are mostly found adjacent to the cell bodies of CAR cells and migrate toward IL-7–expressing CAR cells as they enter the pro B cell stage. Mature B220IgM B cells, in turn, move away from both stromal cell types. The latest stages of B-cell maturation occur intravascularly, within sinusoids, where the dynamic behavior of immature B cells has been visualized in vivo. In addition, early pro B cells (B220CD43) have been shown to accumulate in endosteal zones and gradually decrease in frequency toward bone-distal marrow regions. (iii) Megakaryocytes (MK) are found in close adjacency to the endothelial surface of sinusoidal vessel wall, which they traverse in the form of protrusions from which proplatelets are continuously shedded into the venous circulatory system. Red blood cell development takes place in so-called erythroblastic islands (EI), where erythroid precursors proliferate, enucleate, and terminally differentiate into reticulocytes around a central macrophage. 108 Plasma B cells are long-lived antibody-secreting cells that have been found in physical association to CAR cells, megakaryocytes, and eosinophils (eos). (iv) Although a significant fraction (30 %) of early lymphoid progenitors (Lin-IL7-ra) has been shown to lie proximal to mature, bone-lining osteoblasts, the vast majority of phenotypically defined CLPs are in contact with IL-7–expressing CAR cells. Quiescent CD4 memory T cells are found scattered throughout the BM in contact with perisinusoidal IL-7–secreting stromal cells. Regulatory T cells (Tregs) have been reported to lodge in close proximity to the endosteum of trabecular bone.

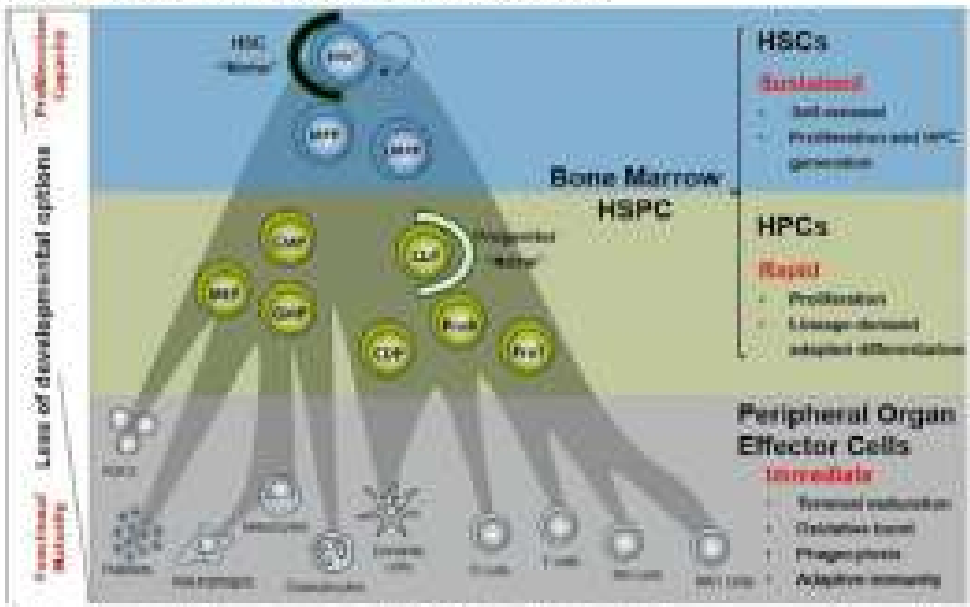
Figure adapted from: Nombela-Arrieta and Manz: Blood Advances, Feb 2017, Volume 1, Number 6

Hierarchical Organization of Hematopoiesis

Hematopoiesis is organized in a hierarchically (Kondo et al., 2001). HSCs stand at the top of the hierarchy, are defined by their capacity to life-long self-renew, and give rise to all mature blood cells. Blood cell production from HSCs occurs in a stepwise process, where HSCs differentiate to HPCs that still have the capacity to produce all blood lineages but that have lost long-term self-renewal capacity. These HPCs then commit via highly proliferative developmental intermediates, increasingly restricted progenitor cells to end-stage differentiated blood cells. Most of these blood cells, with the exception of some lymphocytes and tissue resident phagocytic cells, are post-mitotic and can only be maintained during life by continuous active hematopoiesis from precursors.

With the development of monoclonal antibody technologies and subsequent antibody labeling of cell surface antigens, and with the development of fluorescence associated cell sorting (FACS), it became feasible to isolate rare populations of individual live cells, which subsequently could be molecularly and functionally characterized. This allowed first a population based, and now an increasingly high-resolution single cell, clonal mapping of the hematopoietic tree. A rough, principle model of hematopoiesis is depicted in Figure 3.

Figure 3. Schematic model of hematopoiesis



Schematic model of hematopoiesis depicting the hematopoietic hierarchy and the qualities of cells in the respective developmental sections. HSC, hematopoietic stem cell; HSPC = hematopoietic stem / progenitor cell; MPP = multipotent progenitor; LMPP = lympho-myeloid progenitor; CMP = common myeloid progenitor; MEP = megakaryocyte erythrocyte progenitor; GMP = granulocyte macrophage progenitor; CLP = common lymphoid progenitor; CDP = common dendritic cell progenitor; ProB = pro-B cell; ProT = pro-T cell. Figure adapted from: M.G. Manz, Swiss Medical Forum, 18(18–19); 414–418; 2018

While there is currently agreement on the principle hierarchy, there are still open questions with regard to some of the direct clonal relationships, the existence of additional progenitor populations, as well as the essential versus possible developmental steps in steady state and during hemato-immunological challenges.

We were able to characterize on a clonal level the human counterparts of the initially in mice identified myeloid committed progenitor cells (Manz et al., 2002). In addition, we were able to identify common dendritic cell progenitors in mice on a clonal level and we were able to dissect critical cytokine and signaling pathways that guide dendritic cell development and homeostasis from the earliest progenitors to steady-state mature cells (discussed below).

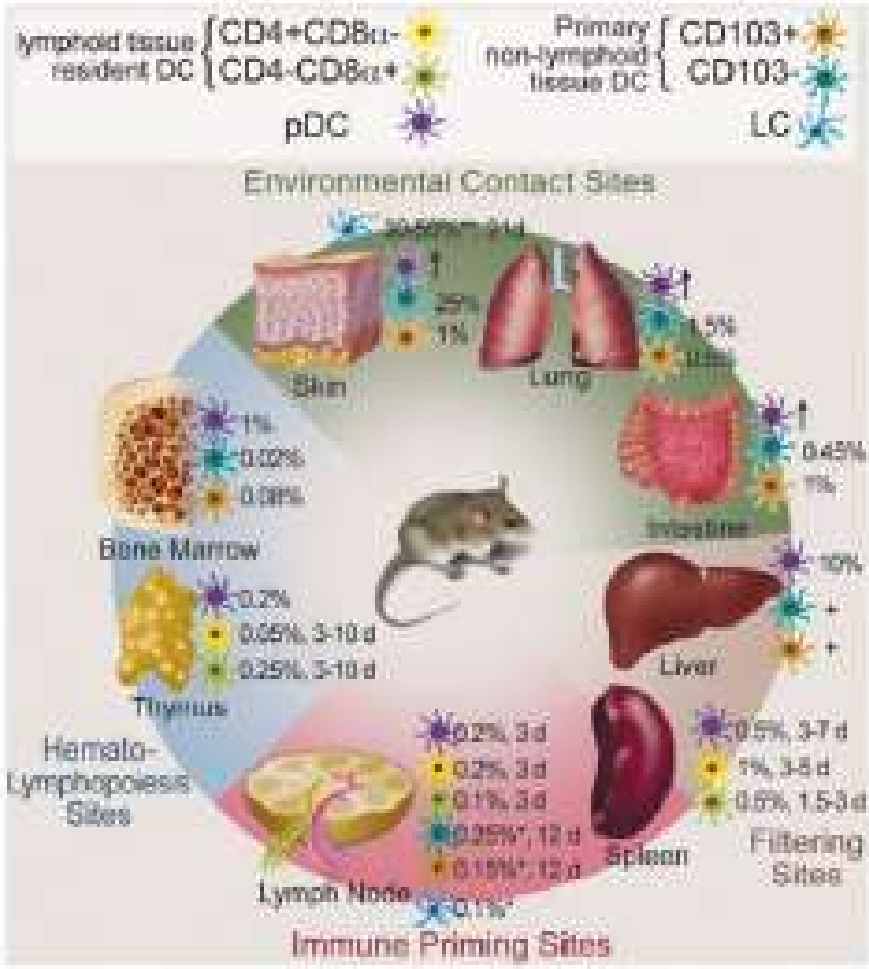
Why is this of relevance? Understanding the fine-tuned hematopoietic hierarchy allows to molecularly interfere, i.e. to support hematopoietic lineage development (e.g. by cytokine or small molecule application as e.g. HSPC-, erythropoiesis-, granulopoiesis-, thrombopoiesis-stimulating agents), or to mobilize HPSCs (e.g. chemokine receptor antagonists). Using this approach, we were able to e.g. show that thrombopoietin-agonists but not granulopoiesis stimulating agents are able to expand HSCs, at least in mice (Kovtonyuk et al., 2016b). In addition, deciphering healthy hematopoiesis helps to characterize the malignant transformed cell counterparts, and to ideally selectively interfere with their molecular machinery (e.g. using fitted kinase inhibitors). Using this approach, we were e.g. able to identify stages and pathways in aggressive transformation of chronic myeloid leukemia (Jamieson et al., 2004).

