Regenerative Medicine and Organ-on-a-chip in Israel

The costs of both Israeli and Dutch Healthcare systems are rising through the roofs. As people are growing older than ever before, body parts, organ and tissues begin to fail. Current solutions like transplantation, artificial joints and pacemakers are not effective anymore. On top of that, the research & development of new medical treatments increased by a tenfold during the last 35 years. For every million dollar spent on R&D, the number of drugs declined from 15 new medicines in the 50s to less than 1 medicine now.¹

Two new fields of technology are developed to govern the increased demand for medical care properly:

1) Regenerative medicine (RegMed) takes the renewal of our body to a next level: repairing dysfunctional body parts with our own tissue. Think of a salamander, able to regrow its own tail and even eyes

2) Organ-on-Chips takes the study into external caused defects, like TBC (bacteria), Ebola(viruses) (Ebola) or toxics (scorpion), to a next level. Those miniature human organ modes provide a more effective and more ethical test environment for new developed medical treatments than current tools like animal testing and cells in dishes.

Hence, the emerging interdisciplinary field of RegMed is aimed at the repair, replacement or regeneration of organs, cells or tissue. Various approaches available to the advancement of RegMed are: gene therapy, stem cell transplantation, tissue engineering, reprogramming of cells and soluble molecules, which helps humanity to beat defects like multiple sclerosis, type I diabetes, heart conditions and Alzheimer. In depth research is required to regrow whole body parts, like the salamander, but the potential is definitely there.

Organ-on-chips contain a dynamic and interactive environment for living and breathing cells to survive outside the body and enables a more effective and safe R&D process for medicine testing. However, to exploit the true power of this innovative technique, researcher must find a way to connect several organs-on-chips to a human-on-a-chip. This allows clinical test environments for separate populations or even a personalized test environment, by using stem cells as input.

¹ The Boston Consulting Group, 2011
Medical Research

Israeli institutes are carrying out cutting-edge research and development projects as part of RegMed, Stem Cell initiatives, and Organs-and-humans-on-chips.

Major hospitals

Major hospitals and clinical centers have initiated their own research programs. At the center of stem cell research there is the Israel Stem Cell Society, a non-profit organization aimed at the exchange of stem cell research and RegMed data in Israel. It connects academic researchers, clinicians, health professionals and the industry.

In Jerusalem, the Hadassah Medical Organization has made major advancements on the successful treatment for ALS and multiple sclerosis. Prof. Eithan Galun is Director of the Goldyne Savad Institute of gene therapy and one of Israel's leading research of liver diseases, liver generation and genetic and cellular treatment.

The Wolfe PGD-Stem Cell Lab of the Tel Aviv Souraksy medical Center under the direction of Prof. Dalit Ben-Yosef focuses on studying issues related to early embryonic and developmental processes, genetic disorders and different aspects of cell therapy using our unique collection of PGD-derived human embryonic stem cells (hESCs).

Prof. Benjamin Dekel is one of the most innovative and internationally recognized investigators in the field of human renal stem cell biology and regenerative medicine. He established the Center for Regenerative Medicine, Stem Cell and Tissue Engineering at the Sheba Medical Center.

In Haifa, the Rambam Health Care Centre (RHCC) has nurtured strong working relationships with medical technology and pharmaceutical companies, which have contributed to stem-cell and population-genetics discoveries and the invention of interventional-device technologies.

Soroka medical center has an Apheresis Unit for Bone Marrow Transplant Unit that provide an inclusive service for the collection, preservation, and processing of stem cells for multiple procedures, including bone marrow transplants and cell transfusions.

Universities

In the academic field, Dr. Yosef Buganim from the Hebrew University of Jerusalem has been honored by the American Association for the Advancement of Science (AAAS) for his work on stem cells and regenerative medicine for researching somatic cell conversion models to identify and investigate the elements that facilitate safe and complete nuclear reprogramming. Prof. Jacob Nahmias from the same university developed a unique liver-on-chip, which already led to a breakthrough insides in the field of nanotechnology-based optoelectronic sensor.

Moreover, Technion in Haifa launched a Biomaterials and Regenerative Medicine at the Department of Biomedical Engineering Department within the Lokey Center that focuses on Stem Cell Biology and Regenerative Medicine to (I) investigate the role of the apoptotic

2 http://www.jpost.com/Jerusalem-Report/Opening-a-door-to-regenerative-medicine-459639
machinery proteins in regulating SC-dependent processes and (II) elucidate and characterize novel SC populations that contribute to regeneration and tumor formation.

The Ben Gurion University of the Negev in the south of Israel has a center for Regenerative Medicine, Cellular Therapy and Stem Cell Research where scientists take skin cells from patients with heart disease and reprogramming them to become heart cells to study cardiac diseases.

