Nobel Minisymposium No. 59

in the series *Frontiers in Medicine*

From models towards regenerative therapies

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Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

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From models towards regenerative therapies

Nobel Forum, Karolinska Institutet, Stockholm Oct 12th , 2022

08.50-09.00	**Welcome address** Eva Hellström Lindberg and András Simon
	Stem cell dynamics – Robert Månsson (Chair)
09.00-09.45	**Stem Cells: Coping with Stress** Elaine Fuchs, Howard Hughes Medical Institute, The Rockefeller University, USA
09.45-10.30	**The niche for stem cells and cancer: fishing for pathways that drive self-renewal** Leonard Zon, Harvard Stem Cell Institute, Harvard Medical School, USA
10.30-11.00	Coffee break
	Model organisms – Kirsty Spalding (Chair)
11.00-11.45	**Understanding the Sources of Regenerative Capacity in animals** Alejandro Sánchez Alvarado, Stowers Institute for Medical Research, USA
11.45-12.30	**The African killifish: a new model to study aging and 'suspended animation'** Anne Brunet, Stanford University, USA
12.30-14.00	Lunch
	Regenerating complex structures – Qiaolin Deng (Chair)
14.00-14.45	**Mammalian regeneration at your fingertips** Freda Miller, University of British Columbia and Hospital for Sick Children, University of Toronto, Canada
14.45-15.30	**Repair and Regeneration of the Gas Exchange Niche in the Lungs** Edward E. Morrisey, Penn-CHOP Lung Biology Institute, University of Pennsylvania, USA
15.30-16.00	Coffee break
	Organoids – Fredrik Lanner (Chair)
16.00-16.45	**Generating human kidney tissue from pluripotent stem cells** Melissa Little, Murdoch Children's Research Institute, Australia and University of Copenhagen, Denmark
16.45-17.30	**Lgr5 Stem Cell-based organoids in human disease** Hans Clevers, Research and Early Development, Roche, Switzerland
	Closing remarks

Abstracts

Stem Cells: Coping with Stress

ELAINE FUCHS
Howard Hughes Medical Institute, The Rockefeller University, USA

Adult tissue stem cells have the ability to self-renew long term and differentiate into one or more tissues. Many stem cells are used sparingly to replenish cells during normal homeostasis. However, even stem cells that are quiescent must be able to respond quickly to injury in order to fuel rapid tissue regeneration. How stem cells balance self-renewal and differentiation is of fundamental importance to our understanding of normal tissue maintenance and wound repair. The regulatory circuitry governing this normal balancing act is must be intricately regulated in normal homeostasis, and then transiently altered to cope with injury responses. Increasing evidence suggests that the mechanism goes awry in inflammation and becomes hijacked in cancers. We use skin as a model to understand how the microenvironment impacts the stem cells and their behavior in health and disease, with the intent to unfold new avenues for therapeutics.

The niche for stem cells and cancer: fishing for pathways that drive self-renewal

LEONARD ZON
Harvard Stem Cell Institute, Harvard Medical School, USA

Blood stem cells are born in the embryo and travels to specific sites such as the fetal liver and bone marrow to make blood. The environment or “niche” can alter the decision of a stem cell to renew itself or to differentiate. We have used the zebrafish to create niche blood vessels and found that the stem cells are attracted to this new environment and divide symmetrically. Another type of niche stimulates the beginning of a tumor. Using zebrafish, we found that the niche forms in a precursor regions that surrounds a stem cell that will become the tumor. This zebrafish provides a new way of examining the origin of cancer.

Understanding the Sources of Regenerative Capacity in animals

ALEJANDRO SÁNCHEZ ALVARADO
Stowers Institute for Medical Research, USA

Under normal physiological conditions, the functions of many organs depend on the continuous destruction and renewal of their cells. Equally remarkable is the fact that the adult tissues and organs of many organisms can be fully restored after amputation. In fact, metazoans have evolved a series of renewal and repair mechanisms to respond to both trauma and normal wear and tear. Such mechanisms are under tight regulatory control such that the form and function of tissues, organs, and systems can be maintained throughout life. As important as repair and restoration are to the survival of multicellular organisms, we know little about how these processes are effected and regulated at the cellular and molecular levels. Here, I will discuss how the study of two research organisms, the planarian *Schmidtea mediterranea* and the African killifish *Nothobranchius furzeri* is beginning to shed light on the way adult animals regulate tissue homeostasis and the replacement of body parts lost to injury.