Dendritic Cell Development from early Hematopoietic Precursor Cells

Dendritic cells (DCs) are hematopoietic-derived, professional antigen presenting cells, key for the guidance of adaptive immunity (Merad and Manz, 2009). DCs are rare cells, comprised of multiple sub-specialized populations that are present everywhere in the body, with a relatively increased frequency at environmental contact sites as skin, lung and gut, and at sites of adaptive immune cell programming, i.e. primary and secondary lymphoid organs. DCs sample and process antigen and move from non-lymphoid to lymphoid tissues to fulfill their effector functions

(one key distinction from organ-resident macrophages). In addition, some DCs are primarily present at lymphoid organs. Figure 4 provides an overview on DC populations and turnover in mice.

Figure 4. Mouse DC populations, location, and turnover in steady state

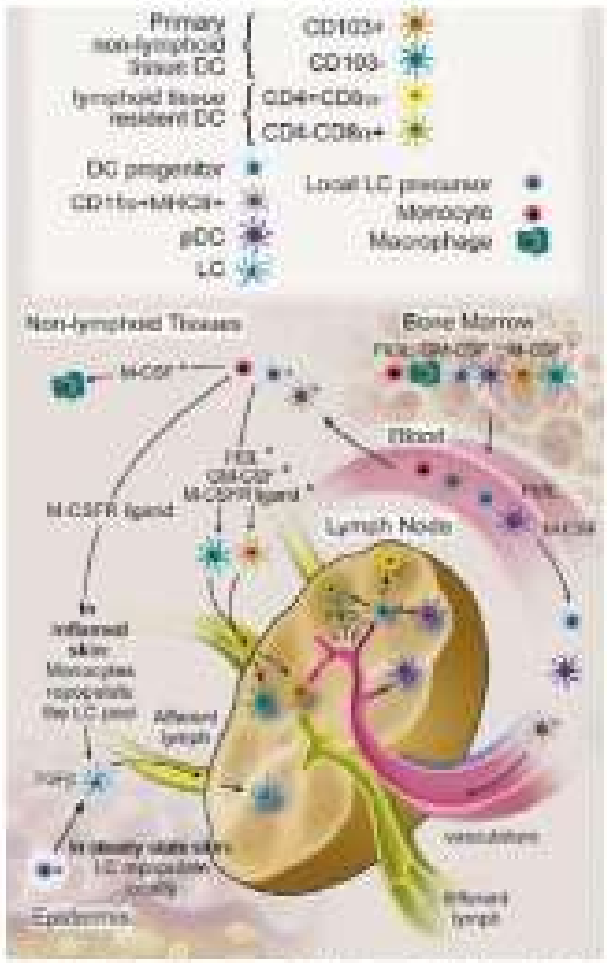


*DCs are distributed throughout the body. The major DC subpopulations at hematopoietic sites, environmental contact sites, filtering sites, and immune priming sites are depicted. Frequencies are given as percentage of total nucleated hematopoietic cells. Time to approximately 50% renewal in steady state is given in days (d). *Skin-draining LC. **epidermis. +present, but exact numbers not known. ~ present in inflammation. Professional illustration by Debra T. Dorter.*

Figure adapted from: M. Merad and M.G. Manz, Blood, Volume 113, Number 15, 9 April 2009.

With the isolation of hematopoietic progenitor cells, it became possible to dissect DC developmental pathways. In *in vitro* and *in vivo* experiments, we were able to show that DCs surprisingly develop from both lymphoid and myeloid restricted progenitors (Manz et al., 2001; Chicha et al., 2004; Traver et al., 2000) and that the capacity to develop to DCs in myeloid and lymphoid populations is confined to cells expressing the receptor tyrosine kinase Flt3 (Karsunky et al., 2003). Indeed, we demonstrated that DC-development incompetent progenitors can be instructed to develop to DCs by artificially expressing and stimulating Flt3 (Onai et al., 2006). Moreover, by isolating hematopoietic progenitors on the basis of Flt3 and M-CSF receptor expression, we were able to identify and characterize committed clonal dendritic progenitor cells (CDPs) in mouse bone marrow (Onai et al., 2007), which was confirmed and extended by co-investigating groups in the field (reviewed in [Geissmann et al., 2010; Merad and Manz, 2009]). In accordance with the important role of Flt3-signaling, we found that orally applied small molecule Flt3 inhibitors generate a lymphoid tissue DC depleted phenotype within ten days of application *in vivo* (Tussiwand et al., 2005). Thus, Flt3-ligand is important in steady-state lymphoid tissue DC development and homeostasis (reviewed in [Geissmann et al., 2010; Merad and Manz, 2009; Schmid et al., 2010]). The role of cytokines, progenitors and migration is schematically depicted in Figure 5.

