

Developmental Biology in Israel

Guest Editors

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Preface

A “Brief History” of Developmental Biology in Israel

We were honored that Israel was chosen to be highlighted in a Special Issue of *The International Journal of Developmental Biology*. While the history of developmental biology in Israel is relatively short, its impact is far-reaching, so we wanted to present a concise perspective on the Israeli developmental biology community, past-present-future. This community has undergone a wonderful, nearly exponential growth over the last three decades. How exactly did this happen? There are approximately fifty research groups that focus on developmental biology questions in Israel today that are members of the Israel Society of Developmental Biology (IsSDB; <http://issdb.org/>). The community has representative groups in a plethora of model systems, such as *Nematostella*, *C. elegans*, *Drosophila*, sea urchin, ascidians, zebrafish, *Xenopus*, chick and mouse, as well as plants, representing all the major universities and their branches, which include Bar-Ilan University, Ben-Gurion University of the Negev, The Hebrew University of Jerusalem, The University of Haifa, Technion - Israel Institute of Technology, Tel Aviv University and the Weizmann Institute of Science. This Special Issue includes reviews and original articles encompassing these model systems.

The Founders: 1960's – 1970's

So how did it all start? Clearly “Developmental Biology” or “Embryology” in Israel started in the late 1950's with the establishment of Hefziba Eyal-Giladi's lab at The Hebrew University in Jerusalem. Her first publications start in the early 1960's with the same amphibian systems she brought back from Pieter Nieuwkoop's lab in Holland. However, in the mid-late 1960's she changed gears and became one of the pioneering forces in developing the chick embryo as a model system. Her seminal work in the 1970's defined the earliest stages of chick development and examined the earliest factors regulating embryonic axis formation during early chick development. Her F1 progeny, Eduardo Mitrani (Hebrew University) and Oded Khaner (Hadassah College) continued to investigate mesoderm induction and axis formation as independent researchers. Hefziba Eyal-Giladi was no doubt the founder of the field of experimental embryology in Israel. Sadly, while preparing this Special Issue, Hefziba Eyal-Giladi passed away on January 7, 2017. It is important to mention that in the 1960-70's, Richard Kulka, a biochemist at Hebrew University, also performed timely biochemical analyses of pancreatic digestive enzyme regulation during chick embryonic development. Fanny Doljanski who joined the Hebrew University Medical School in the 1960's also made significant contributions on how cells interact with the extracellular environment to regulate tissue morphogenesis.

In parallel, at the Weizmann Institute, there were two research groups, not “embryological” *per se*, that were doing groundbreaking cell biology work related to developmental biology questions of cell fate specification and differentiation. These researchers were David Yaffe and Leo Sachs. David Yaffe published his first papers on muscle cell culture *in vitro* during the mid-1960's and by the late 1970's, his lab developed cell line systems that could be triggered to differentiate from myoblasts (muscle precursors) to differentiated myotubes *in vitro*. David Yaffe and colleagues, Uri Nudel (Weizmann Institute), Moshe Shani (The Volcani Center) and Danielle Melloul (Hadassah - Hebrew University) successfully leveraged this system in the 1980-90's to clone and characterize the initial tissue-specific genes turned on during early myogenesis, and they were amongst the first to define a tissue-specific muscle enhancer in the α -actin gene. Moshe Shani was the first independent researcher in Israel to introduce transgenic mouse technology, and his group had many fruitful collaborations within the budding Israeli developmental biology community in the late 1980's - early 1990's. From the mid-1960's - 1970's, Leo Sachs made breakthrough discoveries in the field of hematopoietic cell biology. He developed the first systems for clonal culture of hematopoietic cells *in vitro*, identifying and characterizing the cytokine stimulating factor (CSF) growth factors. His innovative work spanning into the 1980-90's included characterization of how cytokines and CSFs interact in hematopoietic cell lineage differentiation.

Another milestone in the evolving Israeli developmental biology community was the pioneering work in epigenetics by Howard Cedar and Aharon Razin from The Hebrew University. Their labs published their first collaborative studies on DNA methylation in the late 1970's. Over the past forty years, they have elucidated the molecular biology nuts and bolts of DNA methylation and its potential role in transcriptional regulation. Their findings have had an enormous impact on how the epigenetics field was shaped worldwide. Their research was always tightly linked to developmental questions, such as to the role of DNA methylation and transcriptional regulation in cell and tissue differentiation or how DNA methylation patterns are established during embryonic development as a basis for regulating somatic cell gene expression. Together, they encouraged multiple generations of their graduate students to continue in the direction of developmental biology, and they contributed to producing the F1 progeny for the boom in developmental biologists that returned to Israel from postdocs abroad in the 1980-90's. Their ex-students include Yosef Gruenbaum (Hebrew University), Joel Yisraeli (Hebrew University), Dale Frank (Technion), Avihu Klar (Hebrew University), Ze'ev Paroush (Hebrew University) and more recently, Sharon Schlesinger (Hebrew University). Some of the F2 developmental biology progeny of these labs are Ruth Ashery-Padan (Tel Aviv University), Peleg Hasson (Technion), Karina Yaniv (Weizmann Institute), and Tal Burstyn-Cohen (Hebrew University). These Cedar/Razin "graduates and progeny" work on a plethora of model systems, such as *C. elegans*, *Drosophila*, zebrafish, *Xenopus*, chick, mouse and stem cells, asking questions on embryonic polarity, morphogenesis, cell fate specification and epigenetics.

