TERMEX 2018

Sub Sessions

NA-1 Public-private collaboration in support of early-stage translation of advanced therapies: A North American perspective

Michael H. May
CCRM, Canada

CCRM is a Canadian-based commercialization and translation centre accelerating the development of revolutionary new therapies in the field of regenerative medicine and cell/gene therapy. Dr. May's presentation will highlight the key features of the CCRM model, including stakeholder networks, specialized teams and dedicated infrastructure, as well as showcase the major outcomes and lessons learned after six years of operation. He will describe current trends in early stage company development in North America and the role of public-private consortia in driving industry advancement with a focus on advanced manufacturing.

NA-2 Regenerative Medicine - Promising Therapies In Need of 21st Century Solutions

Becky Robinson-Zeigler

Advanced Regenerative Manufacturing Institute, BioFabUSA, USA

Although regenerative medicine emerged as an industry almost two decades ago with the FDA approval of Organogenesis' Apligraf product, only a small number of products are commercially available in the United States. BioFabUSA, a program of the Advanced Regenerative Manufacturing Institute (ARMI), was created to address the gaps and bottlenecks associated with manufacturing of tissue-engineered products in order to deliver on the promise of regenerative medicine to improve the health and life of patients. BioFabUSA is an industry-led public-private partnership, membership-based institute that is focused on making practical the large-scale manufacturing of tissue-engineered products and tissue-related technologies for regenerative medicine. The institute has created a collaborative community that includes both the tissue engineering product developers, manufacturing solution suppliers from commercial firms, and academia to grow this industry. This ecosystem advances ARMI's mission not by focusing on the development of any particular tissue-engineered or regenerative medicine product, but rather by focusing on developing and enabling the technologies, marketed products, standards, development practices and strategies, appropriately-trained workforce and commercial ecosystem necessary for large-scale manufacture of tissue-engineered products. This focus takes shape through efforts in four interrelated areas: (i) traditional trade association activities; (ii) technical projects; (iii) standards development and regulatory pathways; and (iv) workforce readiness projects. Over the next few years, these efforts will move the entire industry forward in a sustainable way.

NA-3 Positioning a Large Medtech Company in the Regenerative Medicine Space

Markus Reiterer
Corp. Science & Technology, Medtronic, PLC, USA

Over the last 70 years devices like pacemakers, spinal implants, and coronary artery stents have been used to treat chronic disease. The next advancement in medical device technology is restoration rather than treatment. Regenerative medicine offers this possibility. Through tissue engineering, regenerative medicine already provides solutions for severe burns. One off proof-of-concepts have been demonstrated for diabetes, cardiac patches, and trachea replacements. In the future, treatments are expected to extend to end-stage organ failure through stem cell therapies or full organ regeneration and replacement. Despite dramatic progress in cell biology, computer science, engineering, and 3D printing in particular, there are many technical challenges that prevent that envisioned future. Technology advances in the regenerative medicine space have be limited by (1) the lack of high volume manufacturing technologies for making complex systems with extremely tight process and quality controls, (2) standardization and harmonization of materials and cell sourcing supply and manufacturing quality testing for viability and function of the solutions, (3) distribution capability for living tissues, and (4) advances in regulatory sciences for appropriate approval of these solutions. Solutions in these spaces will disrupt the current medical technology industry. The tissue engineering marked is estimated to be more than $10B by 2022 at an annual growth rate of about 13%. To help advance the technology in this space, Medtronic has engaged with academic, industrial and government partners to develop the infrastructure necessary to support mature high volume biofabrication of regenerative medicine.

E-1 Development and commercialisation of advanced therapy medicinal products (ATMPs) in Europe: The Holoclar® case

Giorgio Iotti

Chiesi Farmaceutici S.p.A, Italy

Cell and gene therapies represent innovative approaches with the promise to modify the course of potentially incurable diseases.
The introduction of the Advanced Therapy Medicinal Product (ATMP) regulation in 2007 in the European Union opened the field for the pharmaceutical industry.
Despite significant progress in the recent years, there is still a subtantial margin of progress for increasing the uptake and adoption of these therapies.
Key challenges for these therapies are in pricing and reimbursement. Treatment typically requires a single administration with long-lasting effects and the reimbursement process must be adapted. Specific national Health Technology Assessment (HTA) processes and new funding models are needed to guarantee better patients access throughout European countries.
Holoclar® (ex vivo expanded autologous human corneal epithelial cells containing stem cells) has been the first stem cell-based product approved in Europe. The partnership between academia and industry, with the creation of the spinoff company Holostem, has been a key factor in the achievement of this milestone. Since approval, the product has gone through HTA assessment in several European countries and specific cost-effectiveness models have been developed to support its reimbursement.
Another critical aspect to support access of patients to treatment is facilitating cross-border movement and reimbursement. Indeed, ATMPs have often logistic constraints and the products are administered to patients in highly equipped clinical centers.
Key elements for the success of ATMPs is represented by a constant dialogue between industry, academia and regulatory and reimbursement authorities.

E-2 Catapult's role in ATMP development and specificities vs other European Regenerative Medicine clusters & Impact of Brexit of clinical development & market approval of ATMPs

Michael K Bennett
Cell and Gene Therapy Catapult, UK

Within the UK there are a number of organisations sharing the name Catapult. Currently there are 10 Catpaults each of which is an independent not for profit company focussing upon a specific technology space for example Satellite applications, energy storage, offshore renewable energy, cell and gene therapy, etc. The Catapult program is a UK initiative to improve the translation of new technologies into commercial propositions.
The Cell and Gene Therapy Catapult (CGT) was established in 2012 and since that time has worked with numerous companies worldwide to support their activities to develop cell or gene therapies. To enable CGT to do this we have over 180 personnel skilled across all the areas required to develop a cell or gene therapy. CGT has laboratories where we can develop manufacturing processes to supply commercial scale product, pre-clinical team to advise upon data required to gain approval for first in human trials, regulatory experts to assit the filing of necessary documentation with regulators, clinical team to run and manage clinical trials and a health economic and market access team to ensure that your product will be adopted by healthcare systems and reimbursed.
We have recently completed the build of a large GMP compliant manufacturing centre where companies across the world can work with us in a cost sharing model to manufacture commercial volumes of product for supply. The manufacturing centre is a modular building where companies occupy their own manufacturing clean room suite thereby maintaining confidentialy of their processes and materials. The goal of the centre is to derisk the early stages of product development removing the need for companies to build their own manufacturing facilities prior to gaining some market traction.
In my presentation I describe the activities of the Cell and Gene Therapy Catapult through case studies and will also cover some of the issues of Brexit and CGTs view of how Brexit may impact the development or launch of new cell and gene therapies.

E-3 Regenerative Cellular Therapy in Europe: Definition, Case Studies and Perspectives

Vincent Ronfard

Research and Development UNT Fort-Worth/Cutiss AG/ Hairclone, Switzerland

At present time, Regenerative Medicine product per se are very rare. Lots of companies claim to be part of regenerative medicine, but in fact very few are performing true of partial regeneration. After providing definitions and example of Regenerative Medicine products, we will focus on companies related to skin and epithelial regeneration, analyzing their strategies and value proposition. Building and growing viable Regenerative Medicine company is an exciting body of work. However, delivery of regenerative medicine to patient's benefit is a considerable challenge. For instance, risks analysis of the process and final product should also be managed from technical and clinical perspectives: robustness of the manufacturing process and "quality" of the therapeutic product. The road map to make these treatments available to clinicians and patients involve early and constant interactions between scientists, clinicians, regulators, industry and politics. The purpose of this talk is to provide a view the current landscape the European Regenerative Medicine, and to highlight outstanding issues in translational biology using real cases.

E-4 Market Access and Uptake of Regenerative Medicine in Europe

Alain Vertès

NxR Biotechnologies GmbH, Basel, Switzerland

With the approval of several first-in-class gene- and cell-based therapies, the field of regenerative medicine has at long last moved from the realm of R&D to the reality of clinical practice as we are approaching the end of the second decade of the 21st century. The beginning of this journey in the arena of market access has already proven to be a rocky one, from big pharma U-turns to product withdrawals in European jurisdictions on commercial or strategic grounds. History teaches us that such beginnings for the development of any game-changing innovations are to be expected. One of the critical success factors for this new revolution in healthcare to be truly successful is to unambiguously provide, beyond strong confidence in safety and confidence in efficacy, a robust confidence in the relevance to Society of the new therapies, as well as rock-solid confidence in general affordability and manufacturability of the new products to address the unmet needs of patients who experience diseases that cannot be treated using conventional therapeutic modalities. A strategic framework is presented here that serves as a checklist for achieving market access preparedness and for designing the target product profiles of the generations of advanced therapies that will follow these initial steps in transforming healthcare from managing symptoms or achieving disease modification, to curing heretofore untreatable diseases and achieving organ, tissue, and function regeneration. The frontiers where the new technology platforms and their combinations can demonstrate a particularly critical impact undoubtedly include oncology, neurology, and age-related diseases.