Figure 5. DC migration and homeostasis

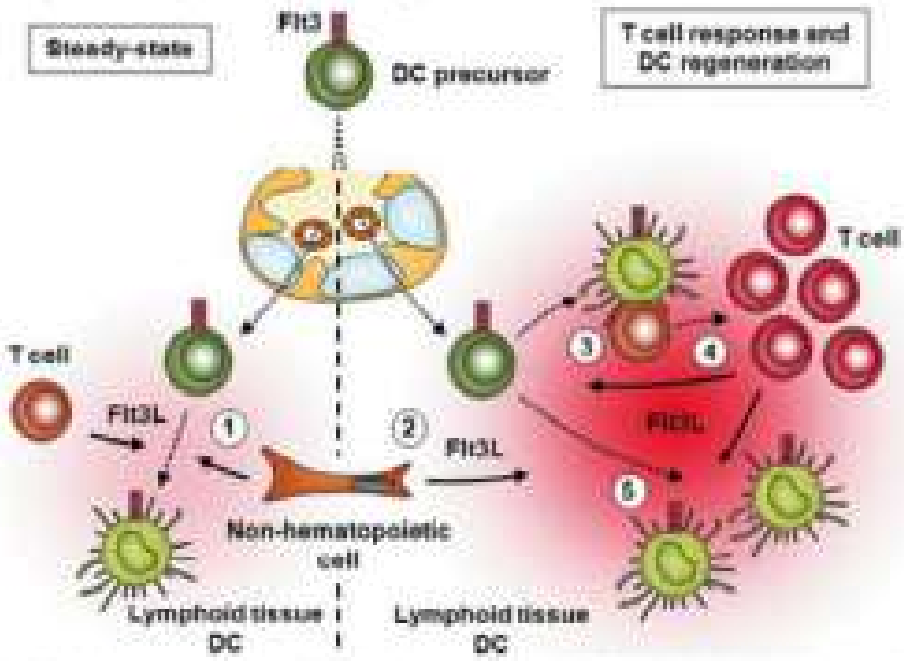


*HSCs produce DC progenitors, pDCs, and DCs in the BM. Flt3 ligand is a nonredundant cytokine for BM DC differentiation, although the exact role of GM-CSF and M-CSFR ligands remains to be determined. BM-derived circulating blood cells maintain, with the exception of epidermal LCs, all known steady-state DC homeostasis in lymphoid and nonlymphoid tissues. We hypothesize that progenitor cells with limited proliferation potential on Flt3 ligand and LT stimulation enter the LNs through high endothelial venules to maintain the majority of LN DCs in steady state. It is also possible that nonproliferating blood DCs follow the same route. In addition, nonlymphoid tissue DCs continuously enter the LNs through afferent lymphatics, but these represent only a minority of steady-state LN DCs. The specific contribution of proliferating DC progenitors, blood DCs, and monocytes to nonlymphoid tissue DCs in the steady state and the relative involvement of cytokines as Flt3 ligand, GM-CSF, and M-CSFR ligands remain to be to be addressed. In contrast to most DCs, LCs repopulate locally in the steady state either through self-renewal or through a local hematopoietic precursor that takes residence in the skin. In inflamed skin, monocytes repopulate the LC pool via a TGF-b and monocyte colony-stimulating factor receptor–dependent pathway. In the steady state, pDCs are recruited to the LN and other lymphoid organs directly from the blood and, with the exception of the liver, enter most nonlymphoid tissues only on inflammation. Whether lymphoid organ pDCs also derive from DC precursors that enter the organs remains to be determined. *Likely, but not formally proven. Professional illustration by Debra T. Dunlap.*

Figure adapted from: M. Merad and M.G. Manz, Blood, Volume 113, Number 15, 9 April 2009.

We subsequently investigated which cells are relevant in Flt3-ligand production in DC homeostasis. Interestingly, we found that Flt3-ligand mediated lymphoid tissue DC maintenance is regulated in two ways, through Flt3-ligand production by non-hematopoietic cells and consumption by Flt3-expessing hematopoietic cells, as well as by antigen-mediated T-cell proliferation and Flt3-ligand secretion of these proliferating cells in adaptive immune responses, thereby stimulating local DC replenishment at lymphoid tissue inflammation sites (Saito et al., 2013). This is depicted schematically in Figure 6. Also, we found that DC progenitors from bone marrow are selectively recruited to inflamed lymph nodes via pattern-recognition receptor activation on progenitor cells (Schmid et al., 2011).

Figure 6. Flt3L produced by proliferating T cells contributes to proliferation of cDCs and their precursors in LNs in vivo

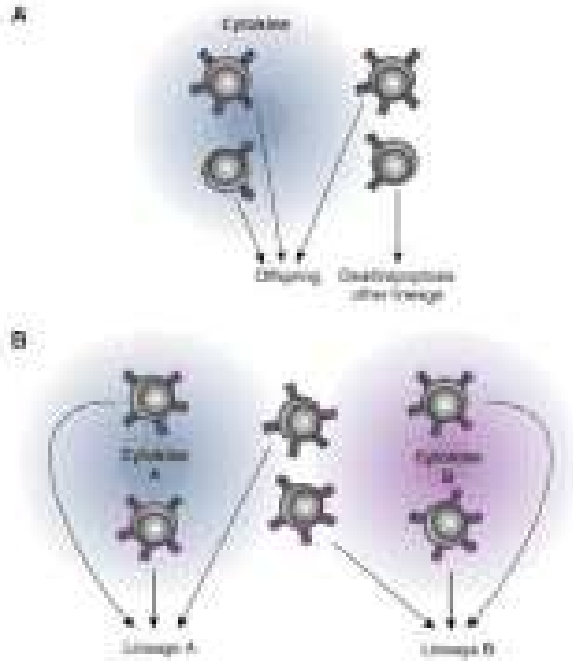


Model for the maintenance of lymphoid tissue DCs by Flt3 ligand. (1) In steady state, Flt3L produced by both nonhematopoietic and hematopoietic cells (mainly T cells) supports lymphoid tissue DC development. (2) During the course of a local immune response, in addition to the production of Flt3L by nonhematopoietic cells, (3) T cells are activated by antigen-presenting DCs, proliferate, and (4) produce overall more Flt3L than in steady state, and thereby (5) enhance local replenishment of lymphoid tissue DCs and their precursors.

Figure adapted from: Y. Saito et al., Eur. J. Immunol. 43:1651–1658, 2013

As with other hematopoietic lineage development, mature DC subtype development is driven by both progenitor cell intrinsic permissive- and responsiveness as well as extrinsic, environmental delivered signals. Consequently, the combination of cytokine concentration and receptor expression determines whether a progenitor receives a sufficiently high signal to differentiate to a particular lineage. This can be achieved in two situations: First, if a high cytokine concentration is available to progenitors (Fig. 7A, left), they will develop irrespective of high or low expression of the respective receptor. This abundance of cytokine will occur at sites or niches where commitment and differentiation typically takes place. Second, if only small amounts of cytokine are available (Fig. 7A, right), progenitors with high receptor expression will still receive sufficient amounts of positive signal to differentiate and give rise to offspring of the corresponding lineage. However, progenitors with low receptor expression will undergo apoptosis or develop into alternative lineages if they are responsive to alternative signals. Usually, more than one cytokine will act in concert on a cell in vivo. Progenitors, which carry the potential to differentiate into two lineages, will express cytokine receptors relevant for both of these. In Fig. 7B, a cell expressing high levels of the receptor for cytokine A and low levels of the receptor for cytokine B (upper cells) and a cell expressing low receptor A and high receptor B (lower cells) are shown to be situated in an environment with overlapping concentrations of these cytokines. When both cells are located in a milieu with high concentrations of cytokine A (Fig. 7B, left), they would differentiate to lineage A, whereas they would both give offspring to cells of lineage B in a milieu with high concentrations of cytokine B (Fig. 7B, right). In the region with overlapping amounts of cytokines A and B (Fig. 7B, center), cells with high expression of receptor A would differentiate to the A lineage, whereas cells with high expression of receptor B would generate cells of lineage B (Schmid et al., 2010).

Figure 7. Hypothesis for cytokine-induced differentiation of progenitors



(A) One cytokine, one receptor scenario. If two progenitors, one with high receptor expression, the other with low receptor expression, are located near high concentrations of the respective cytokine, both cells will acquire sufficient signal to differentiate and give rise to offspring (left). If both cells are exposed to low concentrations of the cytokine, only the cell with high receptor expression will receive sufficient signaling to differentiate, while the cell with low receptor expression will not and will either undergo apoptosis or differentiate into another lineage (right) if it receives signaling through an alternate receptor (not pictured). (B) Multiple cytokines/ receptors scenario. As in (A), if two progenitors, one being receptor Ahigh receptor Blow, the other receptor Alow receptor Bhigh, are exposed to high concentrations of cytokine A, both will differentiate into lineage A (left), or conversely, if both progenitors are near very high levels of cytokine B, both cells will give rise to cells from lineage B (right). If both progenitors are exposed to only low concentrations of both cytokine A and cytokine B, the cell expressing receptor Ahigh receptor Blow will preferentially differentiate into lineage A, while the Alow receptor Bhigh cell will differentiate into lineage B.

