THE XI'AN PAPERS

The World Summit on Regenerative Medicine, held in Xi'an, China, in October 2013, targets the global barriers to the implementation of therapies of regenerative medicine. Many of the world's leaders engaged in the development, delivery and regulation of these therapies have provided written summaries of their initial positions and have committed to discuss and debate their opinions in open session at the Summit.

This is the first time that this immensely important subject has been debated on the global stage, and the outcome should have a profound effect on all aspects, including the scientific, ethical, economic, regulatory, clinical and manufacturing arenas. The Xi'an Papers provide the details of the Summit guests and the statements of the main presenters. The outputs will consist of a principal communiqué and a variety of reports and recommendations targeted towards key stakeholders.

2013
XI'AN WORLD SUMMIT ON
REGENERATIVE MEDICINE

2013 XI'AN WORLD SUMMIT ON REGENERATIVE MEDICINE

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RECONSTRUCTING THE BODY

NORTH HEAD

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GLOBAL BARRIERS AND OPPORTUNITIES IN REGENERATIVE MEDICINE

David Williams and Yilin Cao

The translation of major developments in medical science into routine successful clinical practice has never been easy. In the nineteenth and twentieth centuries, the introduction of anesthesia, antibiotics, transplant surgery and *in vitro* fertilization all had a difficult passage. At that time it was often difficult to discern the inventive genius from the charlatan, and difficult to persuade a skeptical public about the value of a new science that was beyond their comprehension. And, of course, there have been many wonderful developments that did not make it through the tortuous path of peer and public acceptance.

We stand, today, at a medical crossroads. Yes, an abused expression, but real, nevertheless. For over half a century we have had a wide variety of drugs and devices that treat symptoms, replace or augment tissues and molecules, block unwanted pathways and facilitate those we care for; but in general we cannot regenerate or replace those parts of our bodies that have fallen asunder. Whereas a newt or salamander can re-grow limbs at will, our own pathetic attempts usually end with functionally useless scars.

Of course, we would all rather have the brain of a human than that of a newt, and our evolutionary pathway determined that we were better off with good brains than regeneration. But the question arises: if we are now so smart, then why can't we engineer nature to equip ourselves, now and then, with the regenerative power of a newt?

THE IMBALANCE BETWEEN SCIENTIFIC ADVANCES AND PATIENT BENEFITS

Look at what science has delivered to us. We have the cells that can express new tissue – they are already in our bodies or in donor tissues. We just have to tell them what to do, and where, and maybe how, and also when to stop. We have most of the technologies to do this – we can handle and culture the cells and we can program or re-program them. We can alter their genes if necessary. We can track them, we can monitor them, we can give them molecular and mechanical signals to persuade them to do amazing things and we can push them into producing some new

tissue under some circumstances. We just have to manipulate these cells to produce high quality, functioning tissue in those patients who need some form of regeneration, in order to save their lives or remarkably improve their quality of life.

- Why can't we regenerate the dopamine-producing cells in patients with Parkinson's disease?
- Why can't we regenerate the retina in those patients who are going blind through macular degeneration?
- Why can't we regenerate the damaged spinal cord in those individuals who are paralyzed?
- Why can't we develop growing heart valves for children with rheumatic heart disease?
- Why can't we start the process of regenerating brain tissue, or at least slow down the process of degeneration, in the millions of patients with Alzheimer's disease?
- Why can't we regenerate heart tissue in those who have had a heart attack, or regenerate blood vessels in the legs to avoid amputation on those with severe peripheral vascular disease, or regenerate the urethra in those who have urinary incontinence?

The answer is that we do not know that we cannot; indeed we can do some of these things now and then. But the activation energy necessary to get these successes that we have achieved so far into routine clinical practice – within a viable health economic environment and with public acceptance – is proving so high. There are too many barriers in the way, and the transition from an ability to regenerate small parts of skin, cartilage and bone to the ability to address those major areas of currently un-met but massive clinical need, seen in the earlier examples, is proving very difficult.

THE OBJECTIVES AND SCOPE OF THE XI'AN WORLD SUMMIT

This World Summit on Regenerative Medicine, held in Xi'an, China, has been convened with the intention of addressing these critical issues. This is, of course, not the first time that these issues have been addressed. Previous occasions have been largely organized and based on national, regional or sectional interests. The Xi'an Summit has been designed to be truly global. This is an independent forum, involving invited delegates only and with no commercial or political sponsorship. The program has been scheduled in order, first, to enable delegates to hear key opinion leaders identify the key issues, and, then to discuss these issues and produce action points and recommendations that will be widely disseminated.

The analysis of the main causes of the failure of effective and routine clinical translation includes the following important factors.

Ethical constraints have always been important, but they are being addressed. It is necessary for the regenerative medicine community to operate in a positive promotional atmosphere, such that publicity of the tremendous therapeutic potential outweighs negative concerns. While not underestimating the importance of legitimate ethical concerns, appropriate educational tools need to be used to inform patients and the public in general. Especially, we need to differentiate between regenerative medicine and reproduction techniques, in order to maintain public confidence. Research and development (R&D) costs remain a critical factor. Several multinational companies have decided not to invest in regenerative medicine R&D. This is crucial, since business models in the health care technology sector have been based with such large companies, where the R&D costs have been covered by revenue from existing traditional product lines. Enormous costs are imposed on start-ups that do not have any sales revenue.

With basic biological sciences and bioengineering, much has been learnt during the last decade, with massive progress in stem cell science, gene transfection and growth factor delivery, biological scaffolds, bioreactor and biofabrication technologies and imaging of regenerated tissue. The Summit will discuss these sciences. The really critical aspects, however, are concerned with an integration of these different components, where a systems engineering approach is absolutely vital to ensure successful translation of the regenerative medicine paradigms, especially those of tissue engineering. There are also still huge scientific and technical unknowns in the scale-up from small-scale laboratory-based methods to clinically relevant constructs with appropriate quality.

Very few products or techniques are already in routine clinical use. The fast rate of development of the science in the last few years has led to the emergence of potential products into pre-

clinical testing, clinical trials and regulatory phases. Uncertainty is profound within these areas. For example, there are few, if any, scientifically valid, internationally recognized standards for functional testing of tissue engineering products. It is very difficult to predict performance of products in humans. The pre-clinical testing requirements of biomaterials are very out of date and unhelpful in the determination of this ultimate performance. There are major differences between approaches to regenerative medicine products and processes by national regulatory bodies, and, on a global basis, there is a need to coordinate dialogue between agencies and governments. Since it is very difficult to get approval for either trials or product marketing under many jurisdictions, there has been a trend towards opportunistic use of observational studies and possible confusion with medical tourism. International coordination of these practices seems desirable.

Science and engineering are the 'drivers' of regenerative medicine, and the pathways of these therapies incorporate the many different linkages provided by these features. The 'pull' comes from the two ends of the paradigm: the business models that allow the legitimate creation of wealth, at one end, and the un-met but highly demanded clinical need, at the other. There are huge barriers at both of these ends. The economics of heath care are undergoing profound change at the moment, with the two biggest regions, the USA and China, both in turmoil with respect to the restructuring (in the former case) and the introduction (in the latter case) of insurance and reimbursement schemes. Superimposed onto these general factors, a very poor understanding of risk-benefit relationships in regenerative medicine results in low levels of coverage. There would appear to be an opportunity to engage with the insurance sector to explore this.

At the other end, patient demand is potentially overwhelming. With an emphasis on un-met clinical need, for example, with the millions suffering from neurodegeneration, diabetes and serious trauma, it is easy to see that the potential clinical market place may not be manageable. The regenerative medicine industry needs to work with the representatives of patients, especially some key patient support groups, in order to provide realistic projections and to manage expectations.

SUNDAY 20 OCTOBER, 8.30–12.00

INTRODUCTORY SESSION

Co-Chaired by David Williams and Yilin Cao
Opening statement, written jointly by David Williams and Yilin Cao

Opening statement on key technical/scientific challenges ..... *Silvio Itescu*
Opening statement on business models and hurdles to commercialization ..... *Peter Johnson*
Opening statement on key clinical challenges ..... *Paolo Macchiarini*
Opening statement on key economic-regulatory issues ..... *Gail Naughton*
Opening statement on key issues of translation: China's perspective ..... *Kerong Dai*
Opening statement on key issues of global translation ..... *Teruo Okano*
Opening statement on humanitarian opportunities ..... *Scott Hollister*

Discussion leader: *Peter Johnson*

INTRODUCTORY SESSION

BUSINESS MODELS AND HURDLES TO COMMERCIALIZATION

Statement by Peter Johnson

The raison d'être of our work in tissue engineering is to better serve patients who have illnesses that lend themselves to tissue replacement and/or repair. This is a daunting task. The patient lives at the end of what can be described as a long string of related and unrelated hurdles, any one of which may thwart the delivery of tissue engineering technology in an effective manner. The resistances (R) in a series electrical circuit illustrate a simple example of the problem:

R1 -> R2 -> R3 -> R4 -> R5 -> R6 -> User -> R7

In tissue engineering, R1 might be considered the compendium of technical risks associated with the development of the physical 'product'; R2 might be considered the risks associated with financing early development; R3 could be the risk of pre-clinical or clinical failure during testing; R4 might be the risk of lack of regulatory clearance; R5 might be the risk of reimbursement failure and R6 might be the risk of lack of adoption by caregivers or by complex hospital and distribution systems such as group purchasing organizations. R7 would be the risk of technology failure during post-market surveillance. There are many sub-risks in the continuum but these represent the major zones of risk.

As a result of these linked risks, business models in our field need, in many cases, to be conceived at the onset of technology development itself. This implies that early technology developers – generally academics – need to become quite well versed in both clinical applications and business methods; the latter including financing, regulatory, reimbursement and distribution issues. Recently published work indicates that there is a wide – and understandable – gap in this awareness among academics. Work is ongoing to further explore gap areas to which educational forums and supplemental education can bring progress. However, there appears to be an immediate need for consortia of business and academic talents to enable filtering of opportunity and augmentation of 'risk hurdling', as we bring these important technologies forward.