K-1 Overview of Regenerative Medicine (RM) in Korea

Bryan Choi

Strategic Center for Regenerative Medicine (SCRM), Inha University

South Korea has achieved a significant progress in commercializing RM since we had the first cell therapy product approved by MFDS, the Korean regulatory authority in 2001. Now we have 16 cell therapies and 1 gene therapy in the market including 4 stem cell therapeutics, the first of which was market-approved by MFDS in 2011. Korean companies are actively pushing their RM pipelines into the clinical trials for cell therapeutics and gene therapeutics. Korea government is investing a lot of R&D funds and reforming the RM regulation more favorable for market approval. The private funding is abundant in the Bio sector including RM and reimbursement is also easily accessible through the public and private health insurances. In the geographical perspectives, Korea is located at the center of the rapidly growing healthcare market in Asia thus could be a gateway through the nearby countries like China and Japan. With the support of strong government initiatives, favorable regulatory environment and strong R&D and clinical infrastructure, Korea provides a great opportunity for foreign RM companies to launch their products, start new business or find a partner in Korea.

K-2 Commercialization of Allogeneic MSC Cell Therapy Products addressing Unmet Medical Needs

Antonio Lee
MEDIPOST Co., Ltd.

TBD

A-1 A Strategy for Tissue Engineering & Regenerative Medicine in Australia

Dietmar W Hutmacher
Centre In Regenerative Medicine, Institute of Health & Biomedical Innovation, Queensland University of Technology, Kelvin Grove, QLD, Australia

A strategic review of the tissue engineering & regenerative medicine (TE&RM) landscape has been cooperatively undertaken by the AusBiotech Regenerative Medicine Advisory Group. This has sought to identify the opportunities and challenges faced by the Australian (TE&RM) community, bridging discovery, translational science and the demand for clinical delivery. This talk highlights the need for a unifying yet demands driven synergy between the research and industry networks to provide a platform for interactions, strategic objectives and delivery mechanisms. The outcome will be a coherent framework for Australian research and development activity over the next decade to ensure that current Australian TE&RM expertise is successfully built upon to maintain its international competitiveness.

A-2 Progressing one of the largest trade sales in Australian healthcare history

Anthony S. Weiss

Charles Perkins Centre, University of Sydney, Australia

This year, Elastagen Pty Ltd, a clinical stage company developing medical device products based on recombinant tropoelastin was acquired by Allergan plc, a leading global biopharmaceutical company.

The deal consists of an upfront payment plus contingent, commercial payments.

Elastagen's revolutionary technology is based on recombinant human tropoelastin, the self-assembling elastic protein which allows the body to repair elastic tissues in the skin, artery, bladder and lung.

Elastagen's tropoelastin is identical to that present in human tissue and has many potential clinical applications, including treatment for acne scars, stretch marks, aesthetic skin repair and surgical wound repair.

Professor Anthony Weiss, University of Sydney McCaughey Chair in Biochemistry at the University of Sydney founded the company and continued as lead scientific adviser of Elastagen Pty Ltd. He will outline the key steps that led to one of the largest healthcare corporate trade sales in Australia.

J-1 Japanese regenerative medicine development/market and effort for international standardization

Yoshitsugu Shitaka

Astellas Institute for Regenerative Medicine, Japan

In Japan, the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act and the Act on the Safety of Regenerative Medicine were promulgated in November 2014, and clinical trials and developments of regenerative medicine (RM) products have been promoted under the advanced Japanese regulations ahead of the world. To date, 5 RM products have been launched and more than 40 RM programs are being developed in clinical trials (as of May 2018).

Founded in 2011, Forum for Innovative Regenerative Medicine (FIRM) is an organization of RM-related industries in Japan. Currently, FIRM consists of more than 200 companies and active collaborations among participating companies are underway to achieve FIRM's mission to accelerate industrialization of RM in Japan. In addition, FIRM has concluded memorandums of understanding (MOUs) with overseas industry groups and scientific societies to enhance RM industry in collaboration with other countries and territories. To promote international standardization which is critical for industrialization across countries, FIRM supports the "Multisite Evaluation Study on Analytical Methods for Non-clinical Safety Assessment of hUman-derived REgenerative Medical Products (MEASURE)" that is aiming at international standardization of the tumorigenicity test of pluripotent stem cells. Moreover, FIRM leads the "Asia Partnership Conference of Regenerative Medicine Associations (APACRM)" that is a conference on regulatory harmonization for RM products among primary Asian countries and territories such as Japan, India, China, Korea, Singapore and Taiwan. FIRM will continue to fulfill its role as an industry organization so that it can contribute to the creation of innovative RM products.

J-2 Japanese revolutionary regulatory framework and its efforts

Yoshiaki Maruyama

Office of Cellular and Tissue-based Products, Pharmaceuticals and Medical Devices Agency, Japan

On April 2015, Ministry of Health, Labour and Welfar notified to start the SAKIGAKE designation system in Japan. SAKIGAKE is a system to put innovative medical products, including pharmaceuticals, medical devices and regenerative medical products from Japan into clinical use. On November 2014, the Pharmaceutical Affairs Law was revised and renamed the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act (PMD Act). This Act provides the option of a new pathway to obtain conditional and time-limited approval for regenerative medical products. Giving patients better access to innovative medical products by providing the sponsor with generous regulatory and scientific support from an early development stage was also initiated in United States in 2012 (Breakthrough Therapy Designation system) and in the European Union in 2016 (PRIME; PRIority Medicines).

This presentation will give a short introduction to Japan regulatory framework and although the key consideration for developing the regenerative medical products from experience of the Pharmaceuticals and Medical Devices Agency (PMDA) in consultation and review.

J-3 Development of SAKIGAKE-Designated Esophageal Regeneration

Setsuko Hashimoto

President and CEO, CellSeed Inc., Japan

CellSeed Inc. was founded in 2001 to commercialize an innovative and versatile technology in regenerative medicine; “Cell Sheet Engineering” which was developed by Prof. Teruo Okano of Tokyo Women’s Medical University.
CellSeed currently focuses on the development of two regenerative medicine products; esophageal epithelium cell sheets and chondrocyte sheets for knee cartilage regeneration.
Endoscopic Submucosal Dissection (ESD) has become a very popular therapy for the early phase of the esophageal cancer. A new therapy using cell sheets to prevent the stricture after ESD was developed at Tokyo Women’s Medical University. CellSeed has taken over the development and started a Phase III clinical trial at National Cancer Research Center Japan and Tokyo Women’s Medical University in April 2016. In February 2017, it was assigned to "SAKIGAKE (Fast Track) Designation System" by the Ministry of Health, Labor and Welfare, which helps speed up the time to market through close communications and supports by the regulatory agencies.
In April 2017, CellSeed exchanged a contract with MetaTech Inc. to offer exclusive development rights of the esophageal cell sheet product and the chondrocyte sheet product in Taiwan.
With our company’s mission to contribute to the global health care, we proactively seek for further business collaborations with companies globally.

J-4 SAKIGAKE Designation -TAKARABIO’s Experience-

Masanobu Kimura

Gene Medicine Business Unit, Takara Bio Inc., Japan

SAKIGAKE designation is quite a unique system, which enables the industry to accelerate the development process till obtaining the approval. The designation criteria are summarized as follows: (1) innovative medical products for serious diseases, (2) development & NDA in Japan being world’s first or simultaneous with other countries, (3) prominent effectiveness expected on non-clinical and early phase clinical studies. The advantages for the industry can be summarized as follows; (1) prioritized consultation, (2) prior-review (rolling review), (3) prioritized review, (4) review partner (concierge), and (5) extension of re-examination period. TAKARA's TBI-1301 project has been designated as of Mar 27 this year, after 2nd try. We have meetings with “concierge”, who provides us with advice from various aspects. During this presentation, though our experience is quite limited, I will share the information based on TAKARA’s experience.

J-5 FIRM's efforts to promote industrialization of regenerative medicine

Kunihiko Suzuki

MEDINET Co., Ltd., Japan

FIRM was established on June 17, 2011. FIRM's mission is to accelerate the industrialization of regenerative medicine in Japan.

Almost all the sectors related to this space, including pharmaceutical companies, manufacturers of Regenerative Medicine and Cell Therapy (RM/CT) products, and other players from different sectors such as medical equipment and devices, culture reagent and media, finance, construction, and transportation, join FIRM and participate in active discussions across industries.

Through the activities at Expert Committees at FIRM, such as Regulatory, Medical Economics, Supporting Industries, Standardization, the productive collaboration among the members from various sectors has been realized.

For example, Supporting Industries Committee, have made significant achievements in creating six standards for the criteria formulated and approved within FIRM, with respect to peripheral products and services used for regenerative medicine.

FIRM also organizes Japan Mirror Committee for ISO/TC 276 and Committee to Standardize Foundation for Cell Characterization and Cell Production. Both committees consist of experts from academia, government and industry.

In addition, FIRM has an activity as the point of contacts for foreign companies and academia to collaborate in development new products via the events called Crossroad and Venture Creation Support Forum, which are organized by the Regenerative Medicine Industrialization Tactical (RMIT) Committee.