Figure adapted from: M.A. Schmid et al., Immunological Reviews 234, 2010.

Hematopoietic Stem Cell Cycling and contribution to Blood formation in Steady-State and Inflammatory Challenges

During adult steady-state hematopoiesis, more than 80 % of HSCs are in a resting phase, i.e. are quiescent in G0 of cell cycle at any given time. Therefore, hematopoiesis must be supported by a small fraction of HSCs and downstream, highly proliferative HPCs. We and others thus investigate the questions a) why do we need HSC dormancy; b) which fraction of HSCs engage in hematopoiesis at any time, c) does contribution of different HSCs to hematopoiesis vary over time; d) what factors drive HSCs from quiescence to cycling and lineage commitment versus self-renewal; e) is hematopoietic and self-renewal potential of HSCs determined and correlated to HSC divisional history; and d) how does HSC proliferative history under various conditions influence functional HSC ageing, exhaustion, and possibly malignant transformation?

While others used in vivo labeling or elaborated genetic HSC labeling approaches, we modified a robust and noninvasive cellular labeling technique used largely in immunology research, i.e. labeling with 5(6)- carboxyfluorescein diacetate N-succinimidyl ester (CSFE), a cell-permeable dye that covalently binds to intracellular proteins and equally distributes to daughter cells upon cellular division to address these questions (Takizawa and Manz, 2012). This technique allows steady-state HSC transfer, bone marrow homing, in vivo tracking and high-resolution single-cell re-isolation of zero to more than five times divided live cells, and their subsequent testing *in vitro* and *in vivo* in functional assays (Kovtonyuk et al., 2016b; Pietras et al., 2016; Takizawa et al., 2017; Takizawa and Manz, 2011, 2012; Takizawa et al., 2011).

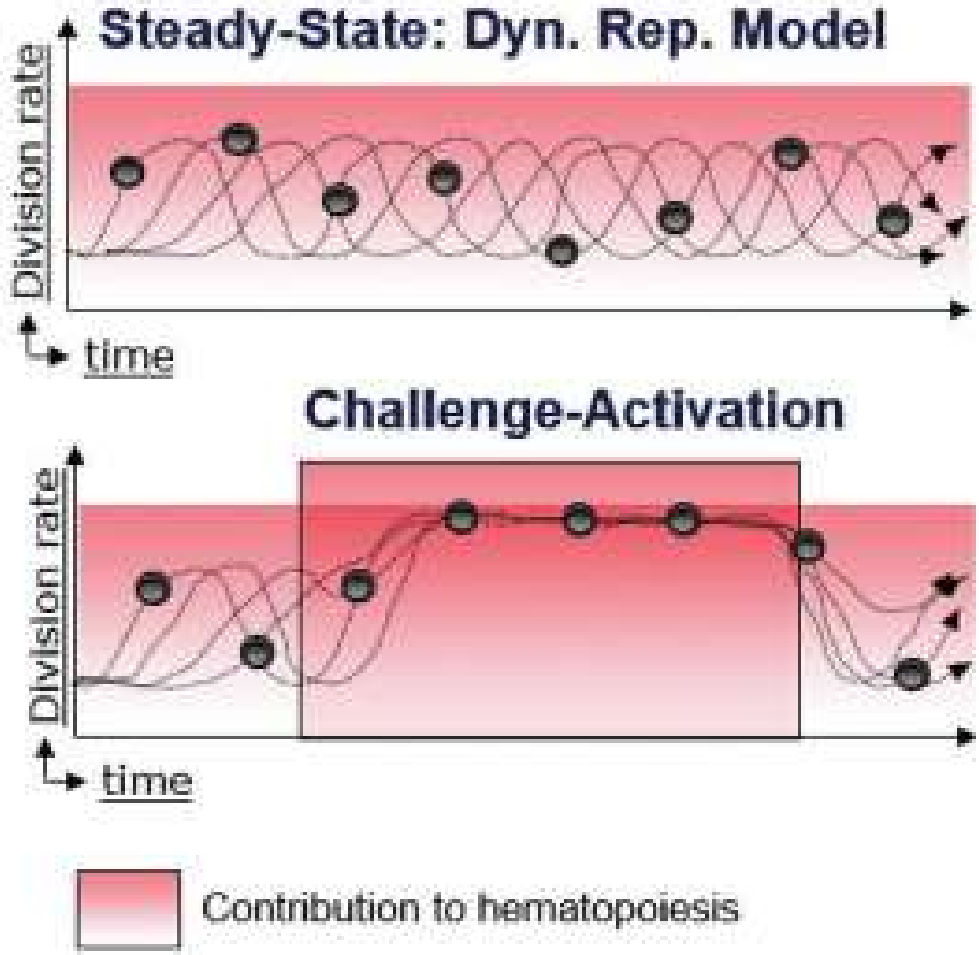
Using this approach, our first finding was that in steady-state, HSCs with equivalent life-long multi-lineage repopulation potential are contained in both frequently cycling cell populations and in quiescent cells that do not divide over 14 weeks. Our second finding was that steady-state fast-cycling HSC populations can slow down over time in steady-state serial transplantation and that HSCs with extensive proliferative history, i.e., HSCs that have gone through extended proliferation in aging or after in vivo challenge by transplantation – are prone to return to quiescence. We also showed that in vivo TLR4 challenge with Lipopolysaccharide (LPS)

recruits in vivo functional quiescent HSCs into proliferation and self-renewal with nonbiased lineage repopulation capacity (Takizawa et al., 2011). Moreover, our mathematical simulation reveals that HSCs with different cycling activity can be contained in one HSC population with relatively broad cycling variation and that, on average, HSCs divide 18× during a 2-yr lifespan of a laboratory mouse (Takizawa and Manz, 2011; Takizawa et al., 2011).

Based on these results, we proposed a dynamically fluctuating HSC cycling model in steady-state, where the turnover of all HSCs would naturally be similar at end of life. This would assure protection of the dormant HSC fraction from cell cycle damaging events, and would allow at the same time overall homogenous use of HSC resources during life. This model is in line with a linear correlation of telomere shortening in human HSCs with aging. Also, it would be in line with an increased risk for the whole HSC population to accumulate genetic events, promoting clonal HSC diseases as myelodysplasia and myeloid leukemia in the aged population.

Steady-state cycling differences of HSCs at any given time in this model would reflect the broad variation of possibilities, but not a static separation of HSCs in distinct classes with different divisional kinetics. Increased cycling of most HSC during hematopoietic challenges via external cues might have developed as an advantage to recruit dormant HSCs in order to better cope with blood cell demand for the necessary time. Broad activation, however, also poses a risk to loose HSCs due to genetic vulnerability and differentiation. Thus, a mechanism to "drive" HSCs to quiescence that increases strength with frequency of total HSC divisions needed to be established. This might be achieved by down-modulation of sensitivity to external stimulation and upregulation of sensitivity to quiescence signals. Indeed, we observed that phenotypically defined HSC populations with extensive proliferative history, i.e., HSCs from aged mice and HSCs that have divided massively after transplantation, subsequently increase quiescence in steady-state environments, likely as an effort to prevent HSC exhaustion (Takizawa and Manz, 2011; Takizawa et al., 2011). Figure 8 shows a graph that illustrates the above-discussed findings.

Figure 8. Schematic model depicting steady-state and challenge-activation of HSCs



HSC repetitively fluctuate in steady-state from quiescence to activation and blood production. At end of life, all HSCs have gone through about the same frequency of divisions. Upon challenge as e.g. massive infection, HSC are recruited from dormancy and contribute to blood formation for the necessary time, to subsequently re-establish fluctuation from quiescence to activation in steady-state.