KEY ECONOMIC-REGULATORY ISSUES

Statement by Gail Naughton

Regenerative medicine has tremendous potential to treat patients suffering with damaged or missing tissues and organs. Early products focused on replacing skin in acute and chronic wounds, with either autologous or allogeneic cell-based products. Such products faced both regulatory and economic hurdles, since no precedence existed for tissue engineered products. The costs of manufacturing autologous epidermal sheets or cartilage substitutes are high, due, in part to the need to have a dedicated manufacturing facility with full segregation of samples. Allogeneic products need to have the starting cells extensively tested for pathogens, viruses and potential chromosomal abnormalities; a tedious and expensive process. In addition, there are no clear guidelines for manufacturing a living product with inter- and intra-lot consistency, a particular issue due to normal biological variability. The regulatory pathway has also been variable, with initial autologous products needing no regulatory approval and later being regulated as a biologic. Allogeneic tissue engineered products were originally regulated in the US as a Class 3 device but are now biologics with a variety of regulatory approvals across the globe. Reimbursement has also been a challenge for these regenerative therapies, with early products taking years to be reimbursed at a fair level, post-regulatory approval, leading to the demise of key tissue engineering companies.

Over the past decade much has been learnt that has contributed to automated manufacturing of tissues and clinical design, which will support outcomes for a clear path for reimbursement. In addition, the industry has seen the benefits of developing multiple aesthetic and therapeutic applications for each product, which significantly reduces the product development timelines and costs. This presentation will discuss the 'lessons learnt' from Advanced Tissue Sciences and new paradigms for accelerating regenerative medicine products from laboratory bench to market.

KEY ISSUES OF TRANSLATIONAL RESEARCH ON REGENERATIVE MEDICINE – CHINA'S PERSPECTIVE

Statement by Kerong Dai

Regenerative medicine has rapidly developed in China, and more than 50 translational centers or platforms have been established in the four years from 2009 to 2012, which shows that Chinese medical communities highly value this field. Particularly, regenerative medicine has become the top priority of translational research in the field of medicine in China. However, many issues need to be resolved before translational medicine steps from an abstract concept to concrete practice. According to our working experiences, at least four aspects should be converted to meet the requirements of translational research: research modes, research objects, roles of the institution and evaluation criteria. These should all reflect the goal of translational research to be 'people and clinically oriented'. In addition, the key issues that should be emphasized in China for translational research on regenerative medicine include: 1) Education: training in the basic concept, proper design and strategies; 2) Emphasis on intellectual property protection: domestic and international patent application and patent license for product development; 3) Implementation of regulatory procedure as early as possible in product development or clinical trials; 4) Enhancement of communication among multi-discipline experts for the creation of novel ideas; 5) Promotion of joint projects with close collaboration among scientists, physicians, engineers, relevant people in industry, regulatory agencies and venture capitalists; 6) Establishment of a better regulatory system to manage the translation procedure with more efficiency and efficacy; 7) Foundation of a specialized translational research institution to promote communication and collaboration among experts within a united system, as well as to strengthen project management and implementation.

INITIATION OF REGENERATIVE MEDICINE AND TISSUE ENGINEERING

Statement by Teruo Okano

World public health has been significantly improved by medicines in the 20th century. A large number of patients have been cured by innovative technologies, which can produce antibiotics, bio-drugs, etc. and create and maintain a huge pharmaceutical industry in the world. At the same time, therapy for damaged tissues or organs has been realized by organ transplantation and the development of artificial organs. Considering the constant shortage of donors and the fact that current science and technologies cannot reproduce the highly complicated functions of the human organs, we have to recognize the future limitations of the current technologies in this field. Even after significant progress in these life science technologies, we still have a large number of patients suffering from difficult diseases or organ damage, and who need to be treated with innovative therapies.

In the 21st century, tissue engineering regenerative medicine is highly anticipated to provide innovative therapies, because it may regenerate the mass production of volumes of cells and engineered tissues for advanced therapies. Thanks to tremendous research efforts by fusing the knowledge of biomedical scientists and physicians, we are getting closer to enjoying effective regenerative medicine. However, we also face a serious conflict between its commercialization and existing pharmaceutical regulations and a zero-risk approach, because we have not yet established proper intelligence nor developed appropriate regulations for innovative regenerative medicine, which has to handle a large volume of living cultured cells or engineered tissues. Innovative consensus and intelligence have to be developed now for regulating tissue engineering regenerative medicine by advanced science-based evidence.

With our combined wisdom, I am expecting active and professional discussion of various aspects among the participants in this World Summit, to create a new regulatory approach to optimize the balance between safety and efficiency, thus enabling regenerative medicine to move from bedside to industry.

HUMANITARIAN OPPORTUNITIES

Statement by Scott Hollister

Medical devices and regenerative medicine therapies are extremely expensive to develop, bring through regulatory approval, and eventually market and sell. Some estimates project that combination therapies may cost over US$ 200 million and take 8–10 years to achieve regulatory approval. Such therapies clearly will be developed only if they address large patient markets (>20 000 patients per year). There are many serious or life-threatening conditions with much smaller patient populations, even down to single patients. This is especially true of pediatrics, for which there is a recognized shortage. Niche markets will continually be neglected if development and regulatory costs remain prohibitive, as they are unprofitable for large and start-up medical devices companies, and prohibitively expensive and culturally difficult for non-profits and research institutes to address.

Addressing these niche and custom markets depends upon reducing costs and regulatory complexity. Recognizing these issues, the Food and Drug Administration (FDA) in the United States established Humanitarian Use Designation (HUD) for conditions affecting less than 4 000 patients in the US and for which there is no existing comparable device. Although it is possible that a HUD device may be approved through a 510K pathway for a Class 2 device, this may be unlikely as, by definition, a predicate (substantially equivalent) device would have to exist. Therefore, HUD devices or therapies will likely have to go through a general Pre-Market Approval (PMA) pathway. However, instead of obtaining an Investigational Device Exemption (IDE) to carry out clinical trials, a Humanitarian Device Exemption (HDE) is required. A major difference between an IDE and an HDE is that HDE devices or therapies are exempt from the effectiveness requirement of

an IDE (that is, the HDE device is not required to be proven as effective in treating a condition as a current clinical treatment). The HDE must show, rather, that the potential benefits of an HUD device outweigh the potential risks. Finally, in the case of pediatric HUD devices, the developer may charge for the device to recoup development costs during the clinical trial.

Despite the easing of regulatory requirements to motivate device development for orphan conditions, developing such a device still remains a daunting task. For biomaterial or tissue engineering therapies, ISO 10993 biocompatibility and large pre-clinical animal testing may run upwards of US$ 1–2 million. A Phase 1 clinical trial may cost US$ 3–5 million. In addition, HUD devices are still required to satisfy FDA Quality Systems Regulations (QSR), unless the manufacturer can prove QSR implementation is not possible and is granted an exemption. In summary, the financial and cultural requirements for humanitarian device approval are still significant, especially since organizations most likely to pursue humanitarian devices (universities, research institutes, non-profit entities) must raise significant capital for an endeavor (product development) that is not traditionally part of their mission.

SUNDAY 20 OCTOBER, 13.30–17.00

CRITICAL TECHNICAL ISSUES

Co-Chaired by Steve Badylak and Rocky Tuan

1.1 Xenogeneic tissue sources ..... *Steve Badylak*
Discussion leader ..... *James Kirkpatrick*

1.2 Embryonic stem cells ..... *Alan Trounson*
Discussion leader ..... *Shi-Jiang Lu*

1.3 Induced pluripotent stem cells ..... *Yoshimi Yashiro*
Discussion leader ..... *Rocky Tuan*

1.4 Mesenchymal stem cells ..... *Arnold Caplan*
Discussion leader ..... *Lee Eng Hin*

1.5 Biomaterials specifications ..... *David Williams*
Discussion leader ..... *XingDong Zhang*

1.6 Bioreactors/Bioprinting: Bioreactors ..... *Ivan Martin*
Bioreactors/Bioprinting: 3D printing ..... *Scott Hollister*
Discussion leader ..... *David Kaplan*

1.7 Hydrogels: Injectable matrices ..... *Jeff Hubbell*
Hydrogels: Peptide hydrogels ..... *Sam Stupp*
Discussion leader ..... *Hsing-Wen Sung*

1.8 Growth factor specifications ..... *Yasuhiko Tabata*
Discussion leader ..... *Simon Cool*

1.9 Functional imaging ..... *Jeff Bulte*
Discussion leader ..... *Robert Guldberg*

CRITICAL TECHNICAL ISSUES

1.1 XENOGENEIC TISSUE SOURCES

Statement by Stephen Badylak

Biologic scaffold materials composed of mammalian extra-cellular matrix are prepared by decellularization of source tissues. These source tissues are typically xenogeneic (porcine or bovine) and include dermis, small intestine, urinary bladder and pericardium, among others. Such materials have been implanted in several million patients in the past decade, with virtually no safety problems. Efficacy for various surgical applications has ranged from excellent to poor, and the reasons for this variability are primarily a result of manufacturing processes. The effects of inadequate decellularization, chemical crosslinking, and the choice of terminal sterilization methods will be discussed, among other variables that affect the host response. The regulatory classification of xenogeneic extracellular matrices (ECM) scaffold materials as medical devices will be discussed. In addition, the barriers to clinical translation and methods for facilitating optimal clinical performance will also be discussed.