In other words, FIRM conducts various kinds of activities such as the above efforts, construct the good collaboration with academia and companies to both domestic and overseas, provide a specific suggestion to Japanese Government, and cooperate usefully for development of RM/CT space.

TERMEX 2018

Academic Poster

1 Surface coating techniques for reducing ancillary components costs for iPS cell expansion

Nicholas Alan Rogers [1, 2] , Sameer Al-Bataineh [1, 2] , Giles T.S. Kirby [1, 2] , Jason D Whittle [1, 2, 3]

[1]Future Industries Institute, University of South Australia, Mawson Lakes, Adelaide, Australia, [2]Cooperative Research Centre for Cell Therapy Manufacturing, University of South Australia, Adelaide, Australia, [3]School of Engineering, University of South Australia, Mawson Lakes, Adelaide, Australia

The requirement for large quantities of GMP-grade growth factors is a serious barrier to cost-effective cell therapies. The Future Industries Institute at the University of South Australia, a participant in the Cell therapy manufacturing Cooperative Research Centre (CTM-CRC), has developed a functionalised surfaces with the potential to drastically reduce the amount of growth factors used in culturing cells. Using surface-immobilized growth factors, adsorbed at low concentration, we have observed beneficial effect on cultured cells at markedly reduced concentrations. It permits the reduction of added growth factors by a factor of 5 to 1000 (dependent on type of cell) without loss of cell yield. The surface immobilisation is thought to stabilise the growth factor and reducing degradation during culture. One of the more therapeutically relevant cells, shown to benefit from this technology was iPS cells.

Recent interest in using iPS cells for the investigation of disease pathogenesis, as well as drug discovery and development, has resulted in a demand for larger production quantities of these cells. As the industry moves to more defined media compositions the requirement for growth factors additives is expanding. Moreover, as iPS cells move closer to the clinic the need for the more expensive GMP-grade factors will also increase.

Studies conducted by the CTM-CRC managed to reduce the required FGF2 growth factor load, over a 5 day iPS cell culture, down to one fifth of normal usage while maintaining cell growth and morphology. Immunohistochemistry results also indicated no loss in pluripotency in both iPS cell lines studied. Interestingly, surface associated FGF2 maintained these effects after coating the 2D surface with ECM components. These data suggest that our surface may act as a reservoir for our associated growth factor that can be accessed, by expanding cells, on demand.

Follow on studies have successfully looked at both increasing and decreasing the growth factor reservoir in vitro, while concurrent studies have started transferring the surface coating techniques onto 3D scaffolds and beads, for commercial applications.

2 Mediating cell-surface interactions

Giles Thomas Sipho Kirby [1] , Andrew Michelmore [1, 3] , Louise E Smith [1, 2] , Emily F Hilder [1]

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As we use more biomaterials it is imperative that we develop consistent methods to advance fundamental understandings. Biological fluids contain diverse mixtures of proteins which adsorb rapidly onto new interfaces meaning that a biological system in fact interacts with both adsorbed protein and the underlying chemical substrate.

A paradigm shift in recent years has led to a change in favoured methods of delivering cell therapies to planar systems such as wounds. Delivering cells without the use of enzymatic treatments, in a simple-to-use format, is one such driving force for novel surface development.

Cells sheets have previously been fabricated using well established cell culture methods, utilizing biological additives such as fibronectin to modulate adhesion and enzymatic treatments for release. Tailored surfaces can provide far more versatile system for culturing and delivering cell sheets with reduced complexity. This can positively impact quality and efficiency of localized cell delivery and drive down the cost of goods.

Plasma polymerization can be used to generate a plethora of consistent and well defined functional surfaces allowing precise tuning of the types of functional groups present on the surface and even the density of these functional groups. Behaviour and fate of mammalian cells cultured upon these surfaces can then be used as outcome measures to better inform surface design for specific applications.

The true scope and importance of surfaces in cell therapies is yet to be fully revealed. Continued research is essential to develop the technology, validate outcomes, drive discovery and reduce cost-of-goods. The future of this field involves elucidating why certain functional groups affect cell-surface interactions, understanding the role of adsorbed protein layers, and determining the downstream effects on the cell product. With recent leaps in proteomics, this is a growth area with an exciting future. Translation from bench to bedside requires navigating issues of scale-up and commercial viability. It is imperative that biologists, clinicians and materials scientists continue to work together to solve these issues to realize clinical outcomes.

3 Can Cell Therapies Improve the Care of Patients in Burn Units?

Philippe Abdel Sayed [1], Michèle Chemali [1] , Nathalie Hirt-Burri [1] , Anthony de Buys Roessingh [2] , Wassim Raffoul [1] , Lee Ann Applegate [1]

[1]University Hospital of Lausanne, Department of Musculoskeletal Medicine, Lausanne, Switzerland, [2]University Hospital of Lausanne, Paediatric Surgery Service, Lausanne, Switzerland

We have developed an allogenic cell therapy in our hospital, using biological bandages made of human progenitor skin fibroblasts seeded on biodegradable equine collagen sheets. The benefits of these biological bandages consist in replacing cadaver skin as temporary cover, and the potential enhancing skin regeneration of 2nd degree burns due to the release of growth factors and cytokines. Thus, first clinical trials using these biological bandages for pediatric burn patients began in 2000 with clinical studies published in 2005-2006 (The Lancet, Cell Transplantation & Experimental Gerontology).

In 2007, a new Federal program on Transplantation of Organs, Tissues and Cells came into force, which involved the adoption of GMP procedures in cell therapy. Thus, the project of a Cell Production Center (CPC) was initiated as part of our hospital Strategic Plan; and since 2015, manufacturing for all types of cell therapy, including biological bandages, is performed at the CPC, which to date is the only GMP accredited infrastructure in Switzerland for cell therapies. In parallel, extensive cell banks of human progenitor skin fibroblasts have been produced under GMP conditions.

Since the last ~10 years the biological bandages have been routinely used for pediatric and adult burn patients. The production of biological bandages has considerably increased from 190 bandages in 2013 to 1045 bandages in 2017, while the indicator of care duration normalized by burned surface decreased from 0.6 in 2014 to 0.2 in 2017, suggesting thus an improvement in the quality of burn patient care, to which the use of biological bandages may have contributed.

Even though there may be inherent differences of patients at their entry, pluridisciplinary patient care changes can have major implications in final outcome. Cellular therapies have an important position for therapeutic pathways integrated in surgically-assisted reconstruction and regeneration of the burn patient.

4 From 15 years of cell banking to the development of cell-therapies – CRIOESTAMINAL experience.

Helena Henriques-Antunes [1] , Margarida Vieira [1] , Carla Cardoso [1] , Sofia Couceiro [1] , Francisco Santos [1] , Mónica Brito [1] , André Gomes [1]

[1]Crioestaminal - Stemlab, S.A., Cantanhede, Portugal

In 2003 Crioestaminal was the first Portuguese company to offer families the possibility of cryopreserving the umbilical cord blood stem cells (UCB) and, since September 2011, umbilical cord tissue mesenchymal stem cells (UCT), for a minimum of 25 years. Cryopreservation of these cells permits their future application in the treatment of several diseases during the lifetime of the newborn and the family [rev. 1]. Our facilities and quality system are certified by the ISO 9001:2000, accredited by the American Association of Blood Banks (AABB), and authorized according to European Directives and Portuguese law by the regulator of the sector, for processing, storage and distribution of UCB and UCT[2] .

At present, 30 years after the first UCB transplant, we can count more than 40.000 transplants all over the world. These applications are mainly related with haemato-oncologic diseases and, recently, other conditions in the context of clinical trials (CT) such as cerebral palsy, stroke, diabetes, cardiomiopathy and many others[3,4] . Nowadays, Crioestaminal is present in several European countries, and had already released several UCB samples for use both in a clinical setting and in CT in Europe and in the US.

More recently, we set to move forward towards the development of cellular therapies. Currently, we are developing a new therapeutic product for a Clinical Trial Phase IIa, CD34+ cells of bone- marrow aspirates for autologous use in acute ischemic stroke [5,6] . Recent studies demonstrated CD34+ cells therapeutic potential *in vitro* and *in vivo*, and a phase I clinical trial already validated the safety and feasibility of administering these cells in acute ischemic stroke patients [rev. 6] . With this purpose we designed and built GMP (good manufacturing practices) facilities in compliance with specific ATMPs (advanced therapy medicinal product) requirements, since this first product is a non-substantially manipulated cell-therapy product for non- homologous use [5] .

At this point, we have dedicated facilities for the development of cell-based therapies, with 3 distinct production areas, that allow us to safely manufacture different types of ATMPs.

