Adult neurogenesis: taking stock in Stockholm

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ABSTRACT
In May this year, Stockholm hosted a Keystone Symposium on Adult Neurogenesis, attracting scientists from around the world despite the lack of customary snow. The symposium offered an extraordinary program, covering diverse topics that ranged from the neural stem cell lineage and regulation of neurogenesis to functional aspects of neurogenesis in homeostasis and disease, and even computational modeling. This Meeting Review describes some of the exciting presentations and emerging themes from the symposium, which reveal how much this young field has matured.

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Introduction
The 2014 Keystone Symposium on Adult Neurogenesis took place in Stockholm from 12 to 17 May, and was jointly organized by Fred ‘Rusty’ Gage (Salk Institute for Biological Studies, La Jolla, CA, USA) and Jonas Frisén (Karolinska Institutet, Stockholm, Sweden). For many scientists, the Keystone Symposia are synonymous with ski, après-ski and, of course, science. But with the 2014 Winter Olympics taking place in subtropical Sochi, a Keystone conference on the shores of the Baltic Sea seemed to fit a trend. Instead of erecting snow cannons to keep participants happy, the Keystone organizers filled the afternoons with extra workshop sessions in addition to the main presentations and poster sessions. A Keystone Symposium in a Scandinavian capital certainly felt different, with a decidedly more downtown touch than the rugged Rockies, but the experiment was a phenomenal success.

The meeting attracted some 240 researchers, including many graduate students, postdocs and junior faculty. This was the third Keystone Symposium on Adult Neurogenesis, with the two previous symposia both held in New Mexico, USA. The move to Europe opened the meeting to a regionally different target audience and allowed many of the European groups to attend with several members of their group. Fortunately, the ‘pond’ did not stop our colleagues from the Americas from joining, even though fewer young researchers from afar could attend. With an international flavor that is typical of Keystone Symposia, this meeting left a lasting impression and set a new trend that ought to be continued.

Since its discovery in 1965, the field of adult neurogenesis has raised some fundamental questions which remain to be fully answered. Perhaps one of the most basic and important questions is: what is adult neurogenesis good for? More specific questions surround the timing and location of origin of adult neural precursor cells, as well as the precise nature of these cells. Understanding the regulation of adult neurogenesis, whether by behavioral factors or at the molecular and niche levels, is another challenging area. Other researchers are interested in more functional aspects: are newborn neurons involved in encoding new memories in the adult brain and, if so, how? How is adult neurogenesis regulated by behavior and how might adult neurogenesis have evolved? All of these topics were addressed in one way or another during the meeting, and although these questions continue to drive the field, it is clear that our research area has come a long way in a short time, with many interesting answers at least partially provided.

The symposium organizers Gage and Frisén assembled a fantastic program, balancing well-established leaders of the field with an exciting showcase of talks selected from the abstracts. One particular appeal of the Keystone Symposia lies in the presentation of unpublished data, which limits how much this Meeting Review can reveal without undermining the trust that these meetings are based on. As such, we will provide an overview of the meeting and discuss common topics and emerging ideas, rather than elaborating on specific data. The emphasis on unpublished work also creates a particular atmosphere of trust that sets the Keystone Symposia apart from larger meetings elsewhere, while the immense scope of the adult neurogenesis field and the many friendships among its protagonists support this remarkable openness. Some speakers will undoubtedly still keep a trick or two up their sleeve in order to keep the field fresh with surprises, but this does not detract from the value of the meeting.

The Keynote lecture by Anders Björklund (Lund University, Sweden) was the perfect opening to the meeting, setting the scene for adult neurogenesis research in Sweden and beyond. Björklund is a pioneer of neurotransplantation and much of his work, conducted partly with Gage, facilitated adult neurogenesis research in the 1990s. In his address, Björklund gave a personal account of the history of cell-based neural repair, which began with pioneering work performed during the 1970s using immature midbrain dopaminergic neurons for cell replacement in animal models of Parkinson’s disease. More recently, this approach has regained interest thanks to the development of refined protocols that allow the generation of authentic and transplantable midbrain dopaminergic neurons from human pluripotent stem cells. Most conferences neglect such a historical perspective and thereby undermine the value of such talks that go far beyond merely a tale of yesteryears. They emphasize the threads along which research progresses, widen the horizon to see the bigger picture and can even help to prevent researchers from ‘reinventing the wheel’ when trying to come up with new experimental strategies.