1.2 EMBRYONIC STEM CELLS

Statement by Alan Trounson

The stem cell field accelerated quickly when human embryonic stem cells (ESCs) were reported in 1998–2000. The ability to produce an immortal supply of pluripotent stem cells that could form any cell of the body provided the potential for cell therapy for an unlimited range of diseases,

injuries and degenerative and genetic disorders. The field advanced from a concentration on bone marrow stem cell (hematopoietic stem cells – HSCs) science and medicine to include many other adult and fetal cells to explore the potential of pluripotent ESCs. This led to the discovery that adult cells could be converted by transcription factor transduction into primitive induced pluripotent stem cells (iPSCs) with properties similar to ESCs. This is a powerful tool to study human disease. Further evolution has taken the field to direct transdifferentiation of cells *in vitro* and *in vivo*, to cell types of regenerative interest, potentially avoiding immune rejection of allogeneic transplanted cells. The field is actively exploring translation of these new stem cell discoveries into clinical medicine. A wide variety of developments may be expected that include destruction of cancer stem cells, possible cure of HIV-AIDS, reversal of type I diabetes, restoration of vision, repair of motor function in spinal cord injury and heart muscle regeneration.

1.3 INDUCED PLURIPOTENT STEM CELLS

Statement by Yoshimi Yashiro

Induced pluripotent stem cells, commonly abbreviated as iPS cells or iPSCs, are a type of pluripotent stem cell artificially derived from a non-pluripotent cell by inducing a 'forced' expression of specific genes. They were first produced in 2006 from mouse cells and in 2007 from human cells in a series of experiments by Shinya Yamanaka's team at Kyoto University, Japan, and by James Thomson's team at the University of Wisconsin-Madison. iPS cells are similar to natural pluripotent stem cells, such as embryonic stem (ES) cells in many aspects, such as the expression of certain stem cell genes and proteins, chromatin methylation patterns, doubling time, embryoid body formation, teratoma formation, viable chimera formation and potency and differentiability. In October 2012, Yamanaka and fellow stem cell researcher John Gurdon were awarded the Nobel Prize in Physiology or Medicine 'for the discovery that mature cells can be reprogramed to become pluripotent'.

In Japan, an important stage for medical applications of iPS cells has been reached. The first human clinical trial using autologous iPSCs has been approved by the Japanese Ministry of Health and will be conducted in 2014 in Kobe. iPSCs derived from skin cells from six patients suffering from wet age-related macular degeneration will be reprogramed to differentiate into retinal pigment epithelial (RPE) cells. The cell sheet will be transplanted into the affected retina, where the degenerated RPE tissue has been excised. Safety and vision restoration monitoring is expected to last one to three years. The benefits of using autologous iPSCs are that there is theoretically no risk of rejection and it eliminates the need to use embryonic stem cells. However, iPSC research is still in its infancy and a number of steps will be needed prior to their widespread use in humans, such as the development of standardized cell lines, proof of safe methods for generation, animal tests of preclinical safety and efficacy, and the development of government policies and regulations on the clinical use of iPSCs. Scientists around the world are working to achieve these goals as rapidly as possible.

1.4 MESENCHYMAL STEM CELLS

Statement by Arnold Caplan

Marrow-derived adult Mesenchymal stem cells (MSCs) can be isolated and culture expanded. Although these cells are capable of differentiating into lineages that result in the fabrication of bone, cartilage, muscle, marrow stroma, tendon/ligament, fat and other connective tissues, MSCs have recently been shown to be intrinsically therapeutic. Such culture-expanded adult MSCs are immuno-modulatory, especially in muting T-cells, and thus allogeneic MSCs have been used to mute or cure graft-versus-host disease and Crohn's disease and are now being tested in certain autoimmune diseases. Furthermore, these allogeneic MSCs set up a regenerative micro-environment that is anti-apoptotic, anti-scarring, mitotic for tissue-intrinsic progenitors and

angiogenic. These immuno and trophic activities result from the secretion of powerful bioactive molecules that, in combination, support localized regenerative events. The MSCs reside in every tissue of the body and function as perivascular cells (pericytes) until a focal injury occurs. At sites of injury, the pericyte is released and functions as a MSC that provides molecular assistance in activities leading to tissue regeneration. Such assistance involves many tasks, including the immuno-protection and trophic activities provided by the MSCs. Although it is proposed that all MSCs are pericytes and have common capacities, it is expected that MSCs from different tissue locations or anatomical sites of injury will not be equivalent. Thus, adipose-derived and marrow-derived MSCs naturally reside as pericytes and have different functional capacities. The fact that uncultured, freshly isolated autologous 'stromal vascular fraction' (SVF) from fat has been shown to be therapeutically effective in horses and dogs strongly argues that the MSCs in the SVF are a potent multi-drug and site-specific delivery vehicle. There are now over 350 clinical trials listed on the clinicaltrials.gov website and these have the potential of changing the way disease and tissue injury are medically approached. This full thesis, that adult MSCs are potent therapeutic agents, is the theme of this presentation.

1.5 BIOMATERIALS SPECIFICATIONS

Statement by David Williams

Tissue engineering involves the collective use of biomaterials and biological molecules to stimulate target cells into generating tissue, usually through a combination of molecular and mechanical signals. The specifications for the biomaterials used in these processes are critical but have rarely been analyzed from a mechanistic perspective. These specifications have to relate to a variety of biological, mechanical and chemical functionalities. It is mandatory that the biomaterial has appropriate elasticity, biocompatibility and degradation characteristics, and is presented to the cells with optimal morphology and architecture. Depending on the prevailing circumstances, the material may require features of self-assembly and injectability and should be compatible with imaging modalities. For obvious and understandably pragmatic reasons, the first-used tissue engineering scaffolds were based on classical degradable materials that had prior regulatory approval in systems such as implantable devices and drug delivery. However, it has become clear that this approach is far from ideal.

A critical point in the development of effective, functioning, tissue engineering scaffolds, or 'templates', as I prefer to call them, is the recognition that their principal specification is the need to replicate the cell niche. In order to stimulate cells, whatever their origin, to express extracellular matrix within the unusual, indeed unnatural, environment of a biomaterial template, that template should simulate as closely as possible the biochemical, biomechanical and morphological characteristics that those cells normally experience. This should also take into account the spatio-temporal variations of the niche. This fundamental specification favors a move away from synthetic polymers produced by top-down manufacturing processes such as solid free-form fabrication, and an increasing emphasis on extracellular matrix-based structures, biopolymers and peptide hydrogels, with obvious due attention being given to nanoscale architecture and self-assembly.

1.6 BIOREACTORS AND BIOPRINTING: BIOREACTORS

Statement by Ivan Martin

Despite the compelling clinical needs, the adoption of cell-based grafts for tissue and organ regeneration is yet limited, predominantly due to the challenges to demonstrate cost-effectiveness superior to conventional treatments. While, from a biology standpoint, it is necessary to increase understanding of mechanisms of action of engineered implants and to define associated potency markers, from an engineering perspective it is critical to enhance the robustness of their manufacturing process. Similar to other sectors of biotechnology (for example, generation of vaccines, antibodies or recombinant proteins), the use of bioreactor systems is expected to introduce monitoring, control and automation features, which are pivotal

to achieve standardization, scaling up and possibly cost-effectiveness. The industrialization of previously established bioreactor technology, however, is expected to require a re-validation of the resulting products, including new pre-clinical and clinical tests. The challenge is, thus, to adopt effective automation within bioreactors early in the development of a clinical program. This strategy requires a higher investment up front but also a streamlined pathway to clinical use and the opportunity to improve production processes according to principles of 'quality by design', as opposed to the development of robotic systems, which merely replicate the often ineffective manual procedures.

A critical point in the delivery to the clinic of engineered grafts is the presence of a living cell component, imposing constraints on their immune compatibility as well as on their storage and distribution. An increasing number of studies indicate that signals capable of instructing regeneration can be entrapped and presented within mechanically suitable extracellular matrices (ECM) and can be effective, even in the absence of living cells. This leads to the conceptual paradigm of engineering cell-based tissues and of decellularizing them prior to off-the-shelf storage and clinical use. Grafts can be generated using appropriate human cell lines without immuno-matching requirements, possibly transduced to overexpress specific factors, thus leading to the engineering of grafts with customized potencies, designed to leverage principles of morphogenesis beyond what can be achieved by decellularized native tissues. Techniques can be introduced to decellularize the grafts without affecting the biological activity and the mechanical properties of the ECM. As for living tissues, culture within bioreactors will allow not only efficient and uniform tissue growth, but also standardization, streamlining and industrialization in the manufacturing of cell-based but cell-free implants.

1.6 BIOREACTORS AND BIOPRINTING: 3D PRINTING

Statement by Scott Hollister

3D printing (also known as additive manufacturing, rapid prototyping, solid free-form fabrication) denotes a family of technologies in which three-dimensional (3D) structures are created by adding material on a layer-by-layer basis, as opposed to traditional subtractive manufacturing technologies. 3D printing includes stereolithography (laser polymerization), laser sintering, nozzle-based extrusion and nozzle-based spray binding technologies. The history of 3D printing in biomaterials/tissue engineering dates to the late 1990s and currently there are FDA-approved titanium devices and resorbable PCL cranioplasty devices (Osteopore; Tissue Regeneration Systems*) manufactured using 3D printing.

3D printing provides numerous scaffold fabrication advantages for tissue engineering and reconstructive surgery. Foremost among these include ready fabrication of complex geometry and the ability to generate custom devices from patient images. Successfully translating this custom capability will help spread regenerative medicine therapies into what have been niche and neglected healthcare markets (especially pediatrics) for traditional device manufacturing methods. In addition, 3D printing allows fabrication of heterogeneous and functionally graded solid to porous structures with highly controlled pore structures, the architecture of which has been shown to significantly influence tissue regeneration. Finally, numerous research groups are investigating 3D printing of cells in hydrogels as tissue engineered constructs, which can provide more rigorous control of cell interaction through controlled cell placement.

