PRL1 TERMIS Global President Lecture: Overview of TERMIS and natural origin materials for TERM

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It has been my honor to serve TERMIS in different leadership roles since its foundation. From 2016 to the end of 2018 I have been/will be the TERMIS Global President. It is in that role that I will dedicate, as it has been the case for other Presidents in Past World Congresses, the first part of this talk to TERMIS. I will present the TERMIS mission and its global and chapter organization. I will discuss membership and ways for you to get more involved. I will also announce coming elections, travel awards and the new fellows of TERM. Finally, I will briefly present the coming chapter meetings that are being organized by our society.

In the second part of the talk I will present some examples of my own research. The selection of a proper material to be used as a scaffold or as a hydrogel to support, hold or encapsulate cells is both a critical and a difficult choice that will determine the success of failure of any tissue engineering and regenerative medicine (TERM) strategy.
We believe that the use of natural origin polymers, including a wide range of marine origin materials, is the best option for many different approaches that allow for the regeneration of different tissues. In addition to the selection of appropriate material systems it is of outmost importance the development of processing methodologies that allow for the production of adequate scaffolds/matrices, in many cases incorporating bioactive/differentiation agents in their structures.
Furthermore, an adequate cell source should be selected. In many cases efficient cell isolation, expansion and differentiation, and in many cases the selection of a specific sub-population, methodologies should be developed and optimized. We have been using different human cell sources namely: mesenchymal stem cells from bone marrow, mesenchymal stem cells from human adipose tissue, human cells from amniotic fluids and membranes and cells obtained from human umbilical cords.
The development of dynamic ways to culture the cells and of distinct ways to stimulate their differentiation in 3D environments, as well as the use of nano-based systems to induce their differentiation and internalization into cells, is also a key part of some of the strategies that are being developed in our research group.
The potential of each combination materials/cells, to be used to develop novel useful regeneration therapies will be discussed. The use of different cells and their interactions with different natural origin degradable scaffolds and smart hydrogels will be described. Several examples of TERM strategies to regenerate different types of tissues will be presented.

PRL2 Overview of JSRM and frontier RM in cardiovascular area

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JSRM, established in May 2001, 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 and 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. The content of the representative policy proposal, the "Yokohama Declaration", has had significant impact on the actual content of the "Act on the Safety of Regenerative Medicine" and "Pharmaceutical and Medical Devices Act" enacted in 2014 and has attracted worldwide attention as a premier approach to legal regulations. Since 2016, JSRM acquired competitive funds called "Regenerative Medicine National Consortium" from the Japan Agency for Medical Research and Development (AMED) In particular, development of the "Good Post-marketing Study Practice" standard compatible database and "National Regenerative Medicine Database (NRMD)" is gaining attention as another global first in the attempt to acquire real world evidence from all clinical cases of regenerative medicine and cell therapy.
We have developed cell sheet technology experimentally and introduced this to the treatment of severely damaged myocardium as a translational research. In a series of pre-clinical experiments, we proved that myoblast sheets could heal the impaired heart mainly by cytokine paracrine effect in cardiomyopathy model. We applied myoblast sheets to 15 ICM patients who showed improvement of systolic function with ameliorated exercise tolerance and symptoms. Recently, myoblast sheet was approved by the government as "Heart Sheet" in the treatment for ischemic cardiomyopathy as a first commercially available case in the world. Moreover, we have developed human iPS cell derived cardiomyocyte sheet and also established large culture system and checked safety of GMP grade iPS cell derived cardiomyocyte sheets for clinical trial by the development in new method for removal of immature iPS cells.
Regenerative technology has some potentials in the clinical treatment of heart failure which has little response to the internal medical or conventional surgical treatment and these technologies may open new era in the treatment of severely damaged myocardium.

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PLL1 Retinal cell therapy using iPS cells

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The first in man application of iPS-derived cells started in September 2014, targeted age-related macular degeneration (AMD). AMD is caused by the senescence of retinal pigment epithelium (RPE), so that we aimed to replace damaged RPE with normal, young RPE made from iPS cells. We judged the outcome 1 year after the surgery. Primary endpoint was the safety, mainly the tumor formation and immune rejection. The grafted RPE cell sheet was not rejected nor made tumor after two years. The patient's visual acuity stabilized after the surgery whereas it deteriorated before surgery in spite of 13 times injection of anti-VEGF in the eye.

