



## Quality by Design in Stem Cell Transplantation: Rational translation from bench to bed

Wednesday, May 1<sup>st</sup>, 2013

Faculty of Medicine, Butnar Building, **Butnar Small Hall**, Ein Kerem, Jerusalem

13:00 – 18:00

### Conference Program and Abstracts of Presentations

**Opening:** 13:00-13:15

**Philip Lazarovici**, The Institute for Drug Research, School of Pharmacy, The Hebrew University of Jerusalem

**Ron Kenett**, President of the Israel Statistical Association

**Plenary talks:** 13:15-14:30

**Yafit Stark**, Teva Pharmaceutical Industries

#### ***Twenty-first century challenges in drug development***

Stem cells have assumed near-mythical status as a possible treatment or cure for many diseases. Cell therapy represents a novel therapeutic paradigm for a variety of diseases. Stem cells represent the capacity to self-renew and to give rise to cells of various lineages. Due to the lack of innovation and the loss of productivity in the Industry, drug companies have begun investigating the potential of stem cell therapy. Currently, the adoption of stem cells for toxicity testing, for the identification of potential new therapies, or the potential of stem cells in regenerative medicine is increasing. The potential to replace body lost, or to rescue a damaged organ has to be approved.

#### **Current Challenges:**

Despite some encouraging earlier clinical trial results, the road of stem cell development is going to be very long and complicated. The safety and the potential effectiveness assessment both in animal models and in humans is not trivial.

#### **Collaborations:**

Major Pharmas tend to collaborate and join efforts with Biotech companies and academia. The Industry must find a way to improve efficiency in order to turn candidate compounds into useful and safe treatments/cures.

Forecast revenue from stem cell technology (Visiongain Global Report): \$B 7.4 in 2014, which could exceed about \$ B10 in 2020. A large share of revenues involves new well established technologies: bone marrow transplant and peripheral and umbilical blood cords containing stem cells. The current situation has tremendous parallels to the early days of recombinant DNA: people could not appreciate the broad and high potential and the underestimation of the difficulties in their development and treatments.

Cross collaborations and joint efforts between the three parties are the key success factor for the development and success of regenerative medicine.



**Ron Kenett**, KPA and University of Turin, Italy

***Statistical dimensions in Quality by Design***

Regulators in the US, Europe and Japan are pushing forward an approach labeled Quality by Design (QbD) that gives science and quantitative methods an increasing role in the development of drug products and clinical research. Health care is now focused on evidence based medicine where data and its analysis are supporting decision making, in all aspects of healthcare delivery. The talk will provide an overview of QbD with an emphasis on quantitative techniques. This will provide a context to the panel discussion at the end of the day.

**Don Kristt**, Molecular Pathology, Rabin and Hadassah Medical Centers

***Tracking BMT outcomes, the Chimertrack application***

The engraftment status of a stem cell transplant is gauged by a molecular DNA assay that demonstrates the relative proportions of donor cells to recipient cells -- present in blood and bone marrow -- or their respective DNAs; ideally this "chimerism" ratio should be 100% donor. It is important to appreciate that this engraftment process is dynamic, entailing complex immuno-biological interactions over time between the donor's stem cells and the host/recipient. Consequently, tracking these dynamics should be critical aspect of the laboratory's contribution to patient management following transplantation. Since longitudinal monitoring typically had been labor intensive few laboratories were prepared to undertake the burden. Also, in many situations the quality of the raw assay data impact critically on the interpretability of the computed chimerism values but an approach for systematically assessing data quality and for QC did not exist. For these reasons, an easy to use Excel® - based software application, ChimerTrack© was developed that made longitudinal chimerism tracking suitable as a routine activity in the transplant support laboratory. The application also allows simultaneous computation not only of chimerism, but several data and analytic quality parameters that can be used as a QC framework. The talk will describe the software in the context of its application to technical and biological issues in BMT monitoring.

**Coffee Break:** 14:30-15:00

**Plenary talks:** 15:00-16:15

**Simcha Samuel**, Hadassa Medical Center

***Challenges in Stem Cell Transplantation: Preparation of Stem cells.***

Bone marrow/stem cell transplantation relies on the transfusion of hematological stem cells with particular biological characteristics. Donors are treated to enhance the mobilization and circulation in the peripheral blood of these cells. However, there are a number of critical challenges in stem cell collection that remain, despite the excellence of this technology, that relate to assessing the success of the collection procedure.

**Reuven Or**, Hadassa Medical Center

***Challenges in Hematopoietic Stem Cell Transplantation***

Hematopoietic Stem Cell Transplantation (HSCT) is one of the most drastic procedures in the modern medicine, but in cases of severe hematological malignancies or genetic diseases of the hematopoietic system, HSCT might be the only curative option. Each step of the transplantation process - from donor search (in case of allogeneic HSCT) through pre-transplant conditioning, stem cells aspiration and transfusion, to management of early and late transplantation complications, has its own risks.

High standards of quality control are required in order to achieve minimal complication rate. HSCT conditioning requires optimization of radiotherapy and chemotherapy selection and



administration. Stem cells processing, encouraging full engraftment and monitoring the degree of chimerism after transplantation in order to evaluate function of the graft including the potential of Graft versus Leukemia effect (GvL), are important steps to promise successful transplantation. Prevention and management of complications such as bacterial, viral and fungal infections, and acute and chronic Graft versus Host Disease (GvHD) are necessary in order to reduce HSCT associated mortality. Quality control of the different phases of the transplant procedure may provide better long term results, and contribute to the safety and efficacy of HSCT process.

**Zvia Agur**, Optimata Ltd. and Israel and Institute for Medical Biomathematics

***Personalizing bone marrow transplantation via Integrative System-Based Models***

Conventionally, cancer patients undergo drug treatment by the 'one-size-fits-all' paradigm. However, progress in human genetics has made it increasingly clear that cancers vary genetically and, hence, may respond differently to drugs. The concept emerging today is to overcome this problem by personalizing treatment according to the specific molecular characteristics of the patient's disease. However, none of the many biomarkers suggested to date, has proven sufficiently efficient as a clinical personalization tool, and the success of personalized oncology is very limited. These disenchanting results can be explained by the complexity of drug-patient interactions. Mathematical models, aimed at describing, quantifying and predicting multifaceted behavior, can aid in sorting out this complexity. In my talk, I will show how personalized models are developed, validated and applied in personalized medicine, and will suggest how they can be implemented in stem cell transplantation.

**Coffee Break:** 16:15-16:45

**Panel discussion:** 16:45-17:45

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**Moderator:** Dr. Yafit Stark

**Conclusion:** 17:45-18:00

***Participation is free but requires pre-registration by sending an email with your name to*** Prof. Abraham Rubinstein, The Hebrew University of Jerusalem, The School of Pharmacy Institute for Drug Research email: [avrir@ekmd.huji.ac.il](mailto:avrir@ekmd.huji.ac.il)

under the subject ***"QbD in Stem Cells Transplantation May 1<sup>st</sup> 2013"***