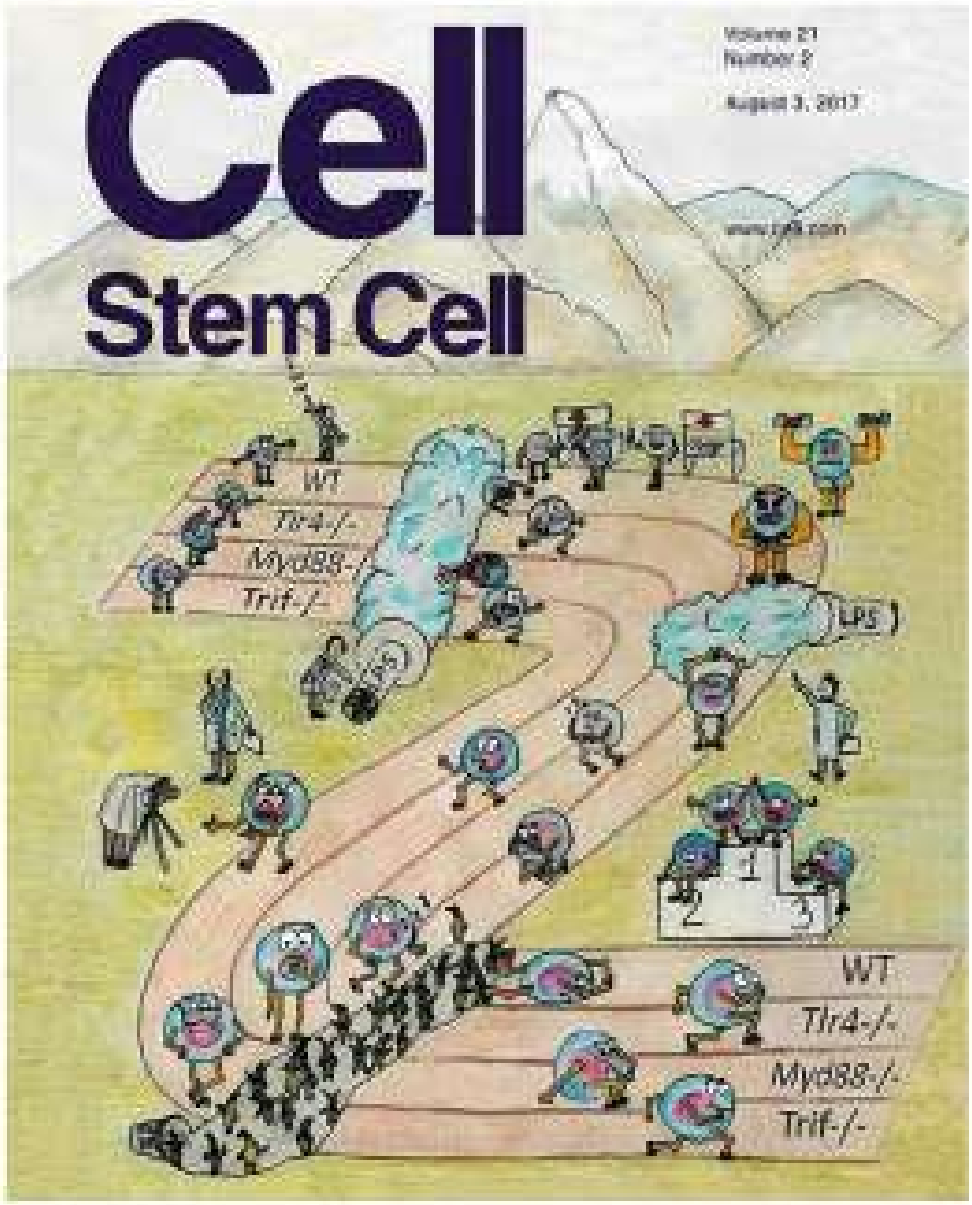
Figure adapted from: H. Takizawa et al., J Exp Med. 2011; 208(2):273-84

To dissect effects of cytokines, chemokine receptor antagonists and direct pathogen-derived stimuli on HSC cycling and function, we further tested *in vitro* and *in vivo* stimulation with thrombopoietin-analoga, granulocyte colony stimulating factor (G-CSF), Flt3-ligand, interleukine-1 (IL-1), and with LPS and life gram-negative bacterial infection (Kovtonyuk et al., 2016b; Pietras et al., 2016; Takizawa and Manz, 2017).

We found that thrombopoietin receptor stimulation on HSCs leads to HSC cycling and expansion without loss of self-renewal capacity (Kovtonyuk et al., 2016b). In contrast, Chronic interleukin-1 exposure drives HSCs towards myeloid differentiation at the expense of self-renewal (Pietras et al., 2016), while G-CSF, Flt3-ligand and CXCR4 antagonists did not affect HSC cycling and potential (Kovtonyuk et al., 2016b). Given the enhancement of multi-lineage regeneration by thrombopoietin-receptor agonists, possibly via cycling and re-expansion of human HSCs in aplastic anemia, we speculate that these also might be tested in clinical settings as an add-on to conditioning chemotherapy before allogeneic HSC transplantation in order to reduce endogenous HSCs. Furthermore, we speculate that, if the thrombopoietin receptor is expressed on malignant counterparts of HSCs, these could also be targeted by thrombopoietin-receptor agonist chemosensitization (Kovtonyuk et al., 2016b).

We also found that self-renewing HSCs directly sense gram-negative bacterial infection through Toll-like receptor 4 (TLR4) activation, which leads to impaired function via proliferative stress. However, this could be prevented by pharmacological blockage of the TLR4-TRIF-ROS-p38 axis (Takizawa et al., 2017). Interestingly, we previously contributed to a collaborative project where we found with our colleagues that very low concentrations of microbial antigens and TLR ligands derived from the intestinal microbiome, well below the threshold required for induction of adaptive immunity, sets the bone marrow myeloid cell pool size (Balmer et al., 2014). Whether inhibition of this pathway as a means of preemptive medicine is able to prevent or delay aging-associated and inflammation-associated HSC defects and malignant transformation will need to be determined in future studies (Kovtonyuk et al., 2016a; Luis et al., 2016; Takizawa et al., 2012; Takizawa et al., 2017; Takizawa and Manz, 2017). Figure 9 shows the related cover of the Cell Stem Cell issue, describing our findings in a cartoon in front of our geographical region.

Figure 9. HSCs in action under inflammation

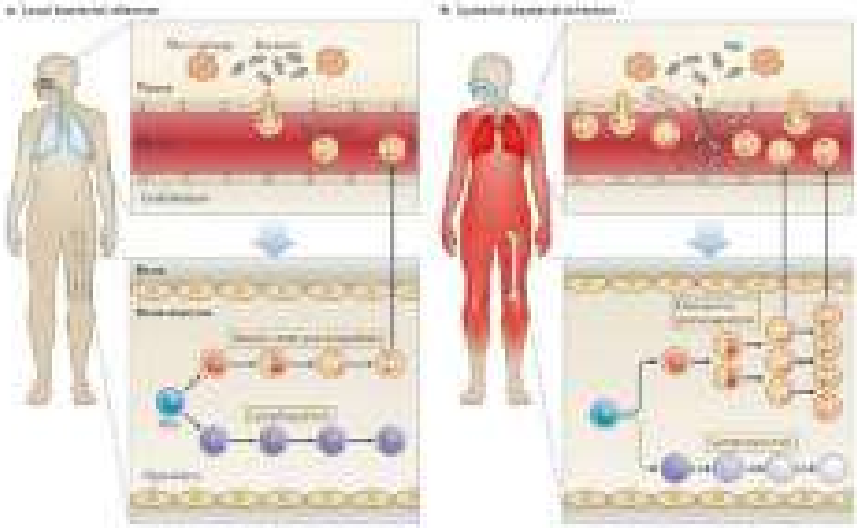


The cover of Cell Stem Cell describes our findings in a cartoon in front of our geographical region. Designed by Larisa Kovtonyuk, Ph.D., member of our laboratory and co-author of the related manuscript. Cell Stem Cell, August 3, 2017

Regulation of Emergency Granulopoiesis

Steady-state hematopoiesis is switched to infection-induced emergency hematopoiesis following detection of systemically disseminated microbial pathogens (e.g. viruses, bacteria, fungi, and parasite). A prototypic and clinically well know response is emergency granulopoiesis, with increase of granulocytes and shift to immature forms in peripheral blood, and release and massively increased production of granulocytes in BM upon lack of local infectious control and systemic spread of bacteria, i.e. bacteriaemia and sepsis (Figure 10).