In the 1980's, the Israel Society of Developmental Biology (ISDB) was founded by Hefziba Eyal-Giladi, Zvi Sachs (Plant Development) and, Eliezer Sekeles (Human Anatomy), all from the Hebrew University. Some of the other active members in the early years were Yehuda Ben Shaul, Boaz Moav, Ruth Shalgi and Lily Vardimon from Tel Aviv University who also established the Switzerland Institute for Developmental Biology, which supports activities in the field (<http://www.swissinstitute.tau.ac.il/>). The ISDB has been continuously active since the 1980's, usually having an annual conference highlighted with renowned invited international speakers, along with all the Israeli research groups. Previous society chairs include, Hefziba Eyal-Giladi (Hebrew University), Talila Volk (Weizmann Institute), Dale Frank (Technion), Eldad Tzahor (Weizmann Institute), and the present chair, Eli Arama (Weizmann Institute). The ISDB belongs to the global-framework of the International Society of Developmental Biology (ISDB).

Second Generation: 1980's - 1990's

In the 1980's a number of key labs were established by returning postdocs that were highly focused on fundamental developmental biology questions; the labs of Yosef Gruenbaum (Hebrew University), Abraham Fainsod (Hebrew University), Chaya Kalcheim (Hebrew University) and Ben-Zion Shilo (Weizmann Institute). Yosef Gruenbaum and Abraham Fainsod collaborated on the role of *hox* genes in early chick development. Yosef Gruenbaum became more focused on developmental questions in *Drosophila* and *C. elegans*, while Abraham Fainsod studies early axis development in *Xenopus*.

Two of the most influential groups that set the tone for hardcore developmental biology research in vertebrate and invertebrate model systems in Israel, were the labs of Chaya Kalcheim and Ben-Zion Shilo. Chaya Kalcheim (a former postdoc from Nicole LeDourins's lab) has done fundamental work on the mechanisms controlling nervous and skeletal system development. She has made huge contributions on the understanding of neural crest specification and migration, in addition to somite cell fate specification. Chaya Kalcheim is recognized internationally as a leader in vertebrate developmental biology research, but she has also promoted the experimental embryology in the dynamic chick embryo community in Israel, a generation downstream from Hefziba Eyal-Giladi. F1 progeny from the Kalcheim lab that continue to utilize chick embryos as a model includes, Dalit Sela-Donenfeld (Hebrew University), Yuval Cinnamon (Volcani Institute) and Ron Goldstein (Bar-Ilan). Other members of the dynamic Israeli chick community are Avihu Klar (Hebrew University), Ram Reshef (University of Haifa), Tom Schultheiss (Technion), Miguel Weil (Tel Aviv University) and Eldad Tzahor (Weizmann Institute). These labs investigate developmental biology topics such as patterning, axis formation, organogenesis, cell migration and polarity in the kidney, muscle, heart, somite and nervous systems.

After a post-doc with Robert Weinberg, Ben-Zion Shilo established his own lab as a *Drosophila* geneticist at the Weizmann Institute. Ben-Zion Shilo's lab has made groundbreaking and seminal discoveries on the signaling pathways regulat-