Although autologous RPE sheet transplantation is scientifically best approach, it is time consuming and expensive and it is necessary to prepare allogeneic transplantation to establish a standard treatment. RPE cells are suitable for allogeneic transplantation because they suppress the activation of the T-cell. From in vitro and in vivo study, it is possible that the rejection is considerably suppressed by using the iPS cell with matched HLA. Our new protocol has accepted by ministry in Feb 2017. We are planning transplantation using allogeneic iPS-RPE cell suspension & sheet, and also autologous iPS-RPE. For the cell suspension transplantation we will not combine CNV removal and apply to milder cases than sheet transplantation.

In Japan, pharmaceutical law has been changed and a new chapter for regenerative medicine was created for clinical trial. Also the separate law for safety of regenerative medicine for clinical research (study) was enforced in 2015. These laws made the suitable condition for the brand new field of regenerative medicine. We are making regenerative medicine in co-operation with ministry & academia.

PLL2

PLL3 Frontiers of human organs-on-a-chip technology

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The development of functional in-vitro tissue chips that combine biological fidelity with high-throughput experimentation for physiologically relevant predictions are now enabling models of the "human body in a dish". To this end, we have established a platform capable of creating interconnected organ systems of high biological fidelity for our future goals of modeling disease and testing drug safety and efficacy, within a configurable functional network of heart, liver, skin, bone, and vascular tissue systems, all grown from the same batch of patient-derived iPS cells, and perfused with a blood substitute. Our goal is to model the systemic off-target responses to cancer drugs such as doxorubicin, a commonly used chemotherapeutic, in a patient-specific manner. Our platform is designed to deliver individualized tissue-specific biomimetic cues (culture medium, regulatory factors and physical signals) to functionally mature each tissue system towards physiological relevance. In this design, each tissue compartment is separated from the vascular compartment by an endothelial barrier. The shared perfusion network, which contains endothelial cell medium with circulating immune cells, flows within each tissue and connects the individual tissues in a desired order, to mimic the circulatory system in vivo. We report the platform design, differentiation of the cell subtypes needed for all included tissues from a single iPS cell source, and current advances in achieving the tissue maturity.

To illustrate the utility of the platform, we also report the cultivation and use of adult-like human cardiac muscle derived from patient-specific induced pluripotent stem (iPS) cells. Cardiac tissue constructs were formed from early-stage iPS-derived cardiomyocytes (iPS-CM), soon after the initiation of spontaneous contractions, and were subjected to physical conditioning of an increasing intensity. After only 4 weeks of culture, these tissues displayed adult-like gene expression profiles, remarkably organized ultrastructure, physiologic sarcomere length (2.2 μm) and density of mitochondria (30%), the presence of transverse tubules (t-tubules), oxidative metabolism, positive force-frequency relationship, and functional calcium handling for all iPS cell lines studied. Tissue maturity was necessary for achieving physiologic responses to drugs and disease modeling.

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PLL4 Delivery of Anabolic Genes, miRNA and CRISPR Systems for Stem Cell Fate Modulation and Tissue Regeneration

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Tissue regeneration requires coordinated functions of cells, materials and appropriate signaling. Recent years have witnessed the marriage of regenerative medicine and gene delivery by which various genes encoding anabolic/catabolic proteins or RNA therapeutics are delivered into cells to potentiate the tissue regeneration. We have employed viral vectors for genetic modification of mesenchymal stem cells derived from bone marrow or adipose tissue for tissue regeneration. In particular, we have extensively exploited baculovirus, an emerging nonpathogenic gene delivery vector, for highly efficient delivery of various anabolic genes and miRNA mimics/sponges to repair tissues such as cartilage, bone and nerve. Furthermore, CRISPR activation (CRISPRa) and CRISPR inhibition (CRISPRi) are newly developed technologies that exploit dCas9 protein and single guide RNA (sgRNA) for programmable gene modulation. We have engineered baculovrius to deliver CRISPRa and CRISPRi modules to control endogenous gene expression in a customizable fashion and regulate the lineage commitment of stem cells, which contributes to enhanced tissue repair. We have also developed a novel CRISRai system for simultaneous stimulation of chondrogenic transcription factor and suppression of adipogenic factor, which allowed us to favorably induce adipose-derived stem cell differentiation towards chondrogenic lineage. These studies collectively demonstrate the potential of baculovirus-mediated gene delivery for stem cell engineering and regenerative medicine.