Figure 10. Local versus systemic bacterial infection



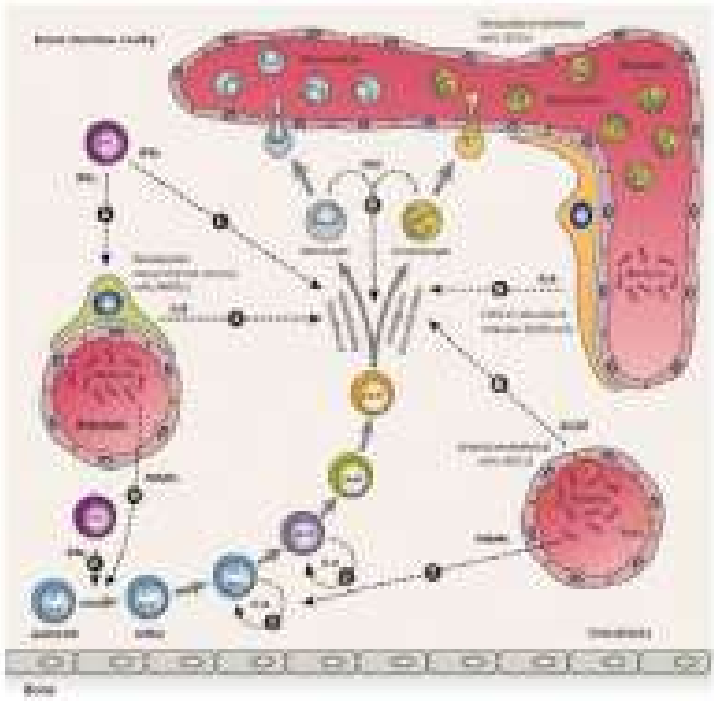
a) During a localized bacterial infection in an immunocompetent individual, several pre-existing antimicrobial effector mechanisms contain bacterial pathogens locally. In most cases, this leads to a rapid resolution of the infection, thereby preventing bacterial dissemination. As a consequence, bone marrow granulopoiesis is unaffected and does not differ from steady-state conditions. b) By contrast, in the setting of severe bacterial infection that overwhelms first-line defence mechanisms, bacterial dissemination occurs and neutrophils are consumed in large quantities, with pre-existing neutrophil pools being used. To counterbalance neutrophil depletion and to provide a supply of urgently needed neutrophils to combat systemic bacterial spread, a haematopoietic response programme termed 'emergency granulopoiesis' is initiated, which is characterized by the large-scale de novo generation of neutrophils from myeloid progenitors in the bone marrow. The expansion of bone marrow granulopoiesis is paralleled by a decrease in bone marrow lymphopoiesis.

Figure adapted from: M.G. Manz and S. Boettcher, Nat Rev Immunol., Vol. 14, May 2014.

How and by which cells sensing of systemic bacterial spread is accomplished, and how this sensing is translated into appropriately, life-saving granulocyte production and subsequent decrease of it upon clearance of infection, was poorly understood. We thus addressed the fundamental question of which cell types act as primary sensors of bacterial dissemination during severe infection and consequently induce the switch from steady-state to demand adapted emergency granulopoiesis.

We approached this by *in vivo* elimination of sensors (TLR4) or downstream signaling molecules (MyD88) in hematopoietic and non-hematopoietic cells using genetic Cre recombinase– mediated tissue-specific ablation approaches. Against our expectations, we found that pathogen sensing by both immature HSPCs and mature hematopoietic cells, including macrophages, is dispensable for the acute process of emergency granulopoiesis. In contrast, we discovered that endothelial cells (ECs) express sensors and, upon ligation of those, are the major producers of G-CSF, which then induces emergency granulopoiesis (Boettcher et al., 2014; Boettcher et al., 2012). Our findings reveal a sophisticated degree of functional interplay between the vascular, the hematopoietic, and the immune systems, which have a common developmental root and might thus be understood as one functional organ. Indeed, ECs are ideally positioned to mark the threshold of local vs systemic infection, and using ECs as safeguards seems a very plausible, danger-adapted defense strategy established in evolution (Boettcher and Manz, 2016, 2017; Manz and Boettcher, 2014). Figure 11 summarizes our proposal for a model of infection-driven emergency hematopoiesis, integrating additional findings from our and other research groups in the field.

Figure 11. Integrated model of emergency hematopoiesis



Multiple distinct and most likely complementary pathways exist and these [28HTDSDIF] govern how pathogen-derived signals are detected and translated into emergency hematopoiesis. Of note, the order of mentioning individual pathways does not indicate their importance. (1) Interferon-g (IFNg) released from CD8+ cytotoxic T lymphocytes (CTLs) promotes emergency monopoiesis by stimulating perivascular mesenchymal stromal cells (MSCs) to secrete interleukin-6 (IL-6) as well as by directly acting on granulocyte-macrophage progenitors (GMPs), thereby favoring a monocytic lineage fate. (2) IFNg can also directly induce hematopoietic stem cell (HSC) cycling and recruit quiescent HSCs into the cell cycle. (3) Pathogen-associated molecular patterns (PAMPs) are also able to stimulate HSC proliferation but it remains to be determined whether it is accomplished directly or indirectly. (4) Reactive oxygen species (ROS) released by bone marrow Gr1+ myeloid cells (including monocytes and neutrophils) during Toll-like receptor (TLR) agonist stimulation enhance upstream myeloid precursor proliferation and differentiation. (5) CXCL12-abundant reticular (CAR) cells are a major source of IL-6 that is of importance to sustain emergency granulopoiesis (S.B. and M.G.M., unpublished data). (6) Granulocyte colony-stimulating factor (G-CSF) secreted from predominantly arteriolar endothelial cells (AECs) following lipopolysaccharide (LPS) recognition in an MYD88-dependent manner stimulates emergency granulopoiesis. (7) Direct PAMP recognition by mainly short-term HSCs (ST-HSCs) and multipotent progenitors (MPPs) leads to IL-6 secretion, which acts in an autocrine/paracrine manner to stimulate emergency hematopoiesis. Abbreviations: CMP, common myeloid progenitor; LT, long term.

Figure adapted from: S. Boettcher and M.G. Manz, Trends in Immunology, May 2017, Vol 38, No. 5.

Future studies will need to determine if there are pathogen-specific differences in the activated emergency hematopoietic pathways, what factors determine the threshold for induction of emergency hematopoiesis, what is the contribution of HSC activation versus myeloid progenitor activation to the overall magnitude of emergency hematopoiesis? Is HSC activation during this process a physiologic response or indicative of a failure to control infection, what are the long-term hematopoietic and immunological consequences and the possible underlying molecular mechanisms of chronic infection and inflammation, and what is the molecular mechanism by which chronic infection/inflammation increases the risk for developing hematologic malignancies (Boettcher and Manz, 2017)?