Despite its significant promise and over 15 years of research, however, numerous challenges remain for the use of 3D printing in regenerative medicine. On the research front, adapting biomaterials to the physics of 3D printing is a difficult task, and only a handful of biomaterials are printed routinely. Resolution remains a limiting factor as well, with routine feature sizes of 200–300 microns at best. Complete realization of 3D printing capabilities also requires integration with sophisticated, multi-scale computational design techniques. These challenges can be addressed by designing and fabricating modular hybrid scaffolds that combine 3D printed scaffolds with biomaterials and delivery vehicles fabricated using other processes. Finally, transitioning 3D-printed constructs to clinical use and regulatory approval remains the greatest challenge, as it does with all aspects of tissue engineering. 3D printing facilities must be embedded within current Good Manufacturing Practices (cGMP) and Quality System Frameworks, which requires monitoring

all aspects of the 3D printing process. Finally, 3D-printed constructs must be thoroughly tested in large pre-clinical animal models and in human clinical trials, for which there are currently but a handful of reports in the literature.

*Disclosure: The author is a co-founder of Tissue Regeneration Systems, Inc.

1.7 HYDROGELS: INJECTABLE MATRICES

Statement by Jeffrey Hubbell

Many applications in regenerative medicine and tissue engineering seek to guide cellular responses by external stimuli. The cells themselves may be endogenous, for example at the margins of a tissue lesion or infiltrating from healthy tissue origins, or they may be exogenous, having been transplanted for therapeutic purposes. To direct the behavior of these cells, biomedical scientists have turned to matrices that can be injected into such a tissue site, where the matrix can provide a milieu marked by its biomechanical characteristics, its immobilized biomolecular characteristics such as structural and adhesive features, and its diffusible biomolecular character, such as growth factors and chemokines. Features of such matrices thus include the following:

Biomechanical structure: Injectable materials require a means for conversion from liquid materials for injection into viscoelastic or elastic solids after injection, and this has been achieved through organic chemical reactions, enzymatic reactions, and (bio)physical self-assembly. Material elastic moduli in the range of a few kPa to tens of kPa have been achieved and have been demonstrated to be useful. Such materials have been engineered to resorb passively, for example by dissociation or hydrolysis, or actively, for example in response to cell-associated proteases.

Structural and adhesion molecules: To provide an appropriate biomolecular niche within the injectable matrices, both adhesion proteins and peptides derived from adhesion proteins have been incorporated into the biomechanical structures described above. Engineering of recombinant adhesion proteins has opened doors to tailoring functionality of such materials.

Growth factors: To further adapt the biomolecular niche inside matrices, growth factors, other cytokines and chemokines have been engineered for incorporation. This has been accomplished through incorporation of affinity ligands or by direct incorporation of the bioactive biomolecules into injectable matrices. Such biomolecules have been explored to recruit stem cells to sites of injection, to support cell survival, to direct cell differentiation and to modulate immunity.

1.7 HYDROGELS: PEPTIDE HYDROGELS

Statement by Samuel Stupp

Biomaterials were first used to rebuild tissues as biodegradable non-bioactive polymer scaffolds that could host an expanded population of the patient's own cells. The function of biomaterials in this tissue engineering approach is mostly to localize the cells in a specific three-dimensional shape of specific size. Regenerative medicine at the present time is a much broader platform, aiming to find strategies to re-assemble 'any' missing or dysfunctional organ or tissue in the human body, ranging from the brain and the heart to bone and teeth. The suite of biomaterials required to achieve this broad objective will need to include 'bioactive' biomaterials that structurally mimic the extracellular matrices of specific tissues.

Among biomolecular structures, peptides offer the most versatile chemistry to develop bioactive biomaterials for regenerative medicine. The primary reason is the fact that they are the basic signaling language of biology and, therefore, peptide-based materials can directly communicate with cells via membrane receptors. Secondly, the synthetic chemistry of peptides is well developed, relative to that of other biomolecules that also participate in signaling, such as

polysaccharides. The relatively simple solid phase synthetic techniques for peptides and advanced hardware for both purification and molecular characterization definitely offers potential scalability for bioactive materials. Biomaterials incorporating peptides were first proposed by covalently incorporating them in conventional polymers. A common form of these biomaterials has been 'hydrogels' based on cross-linked structures. A new class of bioactive biomaterials developed more recently utilizes the rich supramolecular chemistry of peptides that leads to protein folding. These biomaterials not only offer the possibility of signaling cells but also introduce a great deal of tunable structural order across scales from nanometers to macroscopic dimensions. The importance of this structural order is the possibility of mimicking in these biomaterials the features of the natural extracellular matrix, and also to use the peptides themselves to control mechanical behavior that is also a part of bioactivity. The building blocks of these biomaterials are not polymers but relatively small water-soluble peptides that interact to form supramolecular polymers that emulate extracellular fibrils. Examples are known in which small peptides can create, by self-assembly, hydrogels with macroscopic alignment of fibrils mimicking the matrix of brain, heart and spinal cord tissue. The ordered fibrillar structures can form hydrogels at suitable concentrations, or can be injected as bioactive nanostructures in tissues or in the bloodstream. These 'supramolecular materials' have revealed unprecedented bioactivity in many tissues and are presently at the pre-clinical stage. In scientific terms they are a 'supramolecular' rather than a 'molecular' therapy and therefore require development work to create pathways to reproducible structures and bioactivity. Translation to clinical applications also requires significant investment to meet the requirements of regulatory agencies, given their bioactive nature.

1.8 GROWTH FACTOR SPECIFICATIONS

Statement by Yasuhiko Tabata

Regenerative medicine is a new therapeutic trial, based on the natural self-healing potential of the body itself to induce tissue regeneration and repair. The natural potential is based on the inherent activity of cells for their proliferation and differentiation. The idea of tissue engineering is to artificially create a local environment with biomaterials for cells to enhance their regeneration activity. Growth factor is one of the biological substances to enhance the cell proliferation and differentiation. Many growth factors with an ability to enhance the cell-based tissue regeneration have been found and the biological activities have been scientifically elucidated. Thus, it is of practical importance and necessity to develop a biomaterial technology that enhances the *in vivo* activity of growth factor for cell-based tissue regeneration. If a key growth factor is supplied to cells at the right place, time period and concentration, there is no doubt that the body's system will initiate a physiological response, resulting in the natural induction of cell-based tissue regeneration. However, one cannot always say that the growth factor is used to enhance the cell activity for tissue regeneration as efficiently as possible.

A critical point in the biomaterial technology for growth factors is the research and development of drug delivery systems (DDS), which is one practical and possible way to enhance the *in vivo* therapeutic efficacy of growth factor with *in vivo* short half-life period. Considering that the final goal of growth-factor-based tissue engineering is to treat patients clinically, it is preferable to use the biomaterials, which can be used clinically and FDA approved. In addition, the growth factor used should also be clinically applicable. For example, even if the growth factor is highly bioactive, it may not have been used clinically. In this case, it is difficult to apply the growth factor itself to the therapy of regenerative medicine, although the scientific paper can be published. As one trial to tackle the issue, research and development is critical, to discover the drugs that can act on cells to allow them to secrete the necessary growth factor. Another issue is that there may not exist any cells around the site to be regenerated. In this case, it is indispensable to enhance the recruitment of key cells to the site, followed by the subsequent supply of growth factor to cells recruited for the enhancement of their tissue regeneration activity. The DDS technology of cell recruitment factors needs to be developed for cell-based tissue regeneration. In addition, to promote the therapeutic efficacy of cell transplantation, active combination of the DDS technology of growth and cell recruitment factors with cells and/or the cell scaffold is necessary to give the cells a better local environment to promote their tissue regeneration activity.

1.9 FUNCTIONAL IMAGING

Statement by Jeff Bulte

I expect functional imaging to play a key role in evaluating the outcome of clinical trials involving regenerative medicine, be it cells, scaffolds, artificial organs, or all of these combined. In order to facilitate and implement the translation of novel regenerative therapies into the clinic, one needs to be able to monitor the cellular biodistribution and scaffold implantation, biodegradation and tissue therapeutic outcome parameters non-invasively and preferably in a quantitative manner.

Cellular magnetic resonance imaging (MRI), with its superior spatial resolution and excellent soft-tissue anatomical detail, is emerging as the technique of choice to monitor, in real time, image-guided cell delivery, immediate engraftment, and short-term homing. It can now be used to interrogate the composition and disintegration of hydrogel scaffolds, using chemical exchange saturation transfer (CEST) MRI, and is uniquely suited to look at tissue repair, for instance cardiac function, brain myelination, or muscle metabolism. Up until now, eight clinical MRI cell tracking studies have been published; all using superparamagnetic iron oxide nanoparticles (SPIONs) in an off-label fashion. SPIONs have been clinically approved, and they create strong local magnetic field disturbances that spoil the MRI signal leading to hypointense contrast. A major setback is that the clinical formulations have been taken off the market, due to economic reasons for other applications (liver imaging). New MRI methods are emerging, including CEST imaging that is able to report on the viability of cells when they are embedded within hydrogels containing pH-sensitive liposomes. It is also exciting that ‘hot spot’ 19F MR imaging has now entered the clinic in the spring of 2013 as an alternative to conventional 1HMRI. However, the ‘holy grail’ for functional cellular imaging is the development of a robust MRI reporter gene, and many efforts are being directed towards creating an MRI equivalent of green fluorescent protein (GFP).