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Funding

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5 Challenge of Cell-Sheet Regeneration Therapy Ecosystem

Katsumi Katayama [1] , Yuji Ueno [2] , Daishi Suga [2] , Setsuko Hashimoto [3]

[1] Chief Business Development Officer, Cellseed Inc., Tokyo, Japan, [2] Business Development Department, Cellseed Inc., Tokyo, Japan, [3] President and CEO, Cellseed Inc., Tokyo, Japan

The environment surrounding regenerative medicine in Japan has been changed dramatically in the short term since Professor Shinya Yamanaka awarded Nobel Prize for iPS cell development.
On the medical regulatory side, there are enforcement of Pharmaceuticals and Medical Devices Act by Revision of Pharmaceutical Affairs Law, Guidance and Advice through Regulatory Science strategy consultation (former Pharmaceutical Affairs strategy consultation) by Pharmaceuticals and Medical Devices Agency (PMDA) implementation of SAKIGAKE (FAST TRACK) Designation and conditional-approval.
On the administration side, Research and Development for industrialization in regenerative medicine go smoothly and accelerate with the support of Japan Agency for Medical Research and Development (AMED).
Under such circumstances, CellSeed is expanding not only business of temperature responsive cell cultureware invented by Professor Teruo Okano, but also research and development of cell sheet regenerative medicine based on cell sheet engineering with a view to global business development.
As an overseas business development, CellSeed is also expanding its activities in EU through its subsidiary, CellSeed Sweden AB, North America region and Asia Pacific region. In April 2017, CellSeed exchanged a contract with MetaTech AP, Taiwan for licensing products.
We will share the current status and future prospects of our business ecosystem.

6 Expansion of Regenerative Medicine Support Business - Regenerative Medicine Contract Services -

Kazunobu Asano [1] ,Tomomi Takahara [2] ,Masanari Onoe [2]

[1] Director, Sales Department, CellSeed Inc. Tokyo, Japan , [2] CellSeed Inc. Tokyo, Japan

CellSeed Inc. was founded in 2001 to commercialize an innovative and versatile technology in regenerative medicine, “Cell Sheet Engineering”. CellSeed currently develops regenerative medicine products for human use and also operate on manufacturing and marketing of the intelligent cell cultureware such as temperature-responsive cell cultureware, UpCell.
Based on our expertise and experiences of the Cell Sheet Engineering, CellSeed started the regenerative medicine contract development and manufacturing services since 2018, at our Cell Processing Facility in Tokyo which was licensed in March 2017 to manufacture and to process specified cell products (License number FA3160008).
Our contract services in the field of regenerative medicine includes;
1. Development of Manufacturing Methods and Contract Manufacturing for Cell Sheet Products
2. Facility Management and Document Support for Application
3. Training of Cell Culturing Technicians

7 Isolation and Qualification of Canine and Feline Mesenchymal Stem Cells by Monitoring of Glutathione Levels

Kosuke Mitani[1], Yuki Ito[1], Yukio Takene[1], Eui Man Jeong[2], Heun-Soo Kang[2], In-Gyu Kim[3], Toshio Inaba1[4], Shingo Hatoya[4], Kikuya Sugiura [4]

[1] R&D Department, J-ARM (Japan Animal Regenerative Medicine), Osaka, Japan, [2] Cancer Research Institute, Seoul National University College of Medicine, Cell2in, Seoul, Korea, [3] Department of Biochemistry and Molecular Biology, College of Medicine, Seoul National University, Seoul, Korea, [4] Department of Advanced Pathobiology, Graduate School of Life and Environmental Sciences, Osaka Prefecture University, Izumisano, Japan

Introduction: Regenerative medicine is expected to be an efficient method for replenishment of lost cells in many intractable diseases. However, for applying pluripotent stem cells, there are many issues to be solved such as the risk of tumor formation. For these reasons, mesenchymal stem cells (MSCs) have recently been used for the clinical studies in veterinary medicine. On the other hand, quality control methods in cell therapy, which are essential when evaluating the usefulness of therapeutics, have been absent. The core functions of MSCs are critically regulated by their cellular redox status. Glutathione (GSH) is the most abundant non-protein thiol functioning as an antioxidant and a redox regulator. In this study, we report the possibility of quality control assessment for the canine and feline MSCs from adipose tissues (ADSCs) by quantification of GSH dynamics.

Methods: ADSCs were obtained from 3 dogs and 1 cat by using adipose-derived stromal cell culture kits (J-ARM Co., Ltd.). Flow cytometric analysis was performed to evaluate the cell surface markers. Differentiation properties (osteogenesis and adipogenesis) were estimated by von Kossa staining for mineralized matrix deposition and oil Red O staining for fat droplets. Mitochondrial GSH imaging and Colony-forming unit fibroblast (CFU-F) assay were performed to estimate in association with passage for harvesting ADSCs. We have developed two parameters, glutathione mean (GM) and glutathione heterogeneity (GH), for measuring GSH-mediated antioxidant capacity using GSH probe, FreSHtracerTM (Cell2in). GM is the mean of intracellular GSH level of cell population. GH represents the extent of GSH variability in relation to the mean of the population.

Results: Canine and feline cells harvested gave positive results for CD44 and CD90 and negative results for CD14 and CD45. After induction, these cells had osteogenic and adipogenic phenotypes. Dog and cat ADSCs show lower GM and higher GH in a passage-dependent manner. Moreover, these GSH parameters are well correlated with self-renewal capacity (CFU-F) of ADSCs as expected. These results demonstrate that our GSH parameters (GM, GH) could be used to monitoring the stem cell quality of ADSCs during preparation from adipose tissues of dog and cat.

Conclusion: Our results indicate that high glutathione levels are required for maintaining ADSC functions, and monitoring glutathione dynamics and heterogeneity can advance our understanding of the cell quality.

8 3D Bioprinted Human Skin – a Future Replacement for Animal Testing in Cosmetics?

Itedale Adel Namro Redwan [1] , Isabella Bondesson [3] , Evita Ning [4] , Elin Pernevik [1] ,Patrick Thayer [2] , Erik Gatenholm [1] , Hector Martinez [1]

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Objective: 3D bioprinting is a novel technique that shows great promise for the development of translatable tissue models to be used for drug development and cosmetic research. A skin tissue model that mimics native human skin is of great interest for pharmaceutical companies, as it could be used to develop new drugs to treat for example melanoma or psoriasis. For cosmetic companies, biomimetic skin models could be used to either develop efficacious topological creams, or to minimize the risk for skin sensitization from new products. 3D bioprinting is a method of using additive manufacturing in combination with biological systems. It is a novel field within tissue engineering, enabling the complex combination of the benefits of 3D cell culture and the precision of 3D printing. The key component is the bioink, which is a mixture of biomaterials with bioactive molecules, designed to enable both good printing fidelity and cell milieu. The bioink is mixed with living cells, and the final composition and shape of the construct will determine how well the tissue model mimics the native tissue. The objective of this ongoing study is to develop a 3D bioprinted biomimetic human skin model.

Methods: Several bioinks (CELLINK™, Sweden) have been evaluated for the fabrication of 3D bioprinted skin constructs, including methacrylated gelatin and nanocellulose-based CELLINK™-RGD-Fibrin. Human primary dermal fibroblasts (HDFa, Fisher) were mixed with the bioink and printed as rounded discs using an INKredible+ 3D Bioprinter (CELLINK™, Sweden). The constructs were cultured under standard cell culture conditions for one day, then human epithelial keratinocytes (HEKa, Fisher) were seeded on top of the constructs. The constructs were cultured for 28 days, and samples were collected for immunohistochemical analysis and genetic expression of Collagen I.

Results: After 28 days of culture a well-formed stratum corneum was present in the CELLINK™-RGD-Fibrin-based bioink, indicating terminal differentiation. Expression of Collagen Type I was also detected in the 3D bioprinted skin construct.

Conclusions: We have developed potent bioinks and robust bioprinting protocols to generate a functional human skin model. The methods will be further improved by incorporation of Hyaluronic Acid (HA), collagen-based bioinks, and continued development of the construct design. 3D bioprinted human skin models show great potential to provide a future replacement for animal testing in cosmetics.

9 Multilayer Biodegradable Synthetic Barrier Membranes for Periodontal Regeneration

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Periodontal disease is a major health problem with the increasingly old age rate of the population. Conventional periodontal treatments such as Open Flap Debridement (OFD) provide critical access to establish improved periodontal forms and architecture. However, proliferation of fibroblasts in defect area after OFD prevents the formation of a healthy cementum. Guided Tissue Regeneration (GDR) provides an area for periodontal tissue regeneration using a barrier membrane around the periodontal defect to prevent epithelial growth and fibroblast proliferation in the wound cavity. First-generation PTFE and titanium barrier membranes, developed in the 60's, aimed at achieve a combination of appropriate physical properties and minimal toxic response in the host. However main disadvantage of those membranes was requirement of removal [1]. The second generation of barrier membranes was designed with resorbable polymers to avoid second surgical operation. As the tissue engineering approaches has improved, third-generation membranes also developed, which not only act as barriers but also release bioactive agents at the wound site to direct natural wound healing in a better way [2].