In vivo model Systems to study human Hematopoiesis in Health and Disease

Knowledge on human hematopoiesis and immunology is predominantly gained by clinical observation, cautious, safety-oriented in vivo experimentation, and in vitro surrogate assays (Manz, 2007). Progress in clinical research is mostly slow, and rigorous scientific proof is frequently impossible. Given appropriate ethical consideration, most societies agree on research involving worms, flies, and small vertebrates as mice. Indeed, laboratory mice have become the main model for in vivo basic and applied biomedical science. However, approximately 65 million years of divergence in human and mouse evolution have shaped these two species that differ substantially in size, lifespan, reproductive activity, and exposure to environmental challenges, e.g., species-specific infectious agents that coevolved. Concerning hematology and immunology, many similarities exist, however, mice are not men and some loss in translation of achievements between these two species is observed. Humanized mice, i.e. mice that carry human molecular or tissue elements have been generated over the last few decades with the intention to fill this gap, i.e. to model human physiology and pathology in accessible ways *in vivo*. Achievements in generating human hemato-lymphopoietic mice are summarized in recent reviews by us and colleagues working in the field (Legrand et al., 2009; Manz, 2007; Rongvaux et al., 2013; Shultz et al., 2007; Theocharides et al., 2016; Macchiarini et al., 2005).

In brief, we hypothesized that transplantation of human HSCs into the liver, i.e. a hematopoietic active organ, of newborn T cell, B cell and NK cell deficient mice (Rag2-/-gamma common chain-/-) would lead to human hematopoietic cell development and replacement of lacking mouse components. Indeed, the expanding organism provides a suitable environment for high-level human HSC engraftment and lymphocyte development (Traggiai et al., 2004). We, together with collaborators, could show that human-specific lymphotropic infections with Epstein Barr and Human Immunodeficiency Virus (Baenziger et al., 2006; Cocco et al., 2008; Neagu et al., 2009; Traggiai et al., 2004) are possible and some elements of human disease develop. However, due to insufficient adaptive immune cell education and insufficient cross-reactivity of growth factors in the xenogeneic environment, human adaptive immune reactions are weak, human HSCs are not sufficiently maintained over time, and human myeloid cells developed only at very low numbers and did not populate tissues sufficiently. In order to overcome the limitations of insufficient cytokine cross-reactivity and rejection of human cells via the innate macrophage response, we, in collaboration with Richard Flavell's laboratory at Yale and Regeneron, a company specialized in genetic engineering, generated mice that express human HSC and myeloid cell supporting growth factors under the regulatory element of the mouse genes (Strowig et al., 2011; Takizawa and Manz, 2007). Furthermore, we expressed a human SIRPa transgene on the mouse background to avoid human cell elimination via mouse phagocytic cells (Das et al., 2016; Rathinam et al., 2011; Rongvaux et al., 2014; Rongvaux et al., 2011; Strowig et al., 2011; Willinger et al., 2011). Indeed all engineering steps led to stepwise improvement of human cell engraftment and quality of human hematopoiesis and the combination of human growth factors in mice led to human cell development and distribution that closely resembles distribution in humans (Rongvaux et al., 2014; Theocharides et al., 2016). We now use these humanized mice to model specific human diseases (Figure 12).

Figure 12. Possible human disease-specific, tailored mouse models in future research

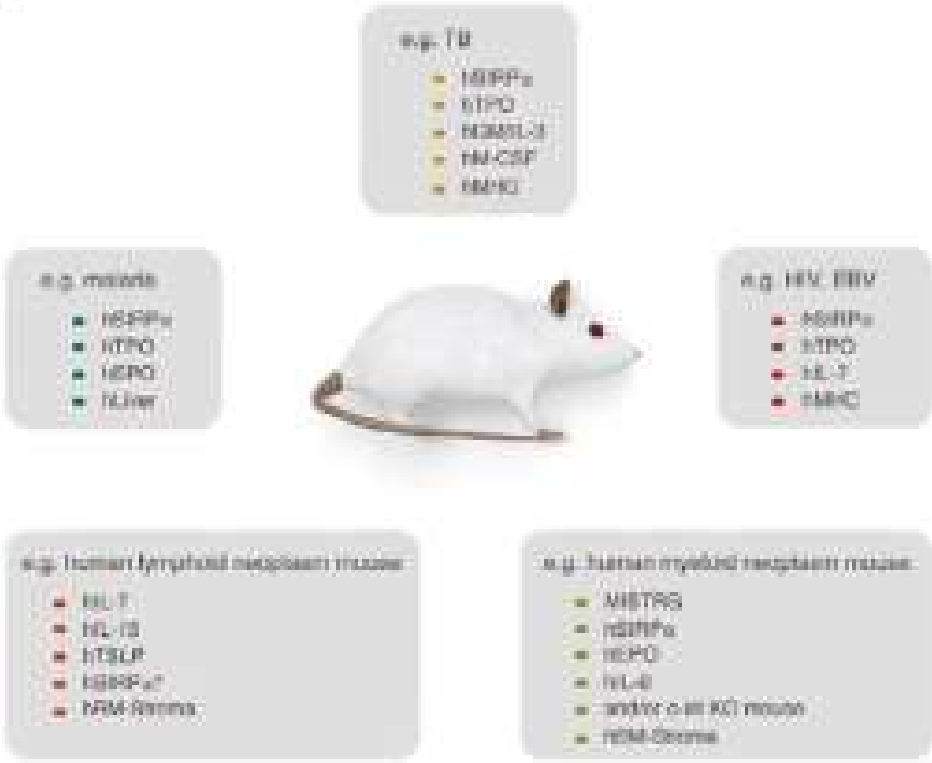


Figure adapted from: A. Theocharides et al., haematologica. 2016; 101(1).

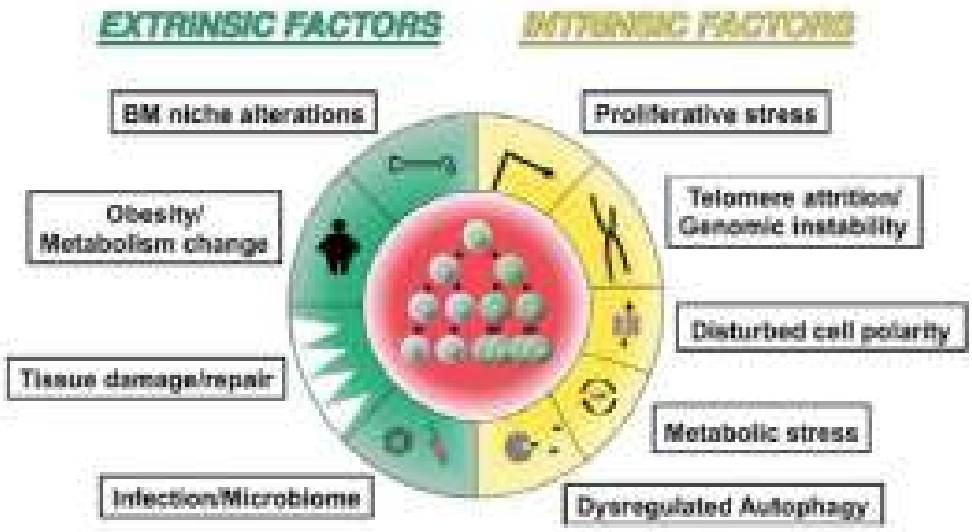
Using these models for human malignancies, we were able to demonstrate a) contribution of human myeloid cells to human melanoma growth (Rongvaux et al., 2014), b) dependence of human favorable-risk AML on macrophage colony-stimulating factor (M-CSF) (Ellegast et al., 2016), and dependence of human clonal plasma cell disease on cytokine combinations including IL-6 (Das et al., 2016). We are hopeful that human-hemato-lymphoid system mice will further be useful for pre-clinically, predictive testing of therapies and thus accelerate development of new successful therapeutic approaches.