Weizmann Institute has set up the Amit lab to study the genomic code enabling immune cells to differentiate to specific subtypes and devise a specific response to invading pathogens. Their main focus is to understand how gene regulatory networks activate this code.

At Bar Ilan University, the department of Prof. Chaya Brodie focusses on cell signaling and tumorigenesis, with a focus on CNS neoplasm and the DAG/PMA receptor superfamily, as well as novel signaling pathways in the self-renewal and differentiation of neural stem cells and cancer stem cells.

The laboratory for Tissue Engineering and Regenerative Medicine of Tel Aviv University currently explores microfluidics-based, nano-technical strategies for engineering thick cardiac tissue, engineers a 3D neuronal network for spinal cord and brain regeneration, and develops smart delivery sytems that recruit stem cells to defected organs.

Private sector
The excellent educational facilities in bioengineering and medicine, the various research programs, a proper academia-industry transition and advanced start-up climate has led to a drastic increase of companies in the regenerative medicine and stem cell field which now prominently represent the industry. Several of the Israeli startup RM companies and SMEs took active part at the Global Investment Forum that took place 8-9 February 2017 in Maastricht.

- **Accelita** (Haifa) offers a simple and effective way to culture pluripotent stem cells in the form of single-cells in suspension, serving as a platform for genetic manipulation, which enables costeffective mass production of stem cells for diversity of purposes.
- **ARTSaVIT** (Yavne (C)) is developing a molecular mechanism of apoptotic-related tumor suppressor (ARTS) induced apoptosis. The company’s goal is to determine how the binding of ARTS to inhibitor-of-apoptosis proteins (IAPs) and other apoptotic regulators causes caspase activation and cell death.
- **BioGenCell Ltd.** (Netanya) is a biotechnology company developing medical therapeutic products for a wide range of diseases from adult stem cells extracted from patients.
- **Biokine Therapeutics** (Rehovot) is devoted to identifying novel molecular and cellular mechanisms that regulate tumor development and metastasis.
- **Biological Industries** (Beit HaEmek (N)) is a global supplier of Tissue culture products for research and diagnostics, including cell culture media, supplements, reagents for stem cell research and potential cell therapy.
- **BMR solutions** (Jerusalem) develops innovative therapeutics for hematologic disorders, including immunosuppressive conditions caused by irradiation and chemotherapy and has the potential to recover bone marrow of chemotherapy patients.
• **Bonus BioGroup** (Haifa) develops a method to grow 3D high-density bone grafts based on multi-cell cultures. BonoFill is derived from the patient’s own cells.

• **BrainStorm Cell Therapeutics** (Petach Tivka) is a biotechnology company developing innovative, autologous stem cell therapies for highly debilitating neurodegenerative diseases.

• **Carticure Ltd.** (Nazareth) has developed an innovative approach for repairing articular cartilage lesions, through the implantation of cartilage-producing cells, harvested from an animal source: the growth center of the lower jaw of new-born mini pigs.

• **Cell Cure Neurosciences Ltd.** (Jerusalem) is focused on the development of cell therapies for retinal and neural degenerative diseases.

• **Cellect Biotechnology** (Kfar Saba) develops solutions for immune system regeneration. Achieving selectivity, specificity, and decreased toxicity, Cellect Biotechnology envisions its products becoming an integral and essential part of bone marrow transplantation, as well as integrated into many aspects of regenerative medicines.

• **CollPlant Ltd.** (Nes Ziona) is a regenerative Medicine Company focused on developing and commercializing tissue repair products, initially for orthobiologics and advanced wound care markets.

• **Gamida Cell Ltd.** (Jerusalem) develops treatments for orphan hematological diseases and malignancies using stem cells and NK cells.

• **Immunovative Therapies Ltd.** (Jerusalem) is a clinical stage biopharmaceutical company specializing in the translation of proven immune mechanisms into immunotherapy products and protocols for treatment of cancer and infectious diseases.

• **Kadimastem Ltd.** (Nes Ziona) is a biotechnology company focused on the industrial development and commercialization of human embryonic stem cell (hESC)-based products.

• **Kidney cure** (Tel Aviv) is testing a cell technology that derives human renal stem and progenitor cells from within fetal and adult kidneys to ultimately treat damaged or degenerated kidneys. Kidney Cure's two processes use nephron-forming progenitor cells to repair diseased ones.

• **MacroCure Ltd.** (Petach Tivka) is a clinical-stage biopharmaceutical company focused on developing a novel therapeutic platform to address chronic and hard-to-heal wounds, such as diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs).

• **LifeMap Science** (Tel Aviv) develops and commercializes next generation sequencing (NGS) analysis solutions. The company's core technology, the Gene Cards Suite Knowledgebase, provides a tool to improve biomedical research and healthcare and enables researchers to effectively navigate the universe of human genes, genetic variants, proteins, cells, biological pathways, diseases, and the relationships between them.