MONDAY 21 OCTOBER, 8.00–13.00

CRITICAL CLINICAL ISSUES

Co-chaired by Wei Liu and Peter Zilla

2.1 Cell therapies ..... *Marian Sturm*
Discussion leader ..... *Alicia El Haj*

2.2 Gene therapies and transfer ..... *Kazunori Kataoka*
Gene therapies ..... *Bumsup Lee*
Discussion leader ..... *Yasuhiko Tabata*

2.3 Regenerative medicine clinical trials ..... *Teruo Okano*
Discussion leader ..... *Antonello Pileggi*

2.4 Clinical target: Brain ..... Molly Shoichet
Discussion leader ..... *Yoshimi Yashiro*

2.5 Clinical target: Heart ..... *Simon Hoerstrup / Peter Zilla*
Discussion leader ..... *Peter Zilla*

2.6 Clinical target: Spinal cord injury ..... *Xiaoguang Li*
Discussion leader ..... *Jianwu Dai*

2.7 Clinical target: Peripheral nerve ..... *Xiaosong Gu*
Discussion leader ..... *Luke Burnett*

2.8 Clinical target: Muscle/tendon ..... *Wei Liu*
Discussion leader ..... *Arnold Caplan*

2.9 Clinical target: Skeletal system: Bone ..... *Ranieri Cancedda*
Clinical target: Skeletal system: Functional regeneration ..... *Rocky Tuan*
Discussion leaders ..... *Alicia El Haj, Shibi Lu and Norimasa Nakamura*

2.10 Clinical target: Sensory organs ..... *Shi-Jiang Lu*
Discussion leader ..... *Molly Shoichet*

2.11 Clinical target: Tubular organs ..... *Paolo Macchiarini*
Discussion leader ..... *Alan Russell*

2.12 Clinical target: Pancreas and diabetes ..... *Antonello Pileggi*
Discussion leader ..... *Peter Johnson*

2.13 Clinical target: Liver and kidney ..... *Guiseppe Orlando*
Discussion leader ..... *Masayuki Yamato*

2.14 Clinical target: Skin ..... *Yan Jin*
Discussion leader ..... *Gail Naughton*

CRITICAL CLINICAL ISSUES

2.1 CELL THERAPIES

Statement by Marian Sturm

Cell therapies encapsulate a range of products for diverse medical conditions. Many have been in use for a considerable length of time. Autologous products for tissue repair, such as keratinocytes or chondrocytes, are widely used and may be manufactured in-house or produced by commercial manufacturers. The most extensive experience, however, is with haemopoietic stem cells, which have been collected and used in the restoration of bone marrow function for more than two decades. There is a high degree of harmonization internationally, since haemopoietic products are freely exchanged, either through worldwide donor registries or from cord blood banks. There are established testing platforms and internationally based quality programs that inform product safety and integrity. As the sector hurtles towards more advanced cell therapies that may be manufactured or traded internationally, the practices and experience of the global haemopoietic sector may assist in progression. Also, universal systems already in place, such as the international labeling standard for bar coding and tracking (ISBT 128), should be adopted by all manufacturers.

There are universal issues facing developers and manufacturers of cellular therapies. Apart from the implementation of technology to increase production rates, the availability and suitability of manufacturing components, including source cells, and the characterization of cell products are crucial to product integrity. Standardization of assays for the determination of viable cell dose would be of benefit in comparing dosing studies. The development and acceptance of

suitable potency assays is essential to ensure function. The detection of ancillary manufacturing materials remaining in the products and that may be potentially antigenic is also critical. If the dose and quality of products is not equivalent, then any variation between products may reflect on safety and efficacy. Conflicting clinical data from products of varying efficacy hinders the translation of the emerging therapies into mainstream clinical application. International harmonization of testing platforms and the development of quality assurance programs to ensure testing competency of characterization assays and for the detection of ancillary materials used in manufacturing would assist both manufacturers and regulators.

2.2 GENE THERAPIES AND TRANSFER

Statement by Kazunori Kataoka

In the biological system, there are many supramolecular structures (nanostructures) with sizes of several tens of nanometer (nm), as represented by ribosomes, which are formed by the precise self-organization of biopolymers and play a role in the important vital function through the dynamic structure change depending on the environment. It is also known that these structures include particulate nanostructures, which will not stay at a specific location, but move freely within a living body, while being involved in the 'fit for purpose' substance transport or transmission of chemical information. Virus is a typical example of such supramolecular structures created by 'mother nature'. Although there are numerous types of viruses, they always form a sophisticated nanostructure in which the DNAs or RNAs forming a compact structure are regularly coated by a protein shell called the capsid and, in some cases, by the membrane structure called the envelope, mainly consisting of lipid bimolecular membranes located on the surface top-layer. This structure is not static but changes dynamically according to the external environment, which is a characteristic useful for achieving the targeting to host cells. In particular, it has a function to properly sense the environmental changes within the host cells, a processing function expressed as subsequent structural changes, and an operation function for the expression of genetic information in a specified position within the cells. This means that the structure is truly worthy to be called the dynamic nanoparticles with the 'smart function'. Viruses are foreign particles that ingeniously enter the living body from the external environment; that is, they are 'uninvited guests' to the host cells. Recently, the fact that the cells constituting the living body may produce nanoparticles by themselves to be used for transmission of chemical information between cells is drawing attention. These nanoparticles are membrane vesicles with a diameter of several tens of nm, called exosomes, which are formed by the secretion of a part of cell membranes. They contain micro RNAs and messenger RNAs, and it is considered that such components are transported from cell to cell to regulate the bodily function.

When changing the viewpoint according to the clarification of the structure and function of nanoparticles in nature, significant progress has been made in the synthesis and functional analysis of supramolecular nanostructures, in which the essence of natural nanoparticles is incorporated. To sum up their characteristics in a few words, three basic functions (sensing, processing and operation) have been incorporated into the extremely small interior of nanoparticles in a sophisticated manner similar to that of viruses, meaning that the device integration has already been completed. In that sense, these nanoparticles can be said to be sophisticated nano-devices that act within the living body. I have no intention of competing with the evolutionary process of viruses or exosomes, but I hope that, after these nano-devices have been delivered into the micro-cosmos of the living body and have been developed by overcoming many problems, they do not only perform the diagnosis and treatment by delivering therapeutic agents or genes to the target site, but they also create an opportunity to clarify the mysteries of living organisms that have not been discovered by traditional science through the exploration of nano-environments within the living body.

2.2 GENE THERAPIES

Statement by Bumsup Lee

Osteoarthritis (OA) is the most common type of joint disease, affecting more than 20 million individuals in the United States alone. There are currently no treatment options available for OA that prevent or reverse disease progression. OA treatment strategies are generally targeted toward alleviating the painful symptoms and improving patients' function and quality of life. If these treatment options fail, microfracture or cell therapies and total joint replacement surgery are considered.

OA and cartilage defects are used interchangeably, thus not being defined precisely for conducting clinical trials and getting labels for approval. In recent years, a few tissue engineered products have been approved for treating both OA and cartilage defects, which indicates the need to clarify the disease indications and drug labels. The fact that cartilage regeneration itself is not capable of saving patients from pain suggests that factors other than cartilage regeneration are required for improvement in OA conditions; for example, improvement in inflammation and bone edema. The chondrocyte differentiation can be achieved with different growth factors, hormones or cytokines, including TGF-ß1, IGF-1, dexamethasone, and the family of BMPs and FGF. Limitations of current OA therapies might be overcome by the adaptation of cell-based gene therapy. *Ex vivo* or *in vivo* gene transfer method can be used to deliver the genes' encoding growth factors, hormones or cytokines essential for cartilage extracellular matrices (ECM) formation, pain and inflammation control.

Arthritis gene therapy has been discussed for nearly 20 years, and a large body of impressive pre-clinical safety and efficacy data has been generated. However, there have been few clinical trials of this therapeutic strategy. Gene therapy could use mesenchymal stem cells (MSCs) from various sources and preliminary data suggest that genetically modified fat and muscle grafts might also be effective. The *ex vivo* transfer of genetically modified, established cell line of chondrocytes that overexpress TGF-ß1 has been initiated in a Phase 3 clinical trial in Korea. Since the cell therapies anticipate a long-term pain alleviation and cartilage regeneration, a question has arisen whether the regeneration of hyaline cartilage is a must and whether the minimal duration of its efficacy is critical for its approval. I would like to discuss how innovative cell therapies utilize proper tools for assessing clinical outcomes; and duration is properly balanced with safety measurements.

2.3 REGENERATIVE MEDICINE CLINICAL TRIALS

Statement by Teruo Okano

Our research has been focused on constructing a novel co-culture, consisting of layered tissue structure. For our goal, we first developed unique tissue culture dishes that equipped their inner-bottom surface coated with the temperature-responsive polymer poly (*N*-isopropylacrylamide) (PIPAAm). The 'intelligent surface' of these dishes possessed the hydrophobicity similar to regular tissue culture polystyrene dishes at 37°C. However, the surface reversibly became hydrophilic at a lower temperature and spontaneously released the cultured cells as a single layer without the need for trypsin or EDTA, thus leaving the cell layer with extracellular matrix (ECM) intact. All the cultured confluent cells were harvested as a single contiguous cell sheet from the temperature-responsive culture dishes and readily applied to other biological and non-biological surfaces, thanks to the ECM. Here, we propose this novel system of cells and cell-layers arrangement be called 'cell sheet engineering'.

Using these cultured cell sheets harvested from the temperature-responsive surfaces, we have established 'cell sheet engineering' to create functional tissue sheets to treat a wide range of diseases, from corneal dysfunction to esophageal cancer and cardiac failure. For example, to overcome the limits of conventional treatments for corneal surface dysfunction, oral mucosal cells expanded *ex vivo* have been used as an alternative approach. While previous studies used various carrier substrates, our method allowed us to create carrier-free oral mucosal cell sheets that can be transplanted on the sites without sutures. The results from clinical trials demonstrate successful transplantation with the recovery of lost visual functions in all cases.

2.4 CLINICAL TARGET: BRAIN

Statement by Molly Shoichet

The brain is the control panel for our bodies – responsible for cognition, movement, senses and emotions. Brain disorders include neurodegenerative diseases, neurodevelopmental diseases, psychiatric disorders and traumatic injuries. The complexity of the brain is further complicated by the blood-brain barrier (BBB), which limits the diffusion of therapeutics (drugs or biologics or cells) across vasculature in the brain. This results in high systemic doses to achieve only low amounts in the brain, often too low for therapeutic benefit with the consequence of significant off-target, systemic effects. Thus traditional delivery strategies of oral, intravenous or even intramuscular therapeutics are not ideal to target the brain.