PLL5 Clinical Cell Therapy of Heart Failure

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So far, cell therapy trials in chronic heart failure have proven to be safe but their outcomes have not matched the high expectations raised by experimental studies, regardless of whether they have used noncardiac or cardiac-committed cells such as c-kit+ cardiac stem cells or cardiosphere-derived cells. While several causes have contributed to this disappointing observation, a key factor is likely the lack of a thorough mechanistic understanding. Actually, two possible mechanisms can be considered. The first is the "remuscularization" of the chronically damaged myocardium by exogenously supplied cells intended to structurally integrate within the recipient myocardium to generate a new tissue. However, the consistent discrepancy between the paucity of a long-term cell engraftment and the maintenance of functional benefits over time has increasingly led to a second hypothesis whereby the primary mechanism of action of the grafted cells is the release of biomolecules that paracrinally foster endogenous repair processes. This distinction has major practical implications which impact on the design of future trials. If the primary objective is the repopulation of extensive areas of scarred myocardium, the grafted cells should be cardiac-committed, scalable, delivered along with supportive cells, combined with a method promoting their long-lasting survival and patterned in such a way that they can homogeneously couple with host cardiomyocytes so as to avoid arrhythmias. If the primary objective is paracrine signaling, cells should first be selected for their high secretory profile; in this context, mesenchymal stem cells are attractive candidates although there is increasing evidence that the best outcomes may be achieved by cells phenotypically close to the target tissue. This rather rationalizes the use of cardiac-committed cells among which embryonic or induced pluripotent stem cells are particularly appealing since their initial undifferentiated state can be leveraged to derive a cardiac progeny, as in our now completed ESCORT trial. A second requirement is to optimize the retention of cells to give them enough time for releasing the factors underlying their protective effects. This can be achieved by dedicated delivery catheters and/or combination of cells with polymers or material-free cell sheets, yielding injectable mixtures which gel in situ or epicardially-delivered patches; focus on early retention, as opposed to sustained survival, should also allow for a more liberal use of allogeneic cells which feature multiple advantages over patient-specific products while their expected rejection may no longer be a limiting issue since this rejection only requires to be delayed, not fully avoided, thereby allowing a shortened, and consequently better tolerated, immunosuppression regimen. One step further, an option could be to use the cells exclusively for producing the cytoprotective factors and then to only administer the secretome, or some of its most biologically active components such as the extracellular vesicles, to the patient. The production process would then be closer to that of a biological pharmaceutic, thereby facilitating an expended clinical use.
Regardless of the prevailing mechanistic hypothesis, the specificities of cell therapy should also lead to revisit the framework of clinical trials through (i) a more accurate selection of the indications, focused on subsets of patients for whom there is a real unmet medical need, (ii) an optimization of the cost-effectiveness of manufacturing based on automated industrial-scale technologies with in-process quality controls and meeting regulatory requirements identified from the very onset of any of these programs, (iii) a streamlining of outcome assessments and monitoring based on robust and straightforward read-outs, and (iv) trial designs relying on alternate statistical models such as the Bayesian ones, which may better fit the specifics of cardiac cell therapy.

PLL6 Cerebral organoids: modelling human brain development and tumorigenesis in stem cell derived 3D culture

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The human brain is unique in size and complexity, but also the source of some of the most devastating human diseases. While many of these disorders have been successfully studied in model organisms, recent experiments have emphasized unique features that can not easily be modeled in animals. We have therefore developed a 3D organoid culture system derived from human pluripotent stem cells that recapitulates many aspects of human brain development. These cerebral organoids are capable of generating several brain regions including a well-organized cerebral cortex. Furthermore, human cerebral organoids display stem cell properties and progenitor zone organization that show characteristics specific to humans. We have used patient specific iPS cells to model microcephaly, a human neurodevelopmental disorder that has been difficult to recapitulate in mice. This approach reveals premature neuronal differentiation with loss of the microcephaly protein CDK5RAP2, a defect that could explain the disease phenotype. More recently, we have been able to generate organoid based models for human brain cancer and demonstrated their feasibility for drug testing. Our data demonstrate an in vitro approach that recapitulates development of even this most complex organ, which can be used to gain insights into disease mechanisms.

PLL7 Biomaterials for Tissue Engineering and Regenerative Medicine

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Advances in biology, materials science, chemical engineering, and other fields have allowed for the development of tissue engineering, an interdisciplinary convergence science. For the past two and a half decades, our laboratory has focused on the development and characterization of biomaterials-based strategies for the regeneration of human tissues with the goal of improving healthcare outcomes. In a collaborative effort with physicians, surgeons, and other scientists, we have produced new material compositions and three-dimensional scaffolds, and investigated combinations of biomaterials with cell populations and bioactive agents for their ability to induce tissue formation and regeneration. We have examined the effects of material characteristics, such as mechanical properties, topographical features, and functional groups, on cell behavior and tissue guidance, and leveraged biomaterials as drug delivery vehicles to release growth factors and other signals with spatial and temporal specificity. This presentation will review recent examples of biomaterials-based approaches for regenerative medicine applications and highlight future areas of growth, such as the use of tissue engineering for validation of cancer therapeutic discovery.