Developmental Biology in Nordic Countries

Guest Editors

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Preface

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It is our pleasure to present to the readers of the *International Journal of Developmental Biology* (Int. J. Dev. Biol.) a Special Issue entitled *Developmental Biology in Nordic* Countries. This Special Issue continues the journal's tradition of presenting, from various viewpoints, the historical and current trends of the developmental and biological sciences in different countries (Special Issues/countries). The idea to assemble this Issue stems, in part, from the early days of the career of the editor, Seppo Vainio, when the *Int J Dev Biol* published its first special issue entitled *Developmental Biology in Finland* (Vol. 33, N. 1, 1989, *Developmental Biology in Finland*, edited by Eero Lehtonen). As an MSc student at an early stage of his career, Vainio had the privilege of contributing to this Special Issue alongside his PhD supervisors, Irma Thesleff, Markku Jalkanen and Lauri Saxén. Saxén was a pioneer of Finnish developmental biology. He worked with prof. Sulo Toivonen with the exciting Spemann organizer problem connected to many fundamental concepts such as the embryonic induction, and embryonic patterning alongside with the central nervous system development. We are privileged to have an elegant contribution of Neiro who has written an article of the history of the organizer and the roles of the Finnish Developmental biology school in these fundaments that offered Hans Spemann his Nobel price from his discovery. The article of Chandel and Hörnblad on the Isthmic organizer is an inspiration with this regard as well to learn how such organizing centers are relevant also later in development.

The progress from 1989 Special Issue to the present day in the field of Developmental Biology has been tremendous. During this journey, Seppo Vainio teamed up with Satu Kuure, the other editor of this Special Issue who trained under Seppo Vainio and Hannu Sariola and currently runs her own research program on renal differentiation, to compile an overview of research carried out in the Nordics. In this compilation, we highlight many of the major technological breakthroughs and conceptual discoveries that have been made over the years in this tremendous scientific field.

First, the maternal screen with the fly laid the foundation for much of developmental genetics. Then, in mammals, the ability to generate transgenic mice via pronuclear injection was established. This was followed by the capacity to generate multipotent embryonic stem cells. These topics are nicely addressed in the current Special Issue in sophisticated paper of Nykänen and Vuoristo who review the current understanding of embryonic genome activation with specific emphasis on *DUX4,* while Hunt and Mannervik introduce to the reader aspects of the classic developmental genetic model, namely the fruit fly from the point of view of enhancer promoter interactions.

The advances in the field made it possible to develop the gene-targeting technologies based on homologous recombination. These technological steps allowed specific gene knockout experiments and other types of genetic engineering assays. The use of genetic engineering strategies has significantly advanced our understanding of biological processes in real physiological context in vivo, as is beautifully highlighted by Scoofs and Mäkinen. They provide in the issue a thorough overview of lymphatic endothelial cell studies with inducible *Cre* mouse line use. They will also discuss about essential experimental parameters to be utilized as experimental recommendations for targeting the lymphatic vasculature. In their paper Sammer *et al.,* go on to address these essential capacities by having targeted the *Ccer1* functions specifically in spermatogenesis.

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Sophisticated *in situ* transcript localization techniques have been developed. Classic organ culture techniques, which provided an excellent way to study organogenesis mechanisms *in vitro*, were followed by the development of mouse stem cell-based organoid technologies. Much of this progress was facilitated by the identification and production of key secreted signals from major developmental control families such as FGF, Wnt, TGF-beta, retinoic acid, and Hedgehog, as well as their secreted antagonists. A new method to modulate signaling activities is used in the original article by Ali *et al.,* In this work the 3' untranslated region of the gene was modified to disturb *Wnt4* expression levels to address Wnt4 roles by such an approach. In their original article Papagno and Mikkola followed up their previous studies with Wnt signaling and discovered that one of the downstream targets, *Ascl4*, is not required for normal skin differentiation in the mouse.

The next biomedical breakthrough occurred when it was unexpectedly revealed that advanced, differentiated cells extracted from humans could be induced back into a pluripotent state as induced pluripotent stem (iPS) cells. These developments led to powerful new methods for easier and faster gene editing. The most recent technology, based on CRISPR/Cas methods, has opened again new frontiers, enabling experimental human embryological studies as well. Some of the publications in our collection reflect the advances in stem cell derived organoids. Unger *et al.,* report the effects of Hedgehog signaling on guiding foregut differentiation through the control of HNF1 during the earliest steps of on-dish pancreas differentiation. The possibilities to model human diseases in iPS cells, either through reprogramming of patient-derived cells or introducing disease-associated mutations into isogenic iPS cells, together with humanizing strategies in model organisms, offers historical opportunities for medical advancements.

Development is highlighted by gene regulatory networks and programs behind morphogenesis and cell differentiation. Such transcriptional networks are co-functioning in the central nervous system to regulate developmental decisions and are reviewed by Achim. Combining these with recent advancements in mapping OMICS data to histological sections, such as spatial transcriptomics, will provide tremendous analytical power across classic developmental biology model systems in the near future. A new development is the discovery that many developmental signals, such as Wnt, are connected to the actions of nanosized, cell-secreted extracellular vesicles (EVs), also known as exosomes. All these advances, along with major progress in 4D imaging at the single-cell level, coupled with multi-OMICS capabilities and computing, are expected to offer new "quantum leaps" in the field of Developmental Biology. Even still today, the problem of morphogenesis remains a major challenge in understanding how genetic developmental programs build complex structures such as a kidney, or a mouse, instead of a flower.

The current set of articles in this Special Issue offers a flavor and a scent, as well as an interesting window into the excellent and vibrant field of Developmental Biology in Nordic Countries, which has a long and exciting history within the life sciences. We wish great moments of discovery for the readers as they explore the achievements from the Northern part of the globe.

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