Lessons from evolution
Regeneration is a highly variable trait across the animal kingdom. Newts, salamanders and zebrafish far surpass mammals in their regenerative capacity. András Simon (Karolinska Institutet, Stockholm, Sweden) outlined how ependymoglial cells, a particular type of glial cell in the ventricular wall, can regenerate cholinergic and dopaminergic neurons in the newt brain and discussed the role that the environment may have had in the evolution of this phenomenon. Simon described his work in
manipulating oxygen availability for newts, which is reminiscent of the varying oxygen levels in their natural habitat. Artificial variation in oxygen levels was observed to regulate neurogenesis in the adult newts, and Simon proposed that adult neurogenesis and brain regeneration in this animal co-evolved with the involvement of reactive oxygen species in the regulation of neural progenitor fate. Elly Tanaka (Center for Regenerative Therapies, CRTD, Dresden, Germany) works on the axolotl system, in which a full spinal cord lesion results in activation of robust neural stem cell self-renewal, followed by neurogenesis to replace all missing neural cell types. She found that injury induces the reactivation of planar cell polarity pathway proteins that contribute to posterior outgrowth of the proliferative neural stem cells, as well as ensuring self-renewing divisions. Michael Brand (CRTD, Dresden, Germany) presented his recent studies focusing on the role of leukotriene signaling in stem cell-based neuronal regeneration in the zebrafish. Among other findings, his work highlighted the power of zebrafish as a model organism and the impressive genetic tools available in this species that can help to advance the field.

From this session it became clear that using diverse scientific model organisms, rather than mice alone, helps us to better understand and appreciate the principles and complexities of regeneration across the animal kingdom, and to determine our own place within this spectrum. To this end, Frisén presented his work on human adult striatal neurogenesis (Ernst et al., 2014), with additional unpublished data. Contrary to common belief, adult neurogenesis in humans is no atavism, but there are unique features that have added complexity to the picture, rather than eliminating the trait, with increasing brain plasticity.

Another related topic was discussed by one of us, Gerd Kempermann (German Center for Neurodegenerative Diseases, Dresden, Germany), during his talk on diversity in adult neurogenesis. Kempermann emphasized that even within one species there are genetic and non-genetic sources of variability in plasticity. The consequences of such variability remain largely underexplored, but with the growing focus on patient-specific disease modeling and ‘personalized medicine’, this might become an increasingly crucial issue.

**The molecular regulation of neurogenesis**

A significant focus of all recent meetings on adult neurogenesis is molecular regulation. This can be investigated at many levels, including genetic and epigenetic control, metabolic control and systemic control. Jenny Hsieh (University of Texas Southwestern Medical Center, Dallas, USA) explained how neural stem cells are kept under control at the epigenetic level during homeostasis. She discussed her data on the role of neuron-restrictive silencer factor/RE1-silencing transcription factor (NRSF/REST) and class I histone deacetylases in preventing precocious activation of neural stem cells (NSCs) (Gao et al., 2011). Sebastian Jessberger (University of Zurich, Switzerland) highlighted a new aspect of the molecular regulation of adult neurogenesis by introducing lipid metabolism into the picture. In addition to the importance of fatty acid synthase (Fasn) in adult neurogenesis (Knobloch et al., 2013), he could show that blocking fatty acid oxidation is sufficient to reduce the number of quiescent stem cells in the adult brain. Continuing with the metabolic theme, Dieter Chichung Lie (University of Erlangen, Germany) reported how running elevates mitochondrial volume in NSCs and facilitates mitochondrial transport (Steib et al., 2014). Energy metabolism in adult neurogenesis has not received adequate attention so far; however, it has become clear from this meeting that inroads are beginning to be made in this intriguing and important area of research. On the whole, this session showed how diverse the regulation of adult neurogenesis is – meetings such as the Keystone Symposia help to strengthen the links between these different areas, but the upcoming challenge lies in integrating the complexity of the entire spectrum of regulators, from epigenetic to metabolic levels and beyond.

**The fate of the offspring**

Increasing complexity is tangible in multiple areas of adult neurogenesis, such as the diversity and fate of the neural stem cell lineage. Arturo Alvarez-Buylla (University of California, San Francisco, USA) discussed how the precursor cell populations in the sub-ventricular zone (SVZ) develop from the embryo to the adult. By devising an elegant method to barcode neural progenitor cells, he and his co-workers traced the origin of newborn neurons from microdomains in the ventricular wall during the course of development (Merkle et al., 2014). He presented a refined and more complex view of the ontogeny of neural stem cells that challenges his previous ‘pine-tree model’ (Alvarez-Buylla et al., 2001).