• **Medegenics Ltd** (Misgav (c)) is focused on fulfilling the promise of genomic medicine to improve the lives of children and adults with rare and difficult-to-treat diseases.

• **Orgenesis** (US, but Sheba originated ) is a development stage company with a novel therapeutic technology that employs a molecular and cellular approach directed at converting a patient’s own liver cells into functional insulin producing cells, as a treatment for diabetes.

• **Pluristem Therapeutics Inc.** (Haifa) is a clinical-stage biotechnology company using placental cells and a unique, proprietary, three-dimensional (3D) technology platform to develop cell therapies for conditions such as inflammation, ischemia, hematological disorders, or exposure to radiation.
- ProCore Biomed Ltd. (Nes Ziona) is a biotechnology company committed to developing solutions with a focus on bone and cartilage regeneration, integrating proprietary hydrogels, growth factors, stem and progenitor cells.
- Regentis Biomaterials Ltd. (Haifa) current efforts are focused on orthopedic treatments using degradable hydrogel implants to regenerate damaged or diseased tissue.
- Regenecure (Jerusalem) develops Regenerative Polymeric Membrane implants for Bone reconstruction and allows excellent proliferation and differentiation of MSCs into bone tissue.
- Stemcell Medicine (Jerusalem) leaps current stem cell R&D practices, technology and first-stage prod developments to pharmaceutical solutions by consolidating existing know-how.
- Sheltagen Medical Ltd (Atlit (N)) develops human bone tissue for implantation in patients with fractures in their bones, bone deficiencies or instability in the spine.
- Theravir Management (Jerusalem), a biotech start-up, was formed to in-license, develop and commercialize new therapeutic drug based on oncolytic (cancer killing) viruses.
- Tissue Dynamics ltd. (Jerusalem) is a groundbreaking biotechnology company that develops and provides advanced toxicology screening services for the pharmaceutical and cosmetic industries.
- VESSL Therapeutics ltd. (Haifa) develops innovative regenerative treatments for vascular-related conditions.

Governmental support
Where many countries like Germany, Portugal and several US states legally forbid research to several regenerative medical therapies, Israeli government is really supportive to the private sector. In contrast to those countries the Israeli government has awarded significant support in terms of funding and establishment of consortia to accelerate the transition of these therapies from laboratories to clinics. This is proven by the cases of Pluristem and Granada that have been awarded with respectively €10 million and €5 million grants by several Israeli governmental authorities during last 5 year, to continue their breakthrough research by replacing embryo stem cells with stem cells from the placenta.

Opportunities for collaboration
There are great chances for both academic cooperation as well as private sector collaborations. Israel is one of the leading countries with a national initiative throughout all sectors in stem cell research. Israeli companies are looking to rapidly upscale their activities and partner with parties in Europe. Furthermore, Israeli researchers are actively seeking collaborations through universities, medical centers and could be funded privately or through EU projects (H2020, Eureka, Eurostars).

The Israeli-Dutch Innovation Centre (IDIC) tries to bring Israeli-Dutch cooperation in the field of regenerative medicine to a next level. They organized a pitching side event during the Global Investors Forum in Maastricht, where 4 Israeli startups pitched for venture capital from the Netherlands and is planning to organize a delegation from the Netherlands to Israel in the field of regenerative medicine in November 2017.

Challenges
Research collaboration in the field of regenerative medicine is mostly challenged by legal and ethical constraints. For instance, the Dutch legal system restricts the use of embryonic
stem cells only for medical scientific research reasons.\textsuperscript{3} Israel passed legislation banning reproductive cloning, but allows research into therapeutic cloning. The ministry of Industry and Trade financially participate in the Cell Therapy consortium and funds in that way several stem cell research\textsuperscript{4}. Without political and ethical constraints, Israel leads in this field with over 5 times the world activity level in adult stem cell and 2.55 the world activity level in embryonic stem cell research. However, lack of funding is a main problem for RegMed research and valorization.\textsuperscript{5}

Conferences:

- [Conference of the Israel Heart Society](https://www.pggm.nl/english/what-we-think/Pages/Dementia-Strategies-The-Netherlands.aspx), April 25\textsuperscript{th} - 26\textsuperscript{th}
- [BioMed Israel Conference & Exhibition MIXiii](https://www.pggm.nl/english/what-we-think/Pages/Dementia-Strategies-The-Netherlands.aspx), May 23\textsuperscript{th} - 25\textsuperscript{th}
- [24th International Conference of The Israel Society of Critical Care Medicine](http://www.mddionline.com/blog/devicetalk/tracking-patents-and-mapping-medical-device-innovation-08-12-15), November 7\textsuperscript{th} - 8\textsuperscript{th}

Regenerative medicine is the solution for the future agile defects, where Organ-on-chips helps us to develop effective treatments for the future defects, caused by external factors. Israeli research and business show an above average performing in both fields and prove human capital to be their main unique selling point.

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