ing cell fate decisions and cell morphogenesis during early *Drosophila* embryogenesis. He also forged the leadership for creating a greater active *Drosophila* community in Israel, which includes labs at all the major universities throughout the country. He was recently awarded the first Israel Society of Developmental Biology Career Award as recognition for his great contributions to the Israeli developmental biology community. F1 progeny from Ben-Zion Shilo's lab are: Eyal Schejter (Weizmann Institute), Ron Wides (Bar-Ilan), Erez Raz (University of Munster), Ronen Schweitzer (OHSU School of Medicine), Eli Zelzer (Weizmann Institute), and Amir Sapir (University of Haifa). Some of the other earlier established labs included Ze'ev Lev (Technion) and later Talila Volk (Weizmann Institute) and Ze'ev Paroush (Hebrew University). From the earlier generation of Israeli geneticists, Ze'ev Lev's F1 progeny are Adi Salzberg (Technion), who works on *Drosophila* peripheral nervous system development, and Eli Arama (Weizmann Institute) who studies cell death. F2 progeny from Adi Salzberg's lab are Adi Inbal (Hebrew University) and Estee Kurant (University of Haifa). Talila Volk investigates muscle and tendon morphogenesis in the fly; her F1 progeny is Hila Toledano (University of Haifa). Ze'ev Paroush studies how signaling pathways regulate transcription factor activity during early development; his F1 progeny is Peleg Hasson (Technion). In the early 2000's, the labs of Uri Abdu (Ben-Gurion University), Tamar Juven-Gershon (Bar-Ilan), Amir Orian (Technion), Oren Schuldiner (Weizmann Institute) and Yoav Soen (Weizmann Institute) joined the vibrant Israeli *Drosophila* community. The Israeli *Drosophila* community, which has grown greatly over the years, studies a large variety of topics, such as body axis formation, musculoskeletal and nervous system development, tissue patterning, morphogenesis and transcriptional regulation. Evolution of arthropod segmentation is studied in Ariel Chipman's lab (Hebrew University), an F1 progeny of Oded Khaner (Hadassah College). Also worth mentioning is the small, but active *C. elegans* developmental biology community, which includes Limor Broday (Tel Aviv University), Yosef Gruenbaum (Hebrew University), Benjamin Podbilewicz (Technion), and Oded Rechavi (Tel Aviv University). These groups investigate cell cycle, cell motility, fusion, cell death, morphogenesis and embryonic epigenetics. Due to the critical mass of active invertebrate research labs, the *Drosophila* and *C. elegans* communities in Israel have an annual one-day joint symposium.

During this time period, several *Xenopus* labs were established in Israel. The labs of Eyal Bengal (Technion), Avraham Fainsod (Hebrew University), Dale Frank (Technion) and Joel Yisraeli (Hebrew University) investigate development in frogs, addressing questions of cell fate specification, cell migration and morphogenesis, embryo scaling and gene regulation in the embryonic neural and mesodermal tissue systems.

Next Generation

The next big change in the Israel developmental biology community was the return of many talented postdocs that trained in mouse genetics. The labs of Karen Avraham (Tel Aviv University), Ruth Ashery-Padan (Tel Aviv University), Nissim Ben-Arie (Hebrew University), Claude Brodski (Ben-Gurion University), Tal Burstyn-Cohen (Hebrew University), Yuval Dor (Hebrew University), David Enshell-Seiffers (Bar-Ilan), Uri Gat (Hebrew University), Yaqub Hanna (Weizmann Institute), Peleg Hasson (Technion), Eran Hornstein (Weizmann Institute), Limor Landsman (Tel Aviv University), Ruby Shalom-Feuerstein (Technion), Eldad Tzahor (Weizmann Institute), Avraham Yaron (Weizmann Institute), and Elazar Zelzer (Weizmann Institute). These groups use cutting edge mouse genetic tools to uncover fundamental processes of development, stem cell biology and regeneration. These groups are addressing basic questions in development that impact on both mammalian embryonic tissue formation and human disease.

An onslaught of zebrafish groups also came onto the scene in the new millennium. The first groups, Yoav Gothilf (Tel Aviv University) and Gil Levkowitz (Weizmann Institute) established their labs over fifteen years ago. Next the labs of Lior Appelbaum (Bar-Ilan), Adi Inbal (Hebrew University) and Karina Yaniv (Weizmann Institute) were established. These groups address developmental biology questions, focused on cell fate specification and function in the nervous, hematopoietic, vascular and musculoskeletal systems.

Where does the future lie? A number of "new wave" next generation Israeli developmental biologists are utilizing state of the art techniques of systems biology, computational biology, biomechano-physics, informatics, and modeling to ask their scientific questions. For many years Uri Alon (Weizmann Institute) and Naama Barkai (Weizmann Institute) have

contributed greatly to the developmental biology community. This next generation of researchers includes Smadar de-Leon Ben-Tabou (University of Haifa), Yaron Fuchs (Technion), Tamar Lotan (University of Haifa), Chen Luxenburg (Tel Aviv University), Iftach Nachman (Tel Aviv University), Oded Rechavi (Tel Aviv University), David Sprinzak (Tel Aviv University) and Haguy Wolfenson (Technion).

Over the years, the Israeli developmental biology community has expanded its horizons, and the research has dramatically changed as a result of the novel genetic, cellular and molecular tools that have been developed for use in various invertebrate and vertebrate models. The Israeli developmental biology community is vibrant, working in a multitude of interesting directions and systems, ranging from the most basic and earliest fundamental developmental processes up to the mechanisms that continue in adult life, such as regeneration, tissue homeostasis, metabolism and congenital disease. The community has deep seeded roots based on historically significant research that we should all take great pride in. The developmental biology community in Israel looks optimistically into the future, filled with young energetic researchers that are not afraid to innovate, to ask and to attack the most cutting edge questions to promote their research. The future looks good!

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