Powerbone multilayered barrier membrane is designed to provide third generation membrane requirements by enhancing bone growth while preventing the gingival tissue down-growth. The first layer, produced by the solvent casting method, avoid to fibroblast proliferation due to the low porosity. The specially designed spray-spinning system is developed to simulate the biomimetic synthetic matrix structure of barrier membranes used for periodontium reconstruction, with suitable fiber size. Intermediate and inner layers with have different pore size and porosity, produced with spray system. The inner layer with its biomimetic structure with average 400 µm pore size, improve cell attachment and facilitating early cell differentiation. Powerbone membrane is designed to support the activity of Powerbone bone substitutes which already received CE mark and has been in medical market for more than two years. The multilayer membrane consists of poly-lactic acid and copolymers with excellent biocompatibility and optimum resorption ratio.

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10 New Approach for Dental Grafting Procedures

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Recently, injectable calcium phosphate-based (CaP-b) grafts have been regarded as promising bone grafts because of their similarity to the mineral phase of the bone and in-situ mineralization support. In addition, CaP-b grafts do not exhibit toxic effects and trigger reactions within the body, are biologically compatible, and most importantly promote bone regeneration even in irregular bone defects. The limiting feature of CaP is its fragile structure, poor mechanical strength and also need for membrane after implantation to enable graft in the defect site. The use of polymeric adjunct materials, amino salicylic acid, and phosphorylated chitosan as a carrier for CaP-b grafts is a common research topic to avoid existing restrictions.

Among these, the most promising agents are synthetic polymers within hydrogel structure. The polymer-ceramic composite paste is injected into the bone defect as a paste, allowing the irregular cavity to be completely filled. In this way, most of the practical disadvantages of the blocks or granules could be overcome.

Requirement of bone grafts as well as dental membranes use increase costs and complexity of the flap surgery in dentistry. The graft material used in the Powerbone Dental Putty is a silicate enriched CaP-b grafts, which is designed as sterile, ready to use (no mixing required) bioactive injectable graft material and above all no demand for dental membrane. Due to its dense and moldable structure, it can fit perfectly the defect shape, stays there without membrane coverage, and increase amount of bone contact which is also increase the cell migration into the graft. The graft material sets hard in the applied area and bonds to the implant and completely resorbed and replaced with native bone tissue in 3 months. Therefore, we predict that Powerbone dental putty will be widely prefered in dental surgeries.

11 3D Bioprinting of Patient-Specific Human Heart Tissues using Vascularized Cardiac Spheroids

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Bioprinting technology is currently investigated as a promising alternative to promote organ and tissue regeneration in humans. It is the layer-by-layer deposition of biological material ("bio-ink") within a bio-compatible matrix ("hydrogel") with defined features to better mimic the target tissue and organ.
We have bio-engineered three-dimensional "cardiac spheroids" (CSs) by co-culturing human primary or iPSC-derived cardiomyocytes, endothelial cells and fibroblasts to approximate the molecular and cellular components of the human heart, with cellular organisation, extracellular matrix and microvascular network that mimic human heart tissue. Cardiac spheroids are used as bio-ink of human heart tissues and have been employed to investigate molecular and cellular mechanisms regulating cardiotoxicity, angiogenesis, fibrosis and regeneration of the heart in vitro and in vivo. Used as building blocks for the bioprinting of human heart tissue, cardiac spheroids offer a promising alternative to current approaches available for cardiovascular disease patients.

12 Biocompatible and stable GO-coated Fe_3O_4 nanocomposite: A robust drug delivery carrier for simultaneous tumor MR imaging and targeted therapy

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Combined targeted drug delivery and sustained drug release, through the application of nanomedicine, shows great potential in cancer therapy and diagnostics. Systems based on folic acid conjugated with graphene oxide-based magnetic nanoparticles (NPs) show distinct advantages for such chemotherapeutic applications. Herein, we prepared FA-Fe_3O_4@nGO-DOX magnetic nanoparticles (MNPs) with a uniform size distribution based on nanoscale graphene oxide (nGO) encapsulated Fe_3O_4, which was conjugated with folic acid (FA) and loaded with doxorubicin (DOX). The prepared MNPs were characterized by various biophysical methods and featured a uniform size distribution. The uniform size of the nGO resulted in a relatively narrow size distribution of the Fe_3O_4@nGO MNPs, which contributed to the stability of the nanocarrier system. Cell viability and in vitro biocompatibility studies of the FA-Fe_3O_4@nGO-DOX NPs revealed their selective uptake by MGC-803 cells. The relative viability was maintained at ~90% after 48h of incubation and the hemolysis ratio confirmed the low toxicity of our modified NPs. The pH-controlled drug release and selective uptake of FA-Fe_3O4@nGO NPs by MGC-803 cells via the FA receptor ensured selective killing of tumor cells. Furthermore, the nanoparticles for magnetic resonance imaging were analyzed in vitro and their signal intensity decreased as the NP concentration was increased. The nanocomposite was highly effective for in vivo imaging.
Additionally, our in vivo antitumor activity and histological analysis confirmed the selective anticancer activity of the FA-Fe_3O_4@nGO-DOX NPs. Notably, our NPs were highly active and mice treated with FA-Fe_3O_4@nGO-DOX showed lower weight loss compared with mice treated with Fe_3O_4@nGO-DOX. More necrotic tissue was observed in the tumors of the FA-Fe_3O_4@nGO-DOX group compared with those observed in the control, Fe_3O_4@nGO-DOX, and DOX groups. Thus, FA-Fe_3O_4@nGO-DOX is an effective and stable candidate for targeted drug delivery.

13 To Improve Regenration of Corneal Endothelial Cells Using the Taurine/Silk Fibroin Film

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Taurine (Ta) promote the expression of connective tissue growth factor that it can repair the damaged tissue. Also, Ta is known as non-toxic. So, Ta is suitable for corneal reconstruction from tissue engineering. And, Silk fibroin (SF) is used as a tissue engineering scaffold because it has good biocompatibility and it can be produced it easily. In this study, Different ratios of Ta (0, 0.25, 0.5, 1 and 2mM) blended film scaffolds were fabricated well with SF. Fabricated Ta/SF films were analyzed using SEM, contact angle, transparency, FTIR, MTT assay, mRNA expression, etc. In results, we can observe that 0.25mM loaded Ta/SF film have good cell proliferation. Also, Ta/SF film support cell growth and these form hexagonal morphology with well-maintained bio- functions. Thus, it can be used the Ta/SF film as a suitable alternative for cornea transplantation because it is having the good water mobility.

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14 Cell Proliferation and Skin Wound Healing Performance of Novel Biodegradable Nanofibrous Mats in Rats

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Nanotechnology-based biodegradable fiber mats open new opportunities to support controlled tissue proliferation. We have developed a new ultrasound-enhanced electrospinning technology USES" [1] for fabricating polymeric nanofibers and advanced nanofibrous mats to be used e.g. in wound healing applications. This technology allows preparation of nanofibrous constructs with unique controlled characteristics (porosity gradients and tailored fiber alignment) aimed for optimal cell proliferation and for controlling the mechanical, topological, moisture permeation, and gas exchange properties of a wound healing platform. In the present study, wound-healing in rats in the presence of nanofibrous wound dressings prepared with the USES technology was studied. Commercial non-nanofibrous wound dressings served as controls. Wistar rats (n = 12; 400-500 g) featuring fixed split-thickness skin wounds (1 cm^2) on the both sides of the dorsal midline were employed. The wound closure rate was monitored for up to 14 days. The *in-vivo* wound healing results showed that the present nanofibrous wound dressings act as hemostatic self-adhesive skin substitutes and accelerate the early-phase healing of split-thickness skin wounds in rats. In addition, *in-vitro* cytotoxicity tests suggested the absence of toxicity on BHK-21 fibroblasts for the present nanofibrous constructs. In conclusion, the study supports the hypothesis that the USES technology could be a promising and safe approach to engineer structures to support cell proliferation both in wound healing and in more complex tissue engineering applications.

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15 Development of Cerebral Organoid based Ischemia Model for Evaluation of Drug Efficacy and Toxicity

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Ischemic stroke, characterized by the disturbance of the blood supply to the brain, is a severe worldwide health threat with high mortality and morbidity. There is no effective pharmacotherapy for ischemic injury even development and clinical trial of anti-Ischemic drugs. Therefore, ischemic injury modeling and evaluation platform required before clinical trials. Technical advances for three-dimensional differentiation of human pluripotent stem cells to neural structures are able to develop human brain recapitulating structures known as brain organoids, cerebral organoids or mini-brain. These brain organoids provide opportunities to study human specific neurological development and disease processes.

Previously, oxygen-glucose deprivation model (OGD model) is widely used as an in vitro model for studying ischemia. While OGD model may provide highly valuable information as to safety and efficacy for therapeutics, there are discrepancies between human brain ischemia and OGD model. To overcome these, we develop ischemic an injury model for in vitro stroke model based on brain organoids.

To determine an optimal ischemic condition to evaluate drug efficacy and toxicity, brain organoids under variable hypoxia condition (1~5% Oxygen), duration, glucose deprivation and reperfusion measured lactate dehydrogenase (LDH) level, live and dead cell assay using Calcein- AM and propidium iodide staining and the apoptosis assay by TUNEL staining and qPCR analysis. To verify our model, the neuroprotective drugs such as MK-801 and Edaravone were treated in brain organoid based ischemic model and effective to rescue ischemic damages.