Several strategies are being pursued to overcome the BBB. These include strategies that temporarily disrupt it, such as localized ultrasound, local administration of concentrated sugar solutions, molecular chaperones (such as TAT-peptides) or polymeric chaperones (such as polyethylene glycol) that can cross the endothelial cell barrier. Other strategies are more invasive and include pump/catheter systems, which deliver therapeutics into the intrathecal cavity in the lumbar space (for example in the treatment of chronic pain) or even have cannula inserted into the ventricles of the brain.

Biomaterials are being investigated for delivery to the brain, with the goal of achieving local controlled release, with a minimally invasive, minimally swelling, biodegradable, cytocompatible system. Epidural injection meets many of these criteria; however, the dura provides a formidable barrier to many therapeutics. Subdural (or intrathecal) injection overcomes the barrier of the dura, yet is more invasive. With care not to disrupt the spinal cord, intrathecal injection is a great alternative, providing direct access to central nervous system (CNS) tissue and circumventing the BBB. Biomaterials in which therapeutics are incorporated enable local, sustained release to the CNS. For the brain, epicortical (subdural) strategies are also being pursued, with the criteria for the biomaterial strategy being largely the same. Less invasive strategies are also being pursued, such as intravenous injection of polymeric nanoparticle micelles for targeted delivery to cancers in the brain. These strategies are also being pursued for other brain disorders, such as stroke, where the vasculature in the brain is at least temporarily disrupted. In addition to the criteria outlined, CNS tissue is variable and soft, thus requiring the biomaterial applied directly to it to be similarly soft, with a low modulus.

2.7 CLINICAL TARGET: PERIPHERAL NERVE

Statement by Xiaosong Gu

Peripheral nerve regeneration essentially involves the regrowth and remyelination of damaged, demyelinated axons as well as the resulting target reinnervation by regenerating axons. And the key of neural tissue engineering strategy for peripheral nerve repair lies in the establishment of a favorable microenvironment for nerve regeneration within a tissue engineered nerve graft (TENG), which comprises, generally speaking, a scaffold and support cells/growth factors. Nowadays, however, TENGs used in the clinic are limited to those composed of a scaffold alone. Briefly, they are categorized into four types: polyglycolic acid (PGA); collagen-based nerve guidance conduits (NGCs); chitosan/PGA; and, acellular tissue-based scaffolds.

The biomaterial-based scaffolds should have suitable mechanical properties, a controllable biodegradation capability and a sufficient porosity for mass transport and blood vessel growth. A scaffold is usually processed into the structure consisting of a hollow lumen NGC and a plurality of intraluminal filaments; and the filaments serve as a directional guide to keep Schwann cells functioning properly and facilitate the accurate pathfinding of axons leading to target reinnervation. Recent case studies reported that chitosan/PGA-based scaffolds – consisting of a chitosan NGC and PGA intraluminal filaments – were used to bridge 35 mm and 30mm long human median nerve gaps, respectively, achieving the desired outcomes. For the clinical use of TENGs, their inflammatory, mutagenic, and carcinogenic potential must be evaluated as they

are the basic standards of biocompatibility during the long period of follow up. For example, the long-term safety of chitosan/PGA-based scaffolds has been validated by our three-year clinical trials and, further, by an experimental study, in which a TENG containing chitosan/PGA-based, mesenchymal stem cells was used to bridge a 50 mm long median nerve gap in monkeys, while blood tests and histopathological examinations were carried out over a one-year period.

An international collaboration among neuroscientists, surgeons, industrialists, and administration officials may accelerate the advancement of neural tissue engineering and motivate the translation of TENGs to the clinic. Their collaborative efforts will be directed at: 1) the generation of ideal scaffolds based on novel advanced biomaterials and capable of closely mimicking the microenvironments in native nerves; 2) the incorporation of support cells, growth factors, and/or extracellular matrices within TENGs for implantation to the human body; 3) the auxiliary use of microelectronic chips to reduce the target muscle atrophy and enhance the regeneration efficacy.

2.8 CLINICAL TARGET: MUSCLE/TENDON

Statement by Wei Liu

Skeletal muscles and tendons are important parts of the musculoskeletal system that support daily activities of human beings. Meanwhile, injury or disease-led dysfunctions of these tissues are also quite common in clinics, and are becoming a major challenge in orthopedic surgery and plastic reconstructive surgery. The substantial and quick development of tissue engineering and regenerative medicine provides an appropriate and practical approach to addressing these clinical concerns. Muscle can be divided into skeletal muscle, smooth muscle and heart muscle; and the latter two will be addressed in other sections. Compared to other tissues, skeletal muscle regeneration remains relatively behind due to its highly vascularized and complicated structure. Even so, decelluarized extracellular matrix has already been employed for muscle regeneration with initial success in clinical treatment of injured soldiers. In the future, decelluarized muscle and cell sheeting technology might also be employed for its clinical therapy, given that both have already been used for other types of muscle regeneration.

In contrast, tendon is an avascular tissue that connects muscle and bone. Similar tissue also includes avascular ligament that connects bone and bone within a joint. The feasibility of tendon/ligament engineering has been proved in small animal study and pre-clinical study in large animals. In this area, different approaches are used, including the traditional strategy of employing cells and scaffolds. The seed cells include tenocytes, dermal fibroblasts and bone marrow-derived stem cells. The scaffolds used include degradable polymer such as polyglycolic acid (PGA) or polylactic-co-glycolic acid (PLGA), silk-based materials and decelluarized extracellular matrix. Decelluarized tendon/ligament might also be a potential strategy. Another approach is to engineer tendon/ligament tissue graft *in vitro* in a bioreactor with proper mechanical loading. This is likely to switch the traditional *in vivo* approach to a typical tissue transplantation approach with available engineered grafts. In the near future, clinical application of engineered tendon/ligament will become a reality.

The critical points in the future development of muscle/tendon regeneration should include: 1) development of ECM-based scaffold materials; 2) enhancing the efficacy of decellular-based regeneration, including enhanced cell penetration and use of growth factors; 3) development of an allogeneic approach; 4) application of stem cell therapy to muscle/tendon regeneration.

2.9 CLINICAL TARGET: SKELETAL SYSTEM: BONE

Statement by Ranieri Cancedda

Repair of critical-size bone defects caused by disease, malformation, trauma or tumor resection remains a major task to achieve successfully. Beginning in the last two decades of the past century, major progress has been made with regard to the fabrication of implantable construct based on a porous ceramic scaffold seeded with autologous (from the same patient) stem/progenitor cells. The implant of this type of construct in human patients was reported in scientific literature for the first time in 2001. Since then, other patients have been implanted by different surgeons in different part of the world. Nevertheless, this therapeutic approach never really took off and, to date, the number of treated patients is limited. There are still some scientific aspects, such as vascularization of large-size implants and identification of the 'optimal' resorbable scaffold that need further investigation. Likewise, significant bottlenecks in the tissue engineering approach are: 1) the difficult logistics of collecting from patients, expanding the culture and returning the cells to the surgical theater; and, 2) the high cost of the culture procedure within the current Good Manufacturing Practices (cGMP) facilities required by the strict rules defined by national and european regulatory agencies.

Therefore, it appears that a tissue engineering approach should be considered only in extreme critical situations and that new strategies should be developed to enable a large number of patients to benefit. Thanks to the rapidly developing knowledge about pathways being activated during bone organogenesis in the embryo and the natural bone-healing process, a novel therapeutic strategy based on the activation of the endogenous regenerative capacity of the tissue itself is presently being investigated by different research groups.

2.9 CLINICAL TARGET: SKELETAL SYSTEM: FUNCTIONAL REGENERATION

Statement by Rocky Tuan

Skeletal biomedicine has long been considered an area ripe for advancements in tissue engineering and regenerative medicine. Because of the spatial, structural and load-bearing properties of the musculoskeletal system, there are unique challenges associated with the repair and regeneration of functional skeletal tissues. In addition to the canonical components of cells, scaffold, and biofactors, a formal requirement is the establishment and maintenance of unique extracellular matrices that act to bear and transmit load, to house cells and maintain their phenotype and metabolic homeostasis, and to serve as depots for biological signals. In addition, the load-bearing characteristics dictate that the repaired or regenerated tissues must rapidly integrate and adapt *in vivo*, in order to minimize or prevent physical compromises that will irreversibly disrupt the nascent tissues and their surrounding host counterpart.

The following specifications are critical for functional skeletal tissue engineering and regeneration:

1. Progenitor cells that are highly and specifically responsive to inductive programming to become biosynthetically active skeletal cells, for example, chondrocytes, osteoblasts, tenocytes and others;

2. Biomimetic matrices that are bioactive – with epitopes and motifs for cell recognition, anchorage and migration – and able to conform to the mechanical properties and macro- and micro-architecture and environment of the target tissue;

3. Agents that will act as or deliver biological signals within the regenerated tissue in a spatially defined and controllable manner to induce and/or maintain the functional, three-dimensional topography of the tissue; and

4. Development of valid, clinically relevant *in vivo* or *in vitro* microtissue models for skeletal injuries and diseases that will allow critical and functional testing.

2.10 CLINICAL TARGET: SENSORY ORGANS

Statement by Shi-Jiang Lu

There are approximately 15% of adults worldwide experiencing some degree of hearing loss, mainly due to the loss or damage of auditory neurons, especially sensory hair cells within the cochlea. Although cochlear implant has been revolutionary in the treatment of deafness, major problems still exist. With the advancement of both embryonic stem (ES) cells and induced pluripotent stem (iPS) cells in the past decade, attempts to replace auditory neurons with cells derived from both ES and iPS cells have been investigated in animal models. However, there are a number of obstacles to the successful treatment for hearing loss using auditory neurons/hair cells derived from ES/iPS cells: 1) efficient differentiation of ES/iPS cells into pure appropriate phenotype *in vitro*; 2) precise delivery of cells into their target site in the cochlea; 3) transplanted cells reaching the whole cochlear scale, especially along a wide frequency range, with integration into the damaged organ and ability to form functional and tonotopic central connections; 4) survival of engrafted cells in an environment with high K+ (150 mM) and the differentiation into correct hair cell type, with correct hair bundle orientation after transplantation; 5) graft-versus-host disease and potential tumor formation of transplanted cells. So far, no clinical trial has been registered using ES/iPS cell-derived auditory neurons for the treatment of deafness.