Hematopoietic Stem Cells, (Inflamm-)Ageing and Clonal Dominance

With increasing age, HSCs get more numerous (about twofold increased, biologically defined HSCs in aged mice compared to young adult mice), however, their differentiation is biased towards myelopoiesis and their overall self-renewal and output capacity is reduced (Kovtonyuk et al., 2016a). While most of the data on ageing of HSCs is derived from mice, similar observations are made in humans. Biology of aged HSCs, similar as biology of other cells in other tissues, is driven by both cell-intrinsic as well as cell-extrinsic factors. An overreaching theme is the association of ageing and inflammatory signatures, even in a steady-state situation. Indeed, by analyzing BM gene transcription in hematopoietic and non-hematopoietic cells and by measuring expression of bone marrow protein presence in ageing and in inflamed situations, a high level of concordance emerges (unpublished data). We and colleagues in this research field are thus referring to "inflamm-ageing" of hematopoiesis, and we summarized potential hallmarks of this process (Kovtonyuk et al., 2016a) (Figure 13).

Figure 13. Potential hallmarks of inflamm-ageing

In this context, it is highly interesting that the occurrence of HSC neoplasia as AML, MDS and MPN are associated with repetitive infection and inflammatory diseases, and, even more so, with ageing. Surprisingly, benchmark studies in humans without hematopoietic diseases demonstrated during the last years, that clonal dominance of genetically altered hematopoiesis is a frequent event in the ageing population (more than 10 % in the over 70 years old) (Xie et al., 2014; Genovese et al., 2014; Jaiswal et al., 2014). Presence of these clonalities was coined as "clonal hematopoiesis of indetermined potential" (CHiP). Indeed, the genetic alterations that cause clonal dominance are frequently affecting the same genes that have been shown before to be associated or cause AML, MDS and MPN. However, only a small fraction (1–2 % per year) of individuals with CHiP develop these diseases. Thus, in this sense, CHiP shows similarities to other clonal, non-disease defining alterations in the hemato-lymphoid system as monoclonal B cell lymphocytosis (MBL) and monoclonal gammopathy of unknown significance (MGUS) (Steensma et al., 2015). Again, one could speculate that what we observe here in the



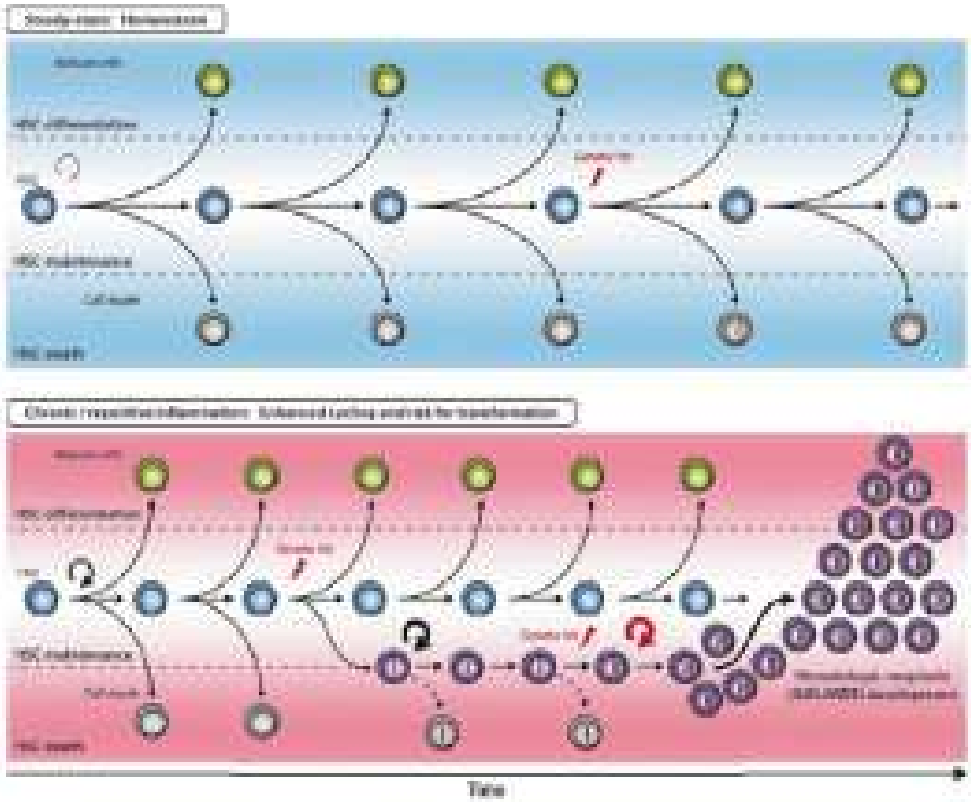
The schematic figure highlights similarities between aging and inflammation-associated changes in hematopoiesis and hematopoietic stem cells: (a) extrinsic factors include bone marrow niche alterations, metabolic changes, tissue damage/repair, and infection/ microbiome; (b) intrinsic factors include proliferative stress, telomere attrition/genomic instability, dysregulated autophagy, metabolic stress, and dysregulated autophagy.

Figure adapted from: L.V. Korotynk et al., Frontiers in Immunology, November 2016, Volume 7, Article 502.

hematopoietic system is similarly occurring in other organ systems without thus far being noticed. While occurrence of genetic CHiP-driver alterations might follow a simple stochastic rule with numbers of cell divisions, we speculate that inflammatory drive in addition might modulate and enhance risk (Takizawa et al., 2012). This is depicted in Figure 14.

Figure 14. Hypothetical model for inflammation-enhanced malignant transformation in early hematopoiesis

A key task is now to understand reasons for progression of CHiP to neoplasia, identify individuals at risk, and develop means to interfere clinically. To this end, we work on a project where we evaluate HSCs and hematopoiesis from one "source" under different environmental conditions. We analyze long-term surviving HSC recipients and their HSC donors for their HSC status on a population and clonal level, and we corre-



The 3 principle outcomes of HSC divisions are self-renewal, differentiation, and death. The balance between these 3 cell fates is closely regulated to ensure balanced blood cell production over the lifetime of an individual. With increased proliferative history in the HSC compartment, the probability of acquiring genetic alterations ("hits") in HSCs increases, but efficient counteractive mechanisms (eg, apoptosis, DNA repair) have evolved to remove or correct genetically altered HSCs from the pool (top). It can be hypothesized that under chronic or repetitive inflammation the likelihood of genetic hit acquisition and subsequent accumulation in HSC is increased by two major mechanisms: First, accelerated HSC cycling and self-renewal enhances the statistical probability of acquiring mutations during DNA replication. Second, genetically altered HSC clones are rescued by signals delivered from the inflammatory environment. Persistent and aberrant self-renewal of the respective HSC clone might enhance occurrence of further genetic hits, eventually resulting in the development of HSC neoplasia, for example, acute myeloid leukemia/myelodysplastic syndrome (AML/MDS, bottom).

Figure adapted from: H. Takizawa et al., Blood, 29 March 2012, Volume 119, Number 13.

late inflammation/infection, proliferative history and function of HSCs with occurrence and progression of CHiP. We are positive that this unique long-term read-out (in some cases more than 30 years) will shed light on the problem, covering both basic and clinically relevant aspects.

Conclusions and Perspective

Since the beginning of my clinical and scientific career more than twenty years ago, gain of knowledge in molecular understanding of benign and malignant hematology and knowledge-driven capacity to clinically interfere and control or even cure diseases lead to enormous leaps forward. Indeed, few treatment approaches are still the same as they have been then, and because of these developments, being a patient today is in an ever-growing fraction more bearable than before. Further, many basic principles observed in easy to access and to test hematopoietic cells and diseases and respective new treatment approaches have been extended and applied to other organ systems. I am motivated by better care through science and humanities and I am hopeful to contribute with our research on hematopoiesis, hemato-immunology, and hematopoietic malignancies pieces of understanding and insight, ultimately adding to maintenance of well-being of an ageing population and to re-gaining health of patients.

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