A novel ischemia model with brain organoids may greatly facilitate to develop drugs for Ischemic stroke.

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16 Two-Dimensional Expansion of Gastrointestinal Lgr5 Stem Cell with a Four-compound Combination

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Epithelial stem cells in the gastrointestinal tract marked by Lgr5, a receptor for R-spondin, are key factors in the homeostasis and regeneration of the injured tissues. Recent advances of three-dimensional culture methodology and understanding niche factors from Lgr5 stem cells isolated gastrointestinal tract have allowed the generation of epithelial organoids. In this study, we try to expand Lgr5 stem cells in a tow-dimensional culture to increase cost-effectiveness of organoid production. When mouse intestinal organoids derived from Lgr5-EGFP-IRES-CreERT2 transgenic mice were dissociated in single cells and seeded on to the Matrigel coated-surface and grown in the standard organoid medium including EGF, Noggin and R-spondin-1, Lgr5 stem cells lose stemness and were completely differentiated. To find enhancing compound for enhancing the stemness of Lgr5 stem cells in two-dimensional culture system, compound combinations with various compounds were tested using organoids from Lgr5-EGFP-IRES-CreERT2 transgenic mice.

As a result, we found a chemical cocktail consisting of four-compounds to maintain Lgr5 positive stem cells in two-dimensional culture system. Furthermore, two-dimensional cultured Lgr5 stem cells with four-compounds were able to form normal functioning organoids again when transferred in three-dimensional culture system without four-compounds. In this study, we developed a cost-effective tow-dimensional culture system to produce large quantity of Lgr5 stem cells and intestinal organoids.

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17 Development and Characterization of Tooth Organoids Using Dental Pulp Stem Cells

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There are no *in vitro* research models so far to discovery drugs and study pathophysiology for tooth disorders. The purpose of this study is developing tooth organoids using dental pulp stem cells (DPSCs) for tooth disease modeling. One approach is that DPSC and Matrigel (extracellular matrix) mixture seeded on multi-well plate and added the culture media and put the plate in incubator for 14 days. Another approach is that DPSC spheroid embedded on Matrigel and differentiate on spinning bioreactors for 14 days. We used six differentiation media compositions; DPSC maintain media, prostate differentiation media, pancreas differentiation media, osteogenic differentiation media, prostate differentiation media with Bone morphogenetic protein-2 (BMP-2 is known as promoting bone formation), prostate differentiation media with osteoclast derived from Raw 264.7. To characterize the tooth organoids from each condition, we conducted experiments such as alizarin red s staining, qPCR and immunostaining using differentiation / undifferentiation markers. Tooth organoid from prostate differentiation media is expressed all differentiation lineages (odonto-progenitor, odontoblast, odontocete). In conclusion, Tooth organoids from pancreatic differentiation media recapitulates teeth features and can be useful for *in vitro* model for tooth disorders.

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18 In vivo evaluation of scaffolds compatible for organoid engraftments onto injured mouse colon epithelium

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Recent advances in long-term 3D culture of isolated intestinal crypts or intestinal stem cells have allowed the generation of intestinal organoids. It is 3D culture model recapitulates *in vivo* physiology because the IEOs contain all the intestinal epithelial cell types proliferated from intestinal stem cells. These models can provide a good platform for studying pathophysiology, screening drug efficacy, and testing drug toxicity. In addition, the organoid can restore the damaged intestinal epithelium when injected into an animal model of IBD. So, it may also be used to develop therapeutic agents to regenerate damaged tissue. Typically, Matrigel is used as an effective scaffold for organoid transplantation. Matrigel is a gelatinous protein mixture secreted from mouse sarcoma cells. It contains laminin, entactin, collagen and various growth factors which can induce extracellular matrix signaling suitable for organoid formation.

However, there is diverse evidence that Matrigel can promote angiogenesis when injected *in vivo*. And its ingredients are poorly defined and the lot variation is so severe that it is difficult to predict the effect on the human. Because of these, materials using Matrigel can't be approved by the FDA, and therapeutics using them are also difficult to obtain approval as clinical treatments. To determine optimal scaffold in organoid transplantation, we injected EGFP labeled organoids into injured mouse colon. After 7 days, engraftment efficacies for each scaffold determined by measuring the EGFP signal range. Then, the recovery effect of epithelial injury was confirmed by histological analysis. It was not only effective for the transplantation of colon organoids, but also had no adverse effects on recipient mice and donor organoids. In addition, it is known to be a higher-purity, well-formulated material. Therefore, it is more suitable than Matrigel for therapeutic use. We propose scaffold for safe and efficient delivery of colon organoids *in vivo*, and provide crucial evidence for therapeutic applications of organoid.

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19 Tissue engineering and clinical repair strategies for intervertebral disc

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Degenerative disk disease (DDD) is a major cause of morbidity worldwide and brings an enormous socioeconomic burden. Operative treatments fail to restore the disc function and are associated with many complications. There has been a growing interest in the biological repair of DDD by both researchers and clinicians. Tissue engineering regenerative strategy appears particularly promising for intervertebral disc (IVD) disease. To generate an overview of the recent advances in reparative strategies for the treatment of DDD, a comprehensive review of the current literature and results of our research group were performed. In this report, several biomaterials and scaffold fabrication methods to engineer annulus fibrosus (AF) or nucleus pulposus (NP) in isolation and AF-NP tissue-engineered constructs were elucidate. The effect of bionic mechanical stimulation on tissue-engineered constructs was also studied. Whole disk transplantation and annulus fibrosus defect repair strategies for IVD in vivo animal model were revealed. Cell-based therapy targeting IVD repair or regeneration in several clinical trials was reviewed about follow-up outcome. Current treatment attempts about AF repair in spinal surgery were also illuminated. It is believed that ongoing research on biological repair of IVD will result in revolutionary progress in the treatment of DDD.

20 Simple 3-dimensional model of the skin to analyze elements of skin physiology and wound healing.

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Introduction: Progress in the fields of cell culture and bioengineering has allowed the *in vitro* development of models of human organs such as skin. The human skin equivalent presents characteristics of morphological differentiation similar to those seen *in vivo*. However, the limited availability of cells used in the skin model and difficulties with generation of human skin equivalents has limited implementation of such models in the research. In this study, we successfully generated full thickness, properly differentiated 3-dimensional skin models using commercially available cell lines and reagents.

Material & Methods: Keratinocyte cell lines: PCS-200-010, HaCaT. Fibroblast cell line: PCS-201-010. Melanocyte cell line: PCS-200-012. 3-dimensional skin model was cultured in Nunc Cell culture inserts using EpiLife Medium with 60 μM calcium and Human Keratinocyte Growth

Supplement, Medium 106 with Low Serum Growth Supplement. During skin model generation, appropriate media was supplemented with inactivated fetal bovine serum, $CaCl_2$, ascorbic acid and Keratinocyte Growth Factor. Hematoxylin & Eosin staining and immunohistochemistry was performed using paraffin embedded tissue sections and fluorochrome conjugated antibodies (ab77684 for Cytokeratin 14, LS-C180221 for Cytokeratin 1, Biolegend 677807 for Vimentin, ab85679 for Loricrin, and ab128759 for Mel.2).

The basal secretion profile of GM-CSF, IL-10, IL-12p70, IL-15, IL-1a, IL-6, IL-7, IL-8, MCP-1, TNFa, and VEGF in 3D models was determined in the 24h culture supernatant using Luminex MagPix platform.

Results: Hematoxylin & Eosin staining as well as immunohistochemistry showed properly developed and differentiated dermis and epidermis of the full thickness 3-dimensional human skin equivalent using PCS-200-010 but not HaCaT keratinocytes. GM-CSF, IL-10, IL-12p70, IL-15, IL-1a, IL-6, IL-7, IL-8, MCP-1, TNFa, and VEGF secretion profiles of the 3D skin model closely resembles the secretion profile of the ex vivo skin.

Conclusion: This study presents simple, reliable and cost-effective method for generation of well differentiated 3-dimensional skin model that can be used for skin and wound research.

21 Macromolecular Crowding as a Tool to Enhance *In Vitro* Fabrication of Extracellular Matrix-Rich Tissue Equivalents – A Step Closer to Clinical Translation

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The clinical translation of novel research ideas into advanced therapies faces many challenges. Current tissue engineering strategies have limited clinical applicability due to prolonged culture periods for the generation of tissue substitutes. A delayed extracellular matrix (ECM) deposition *in vitro* leads to culture times of several months which are frequently associated with phenotypic drift or dedifferentiation. Macromolecular crowding (MMC) has been shown to significantly enhance ECM deposition in permanently differentiated and stem cell culture, by imitating the localised density of native tissues [1].