The human eye consists of three transparent structures: the outermost layer, the cornea and sclera; the middle layer, the choroid, ciliary body and iris; and the innermost, the retina. Corneal diseases and injuries affect the vision of over 300 million people worldwide and transplantations of limbal epithelial and corneal endothelial cells are two options for the most severe corneal diseases. Several groups have reported the generation of limbal epithelial and corneal endothelial-like cells from both ES and iPS cells, but no human clinical trial using these cells has been reported. Macular degeneration – including age-related macular degeneration (AMD) and Stargardt disease (SMA) – retinitis pigmentosa and glaucoma are three diseases associated with retinal malfunction, which represent the major cause for blindness and affect more than 100 million people worldwide. Cell therapy for retinal diseases has been extensively investigated and retinal pigmented epithelial cells derived from human ES cells have been approved by both regulatory authorities of USA and UK for clinical trials for the treatment of AMD and SMD. I will present the opportunities for and challenges to using stem cells for the treatment of ear and eye diseases, and hope the delegates will reach a consensus.

2.12 CLINICAL TARGET: PANCREAS AND DIABETES

Statement by Antonello Pileggi

Restoration of tight metabolic control is a highly desirable goal in the treatment of individuals with diabetes, to help prevent or delay the progression of dreadful and debilitating complications. Transplantation of islets and vascularized pancreas or isolated islet cell clusters obtained from deceased donor can help attain the desirable physiologic metabolic control.

Current challenges to the widespread application of beta-cell replacement therapies remain, with limited availability of transplantable organs/cells and the need for life-long immuno-suppression (to counteract immune rejection and auto-immunity).

Over the last 25 years, steady progress has been recorded with human islet isolation and transplantation protocols and clinical outcomes. The costs associated with the development of dedicated infrastructures for the manufacturing of islet cell products following cGMP guidelines in compliance with regulatory standards (islet transplantation is classified as 'Investigational New Drug') has been a limiting factor. Recognizing the beneficial effects on metabolic control of patients with brittle diabetes, countries have given their approval of allogeneic islet cell

product transplantation as reimbursable procedure (Australia, Canada, France, Italy, Switzerland, United Kingdom, Sweden and the Nordic Network); in the USA, however, only autologous islet transplantation is currently reimbursed, while completion of registration trials by the Clinical Islet Transplant consortium (CIT-06 and CIT-07) will lead shortly to biological licensure by the US Food and Drug Administration. This is an important step, as islet transplant activity in the USA has been severely restricted by limited access to research funds, with the exception of a joint Medicaid/ Medicare initiative that is currently supporting the islet-after-kidney trial (CIT-06). The experience with deceased donor islet transplantation is paving the way to the development of a therapeutic platform for the restoration of beta cell function that could be extended to unlimited sources of insulin-producing cells in the future (that is, xenogeneic cells, stem cell-derived), which should be safe and allow for the achievement of physiological metabolic regulation.

We are currently experiencing an exciting stage of innovation and renewed promise for cellular-based therapies to restore beta-cell function. Novel extra-hepatic transplant sites, combinatorial use of physical, chemical, biologic agents, as well as adjuvant cells and tissue engineering approaches are being explored, which may allow for improved engraftment and sustained function with cadaveric human, xenogeneic or stem-cell derived islet cells in the future.

2.13 CLINICAL TARGET: LIVER AND KIDNEY

Statement by Giuseppe Orlando

The kidney and the liver are complex modular organs (CMO). CMOs are organs consisting of multiple functioning units – the modules, namely the nephron for the kidney and the hepatic lobule for the liver – that are assembled together to eventually constitute the functioning whole. They differ from the more simple hollow organs such as vessels, segments of the upper airways, or the lower urinary tract, in four essential aspects. Firstly, the cellular compartment of CMOs consists of several types of cells (more than 20) each of which must reside in a specific niche within the 3D architecture of the organ framework; differently than in hollow organs, these cells are not distributed merely in layers. Secondly, from a bioengineering perspective, their viability requires the reconstruction of the vascular pedicle that needs to be connected to the recipient's vascular network in order to eventually exert their expected function. Thirdly, CMOs are vital organs. Fourthly, their immense anatomical and functional complexity enables them to perform complex physiological tasks, in contrast to simple mechanostructural duties. For example, the liver consists of two distinct cellular systems of equal importance and sophistication (that is, the hepatocellular and biliary systems). Similarly, the kidney is the playmaker in multiple functions, including the excretion of wastes and the regulation of electrolytes, acid-base homeostasis, osmolality, and blood pressure. Moreover, through the production and secretion of essential hormones, the kidney participates in calcium metabolism and red blood cell homeostasis.

Investigations in the field of kidney and liver bioengineering and regeneration are still in their infancy, but preliminary data are promising. Obstacles in the way of progress in transplantable kidney and liver bioengineering and regeneration include a faulty understanding of the mechanisms underlying organ development and tissue regeneration and repair, inadequacy of currently available bioreactors and methods for revascularization and neoangiogenesis, and an insufficient understanding of the interactions between extracellular matrix and cells. Despite the implantation of over 160 artificial organs so far, an international registry has yet to be established. Previous experiences with abdominal and thoracic organs, along with composite tissue allotransplantation demonstrate that registries are vital to the success of a specific new therapy as they allow strict monitoring and inspection of bioengineered implanted organs, follow-ups, and potential complications. Thus, investigators in the field of kidney and liver bioengineering and regeneration should recognize their natural counterparts in transplantation, in order to facilitate the exchange of information and the understanding of true clinical needs. This will eventually guide research toward the broader goal of better outcomes for patients.

2.14 CLINICAL TARGET: SKIN

Statement by Yan Jin

The developments in cell biology, molecular biology and material science have been propelling biomimic tissue engineered skin to become more sophisticated in the science and more simplified in practice. In order to mimic the treatment process of autologous skin transplantation, sophisticated anatomical structure, such as bilayered structure, capillary network, hair follicle, sensory innervations and subcutaneous adipose tissue were prepared for promoting wound repair. According to traditional views, the closeness to native skin structure will allow the treatment using skin equivalents to be much better. Thus, several powerful seed cells, such as fibroblast, epithelium, endothelium, glia cells and many types of stem cells have already found their applications in wound skin repair and forming anatomical and appendage structures. In allogenic skin transplantations, however, clinical observation showed anatomical structure does not have any positive therapeutic effect on wound regeneration, because they degrade and are replaced by host skin in one or two months. The treatment effect of allogenic skin depends on its regenerative characteristics, including dermal ECM proteins and abundant growth factors.

Numerous studies have proven that several tissue engineered skins contribute to wound regeneration, and the effects were achieved mainly by paracrine growth factors and biomaterials scaffold. In the case of allogenic skin transplantation, the skin equivalent was also degraded and replaced completely by the host skin in the long term. Accordingly, these studies show that the sophisticated structure of tissue engineered skin may not be effective in the treatment of wounds. Additionally, until now, evidence that appendages formed *in vitro* directly participate in skin regeneration has not been observed. Whether regenerative microenvironment or anatomical structure is more important to tissue engineered skin construction should be further investigated. Therefore, understanding the cellular and molecular varying regulation in a systematic view during the role of anatomical structures and regenerative microenvironment in wound repair may be a way for preparing more reasonable and effective tissue engineered skin.

MONDAY 21 OCTOBER, 13.45–18.45

CRITICAL SOCIO-POLITICAL-ECONOMIC-INDUSTRIAL-REGULATORY ISSUES

Co-chaired by Alan Russell and Alan Trounson

3.1 Challenges for bioethics ..... *Kris Dierickx*
Discussion leader ..... *Lee Eng Hin*

3.2 Stem cell commercialization ..... *Shi-Jiang Lu*
Discussion leader ..... *Yilin Cao*

3.3 The developing world ..... *Peter Zilla*
Discussion leader ..... *David Kaplan*

3.4 Strategic communications ..... *John Russell*
Discussion leader ..... *Stuart Spencer*

3.5 Pre-clinical testing ..... *An Liu*
Discussion leader ..... *David Williams*

3.6 Regulatory principles (note – these statements are not necessarily formal agency positions but reflect currents practices and experiences)
Situation in the USA ..... *Karl Nobert*
Situation in Australia ..... *Marian Sturm*
Situation in Japan ..... *Yoji Sato, Kazuhiro Takekita*
Situation in China ..... *Baoting Wang, Chunren Wang*
Situation in Singapore ..... *Raymond Chua*
Situation in Korea ..... *Tae-Gyun Kim*
Situation in Europe ..... *David Williams*
Discussion leader ..... *Mime Egami*

3.7 Manufacturing (1) ..... *Ken-ichiro Hata*
Manufacturing (2) ..... *Yuzou Toda*

3.8 Globalization of R&D ..... *David Kaplan*
Discussion leader ..... *Grace Lim*

3.9 Intellectual property ..... *Alan Trounson*
Discussion leader ..... *Steve Badylak*

3.10 Translation from academia to industry ..... *Masayuki Yamato*
Discussion leader ..... *Peter Zilla*

3.11 Business models ..... *Luke Burnett*

3.12 Public funding mechanisms (1) ..... *Keith McLean*
Public funding mechanisms (2) ..... *Rui Reis*

CRITICAL SOCIO-POLITICAL-ECONOMIC-INDUSTRIAL-REGULATORY ISSUES

3.1 CHALLENGES FOR BIOETHICS

Statement by Kris Dierickx

The development of regenerative medicine (RM) presents a number of ethical issues.

1. Most RM processes require human cells. This will raise the demand for appropriate cells and cell lines, and multiply the number of persons and organizations involved in handling them and their derived products. This will raise new questions regarding 'ownership' of human material and the derived products, and the rights that cell donors and RM specialists can (not) assert. In a globalized world, where cells and the derived products can be easily transferred between countries with different legal systems and ethical sensitivities, and where the level of legislation concerning bodily material varies enormously, this is a challenge.