Changes in cell fate are not restricted to neural lineage progression during development. Magdalena Götz (Institute of Stem Cell Research, Helmholtz Center, Munich, Germany) reported on the direct reprogramming of astrocytes to neurons upon transfection with Ascl1, emphasizing the dependence of lineage on a few molecular restriction points. An important player in the progression from precursor cells to integrated neurons is the anti-apoptotic gene Bcl2.
Adult NSCs seem to be depleted with age – at least under laboratory conditions devoid of stimuli. Grigori Enikolopov (Cold Spring Harbor Laboratory, NY, USA) emphasized this decline in his presentation. Using a variety of labeling and imaging techniques, such as the confetti reporter, multi-isotope imaging mass spectrometry (MIMS), N15-thymidine and double- and triple-S phase labeling, he proposed that decreased neurogenesis is driven by the continuous depletion of NSCs in the adult brain. The question remains as to what happens under more cognitively demanding conditions and also whether neurogenic potential might be maintained at the level of intermediate progenitor cells, possibly consistent with the findings presented by Götz.

The malleability of this system and the molecular hallmarks of different stages of the NSC progeny were discussed by Hongjun Song (Johns Hopkins University School of Medicine, Baltimore, MD, USA), who described what he called a ‘Google Earth view on adult neurogenesis’. This entailed an impressive flight through the murine dentate gyrus, in which Song showed that NSCs exhibit different characteristics, including latency to cell cycle entry, cell cycle exit, fate choice and cell cycle re-entry. How these separate populations are regionally distributed remains an unanswered question.

**New kids on the block: are they up to something?**

Not surprisingly, the function of adult-born neurons receives particular attention at any conference on adult neurogenesis. Function and regulation are increasingly recognized as tightly interdependent. In the rodent olfactory bulb (OB) for example, integration of newborn neurons remodels the existing circuitry in response to learning. This was discussed by Pierre-Marie Lledo (Institut Pasteur, Paris, France) in his presentation on changes in the synaptic plasticity of newborn OB neurons. Lledo discussed how information processing modulates input-specific synaptic plasticity of adult-born neurons and revealed the role of the olfactory cortex in this process.

Alejandro F. Schinder (Fundación Instituto Leloir, Buenos Aires, Argentina) showed that four-week-old immature hippocampal granule cells exhibit a low threshold to become excited by inputs from the entorhinal cortex, which in turn leads to their relatively promiscuous response to all kinds of incoming stimuli. However, once they mature, the new granule cells elevate their spiking threshold and input specificity. This shift in balance has important implications for the functional properties of the network and might help to explain how it offers advantages over other types of plasticity. Henriette van Praag (National Institutes on Aging, Bethesda, MD, USA) discussed how her findings on information exchange between new neurons and other brain regions, and how this can be modulated by physical activity. She explained how initial inputs to newborn neurons come from septal-hippocampal and dentate granule cells followed by entorhinal cortex regions. Such observations highlight that adult neurogenesis takes place in a large functional context, going far beyond the immediate hippocampal network. Discussing experimental results that were among the first to introduce the use of optogenetics to the field, René Hen (Columbia University, NY, USA) showed how subtle differences in the properties of adult-born granule and mature granule cells might underlie their variable impact on pattern separation, which can be broadly defined as the ability to keep separate distinct bouts of information.

The term ‘pattern separation’ has created much confusion during discussions on the function of adult-born hippocampal neurons, as different fields use the term in different ways. Several speakers alluded to this fact and tried to achieve better precision here, agreeing on the term ‘behavioral pattern separation’ instead. This term avoids too narrow a computational definition that would otherwise focus on the issue of how true the output of the network is to the input. In this context, an exciting session towards the end of the conference, featuring Brad Aimone (Sandia National Laboratory, Albuquerque, NM, USA), Sue Becker (University of Toronto, Canada) and Alessandro Treves (SISSA, Trieste, Italy), played a particular role by offering different theoretical perspectives on how adult-born neurons contribute to hippocampal function.

All the findings mentioned above still beg the question: do newborn neurons encode new memories? According to Gage, they do. In fact, the Gage laboratory proposes that adult-born neurons are involved in discriminating between events that occur within very similar contexts. Nora Abrous (INSERM, Paris, France) also spoke about the importance of adult-born neurons in memory. Abrous discussed her view against the notion that new neurons are functional only within a crucial time window during the immature stage and retire thereafter. Instead, she emphasized a role for mature adult-born neurons in memory throughout adult life and in successful aging.