The African killifish: a new model to study aging and 'suspended animation'

ANNE BRUNET
Stanford University, USA

We have pioneered a new model organism for aging research, the naturally short-lived African killifish *Nothobranchius furzeri*. The African killifish lives in ephemeral pools of water in Africa, and has evolved a short life cycle adapted to this habitat. Its embryos can also resist drought until the next wet season in a state of 'suspended life'. In laboratory conditions, the African killifish has a maximal lifespan of about 4-6 months, and is, so far, the shortest-lived vertebrate that can be bred in captivity. The natural short lifespan make the African killifish an ideal model to probe the mechanisms of aging in vertebrates. We have successfully transformed this natural short-lived vertebrate into a usable model organism for aging research. We have completed the first *de novo* assembly of the African killifish genome using deep sequencing and have successfully developed CRISPR-Cas9 mediated genome-editing in this fish. The development of modern genomic tools in the African killifish are major steps in pioneering this species as a new vertebrate model for aging research. Our goal is to use this model to discover new principles underlying aging, longevity, and 'suspended animation' in vertebrates. We already identified several loci associated with survival between different strains of the African killifish from different regions. Using genome-editing, we have generated strains deficient for several genes in nutrient-sensing and epigenetic pathways. We want to develop this system to examine the role of new vertebrate-specific genes in aging. We will determine if perturbing chromatin modifiers affects the lifespan of vertebrates, and if so, whether this triggers transgenerational inheritance of lifespan in descendants. We are excited to use this system to understand the principles underlying 'suspended animation' and whether they have the ability to preserve tissues and organs long-term.

Mammalian regeneration at your fingertips

FREDA MILLER
University of British Columbia and Hospital for Sick Children, University of Toronto, Canada

This lecture will discuss one of the few examples of true multi-tissue mammalian regeneration, the adult murine digit tip, focusing on why the digit tip regenerates when other mammalian tissues do not. Work will be presented showing that the regenerative blastema forms by recruitment of mesenchymal cells from diverse local tissues including the bone, dermis, and nerve, and that all of these tissue-biased mesenchymal cells are then reprogrammed by their environment to acquire a unique regenerative blastema transcriptional state that allows them to contribute to regeneration in a fashion that is agnostic to their original tissue-of-origin. Work will also be presented discussing how the digit tip environment allows this endogenous reprogramming. In particular, discussion will be focused on three key environmental determinants, the nail organ, peripheral nerves and immune cells, and how these three factors determine regeneration versus fibrosis and scar formation.

Repair and Regeneration of the Gas Exchange Niche in the Lungs

EDWARD E. MORRISEY
Penn-CHOP Lung Biology Institute, University of Pennsylvania, USA

Gas exchange between the external environment and the cardiovascular system is essential for the survival of most advanced terrestrial animals including humans. The distal lung alveolus is a complex multi-cellular niche that intimately links with the cardiovascular system to accomplish its critical physiological function. How the various cell lineages within the alveolar niche are generated during development and regenerated after acute injury, as well as the differences between the mouse and human gas exchange interface will be discussed.

Generating human kidney tissue from pluripotent stem cells

MELISSA LITTLE
Murdoch Children's Research Institute, Australia and University of Copenhagen, Denmark

The kidney is a vital organ responsible for fluid balance and nitrogenous waste removal. Unfortunately, all functional units in the kidney, the nephrons, are generated during development and are not replaced during postnatal life. Hence, the kidney is not a regenerative organ, nor are human kidney diseases necessarily well modelled in animals. Based on our understanding of normal embryogenesis, it has recently become possible to guide the directed differentiation of human pluripotent stem cells towards the formation of a model of the human kidney, referred to as kidney organoids. These complex multicellular tissues arise through cellular self-organisation and contain patterned and segmented nephrons within a renal stroma that contains endothelial cells. In this presentation, Professor Melissa Little will discuss the application of human kidney organoids for understanding normal human development, modelling disease and screening drugs. She will also address the challenges that remain to being able to create transplantable kidney tissue for renal replacement therapy.

Lgr5 Stem Cell-based organoids in human disease

HANS CLEVERS
Research and Early Development, Roche, Switzerland

We originally defined Lgr5 as an exquisite stem cell marker which allowed the identification of the intestinal epithelial stem cells. Since then, Lgr5 has emerged as a generic marker for active stem cells in most of not all epithelia of the adult mammalian body. Single sorted Lgr5+ve stem cells can initiate ever-expanding crypt-villus organoids, or so called 'mini-guts' in 3D culture. The technology is based on the observation that Lgr5 is the receptor for a potent stem cell growth factor, R-spondin. Similar 3D cultures systems have been developed for the Lgr5+ve stem cells of human stomach, liver, pancreas, breast etc. Organoid technology opens a range of avenues for the study of development, physiology and disease, for drug development and for personalized medicine. In the long run, cultured mini-organs may replace transplant organs from donors and hold promise in gene therapy.