We use MMC as a tool to generate ECM-rich tissue equivalents in a variety of tissue engineering applications like tendon, cartilage and skin, in order to sustain phenotype maintenance in long term cultures or to induce differentiation. MMC can be applied to cells grown on biodegradable scaffolds and micro-patterned thermo-responsive substrates for the fabrication of ECM-rich tissue-equivalents. We further assess the synergistic effect of MMC with hypoxia or mechanical stimulation to increase collagen deposition and lineage specific marker expression in tenocytes and stem cells [2]. In a first *in vivo* model, we successfully proof the efficacy of a modular collagen-based ECM-rich tissue equivalent for cutaneous wound healing.

In summary, we aim to significantly accelerate translation of promising new therapies by the development of ECM-rich tissue-like supramolecular assemblies as potential implantable devices.

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TERMEX 2018

Introduction of the Local governments, NPO & Private companies

A Overview of Regenerative Medicine (RM) in Korea

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South Korea has achieved a significant progress in commercializing RM since we had the first cell therapy product approved by MFDS, the Korean regulatory authority in 2001. Now we have 16 cell therapies and 1 gene therapy in the market including 4 stem cell therapeutics, the first of which was market-approved by MFDS in 2011. Korean companies are actively pushing their RM pipelines into the clinical trials for cell therapeutics and gene therapeutics. Korea government is investing a lot of R&D funds and reforming the RM regulation more favorable for market approval. The private funding is abundant in the Bio sector including RM and reimbursement is also easily accessible through the public and private health insurances. In the geographical perspectives, Korea is located at the center of the rapidly growing healthcare market in Asia thus could be a gateway through the nearby countries like China and Japan. With the support of strong government initiatives, favorable regulatory environment and strong R&D and clinical infrastructure, Korea provides a great opportunity for foreign RM companies to launch their products, start new business or find a partner in Korea.

B TBD

ARM

C Regenerative Medicine Industrialization Tactical (RMIT) Committee - Toward the formulation of the basis for ecosystem for Regenerative Medicine Industrialization

Fusako Nishigaki [1] , Hidenori Kanno [1] , Kazuhiro Yokota [1] , Fuyuhiko Mori [1]

[1] Forum for Innovative Regenerative Medicine (FIRM)

The missions of RMIT Committee of Forum for Innovative Regenerative Medicine (FIRM) are;
1. Assist business matching between players in the industry,
2. Facilitate the creation of start-up companies, and
3. Develop and promote hubs for Regenerative Medicine Industrialization.

1.1. Business Matching Support
· The RMIT Comm. operates a point-of-contact function at its Nihonbashi office, which provides responses to inquiries and requests.
· The office introduces relevant FIRM member companies to overseas and domestic business entities and research institutes upon their request.
1.2. Holding Partnering Support Event “Regenerative Medicine Crossroad® in Tokyo”
· The RMIT Comm. sets up an occasion for entities, typically from overseas who seek partners in Japan, to help such entities meet potential partner candidates. The event consists of oral presentations and concurrent one-on-one business meetings.
2. Start-up Supporting Seminar ~ RM Product Development & Its Supporting Industries
· The RMIT Comm. holds forums and workshops to support would-be start-ups and early phase developers, in which various informative lectures, tutoring, and networking opportunities with, among others, forerunners and investors are given.
3. One-stop Solution Hubs Encompassing Entire Value-chain of RM Industrialization
· The RMIT Comm. is involved proactively in designing the scheme, operation, and administration for the RM industrialization Hub, Life Innovation Center (LIC) in Tonomachi (King Skyfront), Kanagawa, which is a part of the Keihin Coastal Area Life Innovation Comprehensive Special Zones for International Competitiveness Development. We closely collaborate with Kanagawa Prefecture and an association called RINK (Regenerative Medicine & Cell Therapy Industrialization Network of Kanagawa).
The RMIT Comm. has contributed heavily to designing the Open Lab. in LIC and its instrumentation, which constitutes a vital element for LIC resident start-ups to make progresses in their R&D programs.

D Activities and Efforts of the Forum for Innovative Regenerative Medicine to accelerate Industrialization of Regenerative Medicine in Japan

Fusako Nishigaki [1] , Hidenori Kanno [1]

[1] Forum for Innovative Regenerative Medicine (FIRM)

Founded in 2011, Forum for Innovative Regenerative Medicine (FIRM) is a Japanese organization of Japanese Regenerative Medicine (RM) related industries and currently consists of more than 200 companies. FIRM's mission is to accelerate industrialization of RM in Japan, in order to deliver superior treatment to patients who could not obtain a cure effect by existing treatment as soon as possible.

Almost all the sectors related to this space, including pharmaceutical companies, manufacturers of RM and Cell Therapy products, and other players from different sectors such as medical equipment and devices, culture reagent and media, finance, construction, and transportation, join FIRM and participate in active discussions across industries.

FIRM's activities have been realized through Expert Committees, Management Committees and Specific Committees of national project at FIRM. For example, Supporting Industries Committee have made significant achievements in creating six standards for the criteria formulated and approved within FIRM, with respect to peripheral products and services used for regenerative medicine. FIRM also organizes Japan Mirror Committee for ISO/TC 276 and Committee to Standardize Foundation for Cell Characterization and Cell Production.

In addition, FIRM has an activity as the point of contacts for foreign companies and academia to collaborate in development new products via the events called Crossroad and Venture Creation Support Forum. FIRM concludes a memorandum of understanding to collaborate with overseas corporate groups, activate collaboration with academia and companies, and corporate organizations in other countries to build information sharing system to lead to grow excellent product seeds.

Moreover, FIRM supports the "Multisite Evaluation Study on Analytical Methods for Non-clinical Safety Assessment of hUman-derived REgenerative Medical Products (MEASURE)" that is the aiming at international standardization of the tumorigenicity test of pluripotent stem cells. FIRM leads the "Asia Partnership Conference of Regenerative Medicine Associations (APACRM)" that is the conference on regulatory harmonization for regenerative medicine products among primary Asian countries and territories. The APACRM hope to lead Asian big market with promising future such as India, China, Indonesia, and so on.

FIRM will fulfill its role as a corporate organization so that it can contribute to the creation of good regenerative medicine products.

E MESURE: Identifying and Optimizing Methodologies to Evaluate Cell Therapy Safety: Predictive Methods to assess the Tumorigenicity of Human Cell-Based Therapeutic Products

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Tumorigenicity risk is one of the major concerns for human pluripotent stem cell-based therapeutic products (PSCP) in its clinical use although no internationally accepted consensus on the regulation or evaluation methods for safety and quality control exist.

In "Multisite Evaluation Study on Analytical Methods for Non-clinical Safety Assessment of hUman-derived REgenerative Medical Products (MEASURE)" initiative international regulatory policies on the safety evaluation and quality control and methods for hazard/risk assessment for tumorigenicity are investigated (Step 1). Standard protocols for several tumorigenicity assays (both in vivo and in vitro) are being developed, and the multi-site validation studies will be conducted in order to clarify the utility and reproducibility of these assays (Step 2). MEASURE is expected to be the basis for international consensus tumorigenicity evaluation of PSCP.

F1 Role and Activities of JSRM; the world's largest Regenerative Medicine Society

The Japanese Society for Regenerative Medicine

The Japanese Society for Regenerative Medicine (JSRM) is the largest society for regenerative medicine in the world, with approximately 6000 members involved in research in a wide variety of fields in the natural sciences such as basic medicine/dentistry, clinical medicine/dentistry, tissue engineering, and cell biology, as well as fields in the humanities and in sociology such as bioethics, regulatory science, law, and medical economics. The participating members come from various domains of academia, industry, and government, and JSRM is recognized as the only platform beyond institutional borders where they can engage in discussions regarding a host of challenges brought about by the new field of Regenerative Medicine. The activities of JSRM are not limited to only publishing an academic journal that is common with general academic societies and also include other diverse activities, such as actively making policy proposals as a community, engaging in voluntary research/development and research promotion, and exploring new avenues of clinical research in collaboration with patients and citizens. To actively promote awareness of the "Act on the Safety of Regenerative Medicine" and "Pharmaceutical and Medical Devices Act", which have garnered worldwide attention, activities are being undertaken with the goal of achieving dramatic economic improvement in health care, such as cultivating safe clinical research and treatment (voluntary medical examination and treatment) all over Japan, continued strong support for enabling development of regenerative medicine products, delivering new treatment options to patients who do not benefited by existing therapies, and establishing new curative treatments in place of existing ones for diseases. JSRM is actively pursuing globally acclaimed activities such that Japan does not fall behind despite the initial advantage gained through the discovery of iPS cells.