An exciting twist in the tale of the function of adult hippocampal neurogenesis came from Paul Frankland (University of Toronto, Canada), who provocatively suggested that neurogenesis mediates forgetting and can thus be linked to infantile amnesia (Akers et al., 2014). In this study, memory persistence after fear conditioning was inversely correlated with adult neurogenesis, whereas increasing neurogenesis was sufficient to induce forgetting. The study stimulated a lot of insightful discussion – the idea of adult neurogenesis being involved in rewiring the brain during childhood and puberty is reminiscent of what Joseph Altman proposed in 1973 (Altman et al., 1973) and has since been discussed by Amrein and Lipp (2009). The interesting issue will be whether this aspect of plasticity is really about forgetting per se, and how it relates to the general role of adult-born neurons in memory retention. Frankland’s results and the ensuing discussion clearly mark an important step forward in this respect.

**When things go wrong**

Understanding the regulation and function of adult neurogenesis under normal homeostatic conditions can shed light on how deficits in adult neurogenesis might contribute to disease. So far, the pathological perspective has focused more on the regulatory aspects than on specific functional deficits that might occur. Guo-Li Ming (Johns Hopkins University, Baltimore, MD, USA) discussed how disrupted in schizophrenia 1 (Disc1) regulates dendritic morphology and mechanistic target of rapamycin (serine/threonine kinase) (Mtor) activity and how disruption of these processes is linked to disease. She showed how the specific loss of Disc1 in newborn neurons impaired object-place recognition memory, induced depressive behavior and caused synaptic defects in mice. Brian Christie (University of Victoria, Canada) introduced an ontogenic angle into functional neurogenesis and showed that prenatal ethanol exposure (PNEE) seriously affects synaptic plasticity and learning postnatally. One of the central players in PNEE is glutathione, which is reduced by PNEE and elevated by exercise. An intriguing aspect of his work is the attempt to directly translate his research to human subjects.

A presentation by H. Georg Kuhn (University of Gothenburg, Sweden) gave insight into OB neurogenesis in disease. Kuhn reported that epidermal growth factor (EGF) can induce the formation and vascularization of polyps in the SVZ, highlighting the link between angiogenesis and neurogenesis.
The field of adult neurogenesis research overlaps with induced pluripotent stem cell (iPSC) research with respect to advanced cell replacement strategies for neurodegenerative diseases. Olle Lindvall (Lund University, Sweden) discussed his group’s efforts in generating human cortical neurons from iPSCs in order to provide possible replacement cells for the treatment of stroke. Among other things, his talk demonstrated how far the field has come in such a short time, closing the loop to Björklund’s keynote lecture on the pioneering days of transplantable cell therapies.

**The adult neurogenesis field in transition**

In summary, the 2014 Keystone Symposium on Adult Neurogenesis revealed the progress that the field has made across a broad spectrum from phenomenology to functional insight. Regulation of adult neurogenesis is increasingly related to the functional contexts. If ‘plasticity’ is the reciprocal interaction between structure and function, then adult neurogenesis starts emerging as a true, even though highly complex, plastic process. The identification of individual regulatory factors and genes starts playing less of a role: it has become obvious that the field is moving to a more systems-based perspective, looking at pathways, networks and large-scale regulatory processes.

One interesting aspect of this particular Keystone Symposium on Adult Neurogenesis was that every talk was translated into sign language in real time by one of three sign language interpreters. This primarily catered to one attending deaf researcher but also led to interesting discussions: how does one sign phrases like ‘adult neurogenesis’, ‘Ascl1’, ‘pattern separation’ and so forth? The three signers were eager to discuss this issue, which led to a number of unexpected and profound exchanges about the nature of our terminology, the dependence of concepts on the language used to express them and the nature of spatial representations in general. Given the role of the hippocampus and hence adult neurogenesis in spatial memory and navigation, these extracurricular discussions were more than fitting. In a philosophical sense, this added a layer of complexity to the conference: the translation of our linear spoken language into the three dimensions of sign language stood to remind everybody of the dimensionality in our work that we often do not see.

Atmospherically, the meeting had a unique touch. This might have been influenced by the experience of Nordic hospitality and the Swedish sense of equality and style: the openness of the speakers to share unpublished work and the intensity of the scholarly discussions after the talks and during the poster sessions were very stimulating. The field needs these meetings to foster growth and communication, and the meeting organizers as well as the Keystone Symposia staff are to be congratulated and encouraged to uphold what was truly a fantastic meeting.

**Competing interests**

The authors declare no competing financial interests.

**References**