F2 Establishment of the National Consortium for Regenerative Medicine and National Regenerative Medicine Database in Japan

The Japanese Society for Regenerative Medicine

With its aim to regain the function of organs damaged by illness or injury, regenerative medicine has been the global focus of research. To accelerate the development and the establishment of sufficient safety measures in regenerative medicine in Japan, the new legislation, “Pharmaceuticals and Medical Devices Act” and “Act on Safety of Regenerative Medicine” was enacted in 2014. On the other hand, the advancements in regenerative medicine are anticipated to draw attention toward the development of a system that consolidates and utilizes valuable data from studies performed from pre-marketing to post-marketing stage. Data gathered from pre-marketing to post-marketing stages of clinical research would promote a new development avenue that would lead to the establishment of an appropriate evaluation method for novel regenerative medical products by validating the data. Against this background, the Japanese Society for Regenerative Medicine has been working to establish the national consortium for promoting regenerative medicine and construct a large-scale clinical data registry, named as “National Regenerative Medicine Database (NRMD)”. This poster aims to introduce the current framework of regenerative medicine in Japan, with a particular focus on the activity for establishment of national consortium for regenerative medicine and NRMD.

G Japan Regenerative Medicine Project

Japan Agency for Medical Research and Development (AMED)

The Japan Agency for Medical Research and Development (AMED) was established in April, 2015 to engage in research and development in the field of medicine, establishing and maintaining an environment for this Research and Development, providing funding and managing R&D projects.

AMED aims to act as a 'control tower' that directs integrated research, from basic research to practical application and promotes leading-edge medical innovation from discovery and development to clinical application. Focused on nine key fields, everything AMED does is guided by the Japanese government’s Plan for Promotion of Medical Research and Development.

In the Plan for Promotion of Medical Research and Development, Japan Regenerative medicine project is one of the nine important projects. Thus AMED is strongly promoting the “Japan Regenerative Medicine Project”, which is jointly supported by the three Ministries, the Ministries of Education, Culture, Sports, Science and Technology (MEXT), the Ministry of Health, Labour and Welfare (MHLW), and the Ministry of Economy, Trade and Industry (METI). In order to realize regenerative medicine with iPS cells etc., rapidly, AMED provides seamless support from basic research to clinical use, supports improvement of the infrastructure for regenerative medicine program and promotion of utilization of iPS cells etc., as the supporting tool of drug discovery to improve the efficiency of new drug development.

Funding programs and examples of R&D which AMED has been supporting are introduced to present as the AMED’s effort to realize regenerative medicine since 2015.

I Innovation of Regenerative Medicine and Cell Therapy from Kanagawa -Tonomachi Life Innovation Center-

Advanced Medical Industry Group, Healthcare New Frontier Promotion Headquarters Office, Policy Bureau, Kanagawa Prefecture Government

Promoting advanced medicine and medical technology is one of the key initiative of Kanagawa Prefecture Government. For industrialization of regenerative medicine and cell therapy, we established “Life Innovation Center (LIC)” by public-private collaboration in Tonomachi area, Kawasaki City, Kanagawa Prefecture. LIC provides one-stop services for industrialization of regenerative medicine and cell technologies starting from R&D, quality control to product delivery. We developed the framework to create innovation from LIC, for instance, providing open-lab with various measuring devices, creating investment fund for start-up healthcare businesses, or building a value chain network. In addition, Kanagawa Prefectural Government and Takeda Pharmaceutical Company Ltd. concluded Memorandum of Understanding for the cooperation in healthcare fields in April 2018, and will implement several projects for realizing innovative healthcare technologies under the cooperation of LIC and Shonan Health Innovation Park. We are going to share our policies and supports, and would like to expand network regarding regenerative medicine and cell therapy.

J Aiming for the Industrialization of Regenerative Medicine

Stem Cell Evaluation Technology Research Association (SCA)

The Stem Cell Evaluation Technology Research Association (SCA) is promoting the project toward the goal of industrializing regenerative medicine, in the project titled “Development of Cell Manufacturing and Processing Systems for Industrialization of Regenerative Medicine.” (NEDO project, in fiscal 2014, AMED project from fiscal 2015)

In September 2017, SCA added more members and commenced approaches to a new project of research and development upon adoption for the AMED project titled “Development of Basic Technology to Support Drug Discovery Applying Regenerative Medicine Technology.”

In the project for cell manufacture and processing systems, SCA is developing a new manufacturing system interconnecting the various processes, for the manufacture and processing of regenerative medicine products and the human stem cells that serve as the materials for manufacturing these products.

The project for development of basic technology to support drug discovery is aiming at accelerating use of stem cells for drug discovery research by applying cells from various organs derived by induced differentiation from ES and iPS cells, thereby developing fundamental technology for a system in evaluating the safety, pharmacokinetics, and other properties of drug candidate compounds.

We will bring together the knowledge and technology of academia who participate in our projects and the many companies who participate in SCA, and go forward towards the practical use and industrialization of regenerative medicine.

TERMEX 2018

BPC Prize Finalist

BPC1 Supporting innovation and entrepreneurialism in tissue engineering and regenerative medicine: The TERMIS World Congress Business Plan Competition Finals.

Oliver Ball, Suzanne Tabbaa

TERMIS-WC Business Plan Competition, United Kingdom

Tissue engineering and regenerative medicine (TERM) are cutting edge fields with the potential to change the face of medicine. While the academic research environment remains a hotbed of technological advancement, translation into real-world application requires a combination of technical expertise, entrepreneurial skills, financial management, regulatory awareness, and peer support.

The TERMIS Business Plan Competition (BPC) is the only start-up competition operating exclusively in the TERM fields. We aim to support academics and early-stage entrepreneurs wishing to accelerate technologies from bench to market by providing an opportunity to these groups to seriously consider their business strategy, and receive mentorship and support in this endeavour. Each year, the best 5 entrants to the competition are assigned expert mentors to guide the development of their business plan and investment goals. Since 2016 we have been supported by TERMIS to deliver three successful international events, and have supported the transition of many participants into a career within industry. Our sponsors, who have previously including J&J Innovation, GSK, and PROTiP Medical, have the opportunity to develop partnerships with participants and the wider community, keeping a 'finger on the pulse' to help realise life-changing medical solutions while building value into their own companies.

This year sees the collaboration between our European and North American Chapters to deliver a competition on a global scale. The BPC finals, here at TERMIS World Congress, will itself represent the interdisciplinary participation of academics, entrepreneurs, and industry experts from every corner of the globe to encourage and support innovation and entrepreneurialism in TERM research.

BPC3 Goodbye flattened biology

Raphaël F. Canadas

I3Bs, University of Minho, Portugal

Have you ever wondered why drug development are so costly and take so long to reach the market? BIOreACT vision is to make drug and cosmetic testing realistic before clinical trials and our mission is to provide reliable and ethical in vitro testing solutions and avoiding animal models issues. We offer to the Pharmaceutical and Cosmetics Industries an advanced 3D in vitro cell culturing solution for boosting drugs/cosmetics screening. Unlike the current 2D and 3D testing methods and animal models, our 3D Bioreactor platform is dynamic and designed for biological interfaces. Overall, our solution fills the research gap between pre-clinical and clinical trials. Our fluidic system is composed of disposable interconnected dual-chambers which are adapted for mono- and co-cultures. Furthermore, BIOreACT allow the breakthrough of testing 2 different scenarios in a more realistic 3D microenvironment and interfaces. Our dual-chambers fit the commercial 6-well tissue culture plates and can be used standalone or copulated to our proprietary rotational platform. The rotational platform enables the control over cell seeding homogenization, improves culture medium diffusion in 3D constructs, and induces physical rotations similar to the human body movements. These features do result in an increased metabolic activity of 59%, maturating constructs homogeneously and generating cell phenotype spatially controlled through the 3D constructs. Overall, BIOreACT patented technology triggers a paradigm shift for drugs and cosmetic testing, by hybridizing the concepts of bioreactors and microfluidics, which ultimately reduces the costs and time-to-market for drugs and cosmetics.

BPC5 ExTherea: Exosome-based Therapy for Healing Diabetic Foot Ulcers

Sophia Bou-Ghannam, Sebastian Sjöqvist

Institute of Advanced Biomedical Engineering and Science, Sweden / Japan

Every 30 seconds, one lower limb is amputated due to diabetes-related complications. With the incidence of diabetes on the rise worldwide, increasing from a current 347 million people globally, the rate of amputations can only be expected to magnify. Eighty-four percent of these amputations are preceded by a diabetic foot ulcer (DFU). The current treatments for DFU are based on surgical debridement, off-loading, and various wound dressings. Unfortunately, approximately 23% of DFUs will not heal within one year, despite such treatment. Economically, DFUs represent a massive burden on healthcare spending with each wound costing up to $28,000.

The ExTherea vision is to harness the natural and exceptional healing capacity of the oral mucosa to produce a unique next-generation therapy for DFU patients. Our innovative approach is based on exosomes – small, biological nanoparticles that can transmit signals to recipient cells. Our recent data proves that our unique stock of exosomes exhibit pro-regenerative properties *in vitro* and accelerate healing of full-thickness wounds in rats, without any signs of adverse effects. Compared to cellular-based therapies, exosomes exhibit a much greater stability and we expect the final product to have a shelf life of several months while still being available for use within minutes. Further, a simple spray-technology provides excellent ease-of-use for widespread clinical adoption.

We believe that our innovative product can be greatly cost-efficient and, more importantly, prevent amputations and increase the quality of life for a significant patient cohort.