2. Ethical issues persist in the development of clinical trials and follow-up of participants and patients. The final introduction of RM products in persons resembles more common interventions, thus creating the perception that it is a variant of existing technologies. However, the aim and mode of their action differs, presenting unique challenges regarding their production, the design and conduct of clinical trials, and their introduction in therapy. We identify two problems: clinical trials require the researchers' equipoise about the considered interventions and the participants' informed consent. As so little is known about the syntax of tissue regeneration and, consequently, of short- and long-term effects, risks and benefits, both aspects may be problematic to achieve, which challenges us to define criteria for the conduct of trials and for achieving genuine informed consent.

3. As the research in the field of RM includes more genomic applications, the field faces the question: what to do with incidental findings? What to do with research results that also have relevance for clinical utility, even if that was not the first goal? From research on ethical questions in genome medicine, the field of RM has to learn how to deal with these very recent ethical challenges.

4. So far, attention has been focused on RM for therapeutic purposes. However, RM products and strategies could also be applied to develop tools for research, for example tissue models for specific diseases; and to use RM principles to prevent ageing, for enhancement or for cosmetic purposes. Especially these derived issues need further consideration, as most of the current regulations do not take these applications into consideration. Creating viable tissues outside of the body and regenerating the body may raise visions of post-humans having eternal youth. Earlier discussions concerning the moral implications of enhancement technologies may reappear once RM becomes a better understood and more applied technology. RM may also alter our perception of the life-cycle and of the bodily integrity, if the person's body can be reconstituted and rejuvenated, using living material derived from various persons, making the person into a hybrid. If *in vitro*-created RM products eventually become perfect replacements for 'natural' tissues and organs, the Cartesian view of the body as a machine may become even more the predominant view, resulting in interesting anthropological discussions.

Reflecting on ethical issues needs to be done at every stage of the development of RM, by all stakeholders involved. In this reflection, the product itself should not be the central issue, but the (vulnerable) persons involved.

3.2 STEM CELL COMMERCIALIZATION

Statement by Shi-Jiang Lu

Regenerative medicine is the process of replacing, regenerating, restoring or repairing (4R) injured/damaged human cells, tissues or organs to re-establish normal functioning in the body. The ability of human pluripotent stem cells, including human embryonic stem (ES) and induced pluripotent stem (iPS) cells to divide indefinitely, without losing pluripotency and to theoretically to differentiate into any cell type in the body, makes them highly attractive cell sources for regenerative medicine purposes. During the past decade, significant progress has been made towards controlled *in vitro* differentiation of human ES/iPS cells into specific replacement cell types, including neurons, retinal pigment epithelium (RPE), insulin-producing cells, hepatocytes, cardiomyocytes, muscle cells and hematopoietic cells, among others. Adding another dimension to the field of regenerative medicine, the advent of human iPS cells may allow patient-specific therapies to be produced, thus circumventing potential issues with HLA mismatching and immuno-incompatibility. However, before human ES/iPS cell-derivatives can be used in the clinic, it is important to understand the steps involved, as well as the risks and challenges associated with the production of therapeutic products. Cell products derived from human ES/iPS cells face many hurdles, in both the laboratory and in the manufacturing suite prior to reaching approval for use in the clinic. Major issues are: cell sources, safety, product consistency, immunogenicity and potency. I will present these issues in detail and use human ES cell-derived RPE as an example to outline the process for human ES/iPS cell-based product development.

3.3 THE DEVELOPING WORLD

Statement by Peter Zilla

The gargantuan efforts by governmental and philanthropic organizations to combat infectious diseases in the developing world begin to bear fruit. At the same time, the World Health Organization predicts that non-infectious diseases will overtake infectious diseases as the main cause of death in these regions by as early as 2020. This trend is most dramatically epitomized by heart disease. It is estimated that 30–75 million patients suffer from rheumatic heart disease in the developing world. Due to a lack of access to both open-heart surgery and affordable and suitable replacement valves, a majority of these patients will eventually succumb to the disease. In contrast, the vast majority of the fewer than 400 000 patients needing a heart valve replacement

in the developed world drive an industry that generated an estimated $US 828 million in product sales in 2010, and is globally expected to reach a value of over $US 2.5 billion in 2017.

The expansion drive of this industry has recently led to a new focus on emerging markets, without adjusting their products to the totally different needs of the patients concerned. The bioprosthetic material, for instance, that is the backbone of contemporary replacement heart valves usually outlasts the often octogenarian recipients in the USA, Europe and Japan. The very same material, however, leads to rapid calcific degeneration in the mostly young patients of countries like India, Brazil or South Africa. This highlights the first crucial challenge for us as a world community that searches for solutions to functionally and/or physically replace diseased organ parts: the current first world products are simply not good enough for both emerging economies and developing countries. Counter intuitively, a patient population that is one hundred times larger than the one constituting the market for the established billion-dollar industry is the one that really needs devices that incorporate the most sophisticated developments that make them more durable – either through tissue regeneration or novel biomaterials.

The second key need of these neglected millions of people concerns access to such devices. Open-heart surgery is non-existent in most developing countries and dramatically underprovided in the majority of emerging economies. Rather than helping a handful of patients through 'fly-by-night' missions of teams from industrialized countries, we are challenged to help find solutions that allow the mass insertion of devices, such as replacement valves, on the basis of the existing infrastructure of the developing world. And lastly, any solution for 'the many' must be on the basis of affordable, mass-producible materials, whether the goal is tissue regeneration or improved *in vivo* acceptance of biomaterials.

3.4 STRATEGIC COMMUNICATIONS

Statement by John Russell

Challenges and objectives

Previous speakers have outlined some of the challenges and 'head winds' to the advances of regenerative medicine. These include:

1. Persuading a skeptical public about new science they do not understand. Public acceptance – at least obtaining an open attitude or neutrality – is a necessary condition for success.

2. Overcoming reservations about regenerative medicine that are normally based on strongly held religious and ethical beliefs. Importantly, people of such ilk are not reticent to form and engage in the interest group politics that are prevalent in many countries, especially North America and Europe.

3. In communications terms, the supporters of new science are reticent and disjointed. Coalescing public and regulatory attitudes from the range of disparate and uncoordinated interests – national, regional and sectoral – is challenging. Even in the healthcare sector, there are competing business interests along the supply and distribution chains. Getting the model right and balancing the costs and profitability across the entire value chain is a precondition for the healthcare sector itself to operate as a coherent advocate for regenerative medicine.

Developing an effective response

In this competitive 'marketplace of ideas', success comes to those who can build trust with patients and the public, so providing comfort to politicians and regulators that their decisions will not elicit unacceptable criticism. The techniques of risk communications should usually be employed.

An effective campaign for regenerative medicine entails interweaving three pillars or types of communication: scientific, economic and social.

1. For articulating the technology and science underpinning regenerative science we have, in this room, probably the best group of potential spokespersons, who, with a little bit of coordination

and coherent messaging, can drive the international debate. But science is not the whole story and, I regret to say, you are not the best spokespersons for dealing with the other two pillars. For the social and economic pillars we need to look elsewhere and co-opt and energize some allies.

2. The social impact can be achieved by articulating the real and potential impact for saving lives or remarkably improving their quality. This is best achieved by marshaling patients, potential patients, their family and friends; giving them voices and amplifying and propagating their messages. Their communications are compelling; poignant. Importantly, this emotive style of communication is much more effective than technocratic and scientific styles in neutralizing conviction-based communications of those opposing the advancement of regenerative medicine for religious reasons. Also, experience indicates that such people-oriented communications have more resonance with the general (and voting) public. This 'populist style' is much more effective in building positive attitudes across broad spectrums of the public. These can later translate into political and regulatory priorities for action.

3. The third component is making a convincing economic case. In practical terms, regenerative medicine is in competition for research and development funds and healthcare budgets with alternative therapeutic disciplines within companies and governments. The costs of developing and implementing new therapies are judged against returns on investments by companies and on existing expenditures for Parkinson's, Alzheimer's, rheumatic heart disease, those paralyzed by spinal damage and so on. Economic research institutes are possible sources of allies and advocates.

Elements of a communications campaign

Modest starts with limited objectives are recommended, with initial emphasis on internal communication, to ensure coordination and to construct the 'communications toolkit'. This includes cohesive messaging, broad strategy objectives, stakeholder mapping and exchanges to make use of opportunities as they appear. Perhaps a quarterly internal e-newsletter can be developed. This framework can be scaled up as needed and resources become available. A phased approach is normally employed for such a campaign.

Components can include:

1. *Media relations*, with components for healthcare trade, business media and perhaps lifestyle. Broadcast and social media channels and platforms can be added later.

2. *Thought leadership*, including speaking opportunities and placement of opinion pieces covering the three pillars. This will require constructing an international pool of advocates, especially for the social and economic pillars.

3. Outreach to *patient groups*, with a phased approach to raise, initially, awareness, then understanding, and, if required, engagement in debates.

4. Background briefings to *government policy makers* in priority markets; moving on to policy advocacy when necessary.

5. Developing a communication module directed to the *business community*, raising the profile and appeal of regenerative medicine as a subject for innovation and investment. In addition to the traditional sectors of healthcare, collaterals and activities should cater to the needs of the financial sectors, especially private equity (PE) and venture capital (VC)

6. Mapping and *segmenting sources of opposition* to regenerative medicine are advised. If time and resources allow, outreach to moderates can be useful to neutralize their opposition; thus marginalizing entrenched opposition as extreme.

The above is a strategic communications framework and an approach that may be useful. Much additional research and work is required to flesh out the details of such a communications campaign to ensure that expectations and efforts are feasible, appropriately targeted and subsequently effective.

3.6 REGULATORY PRINCIPLES: SITUATION IN THE USA

Statement by Karl Nobert

Stem cells intended for use in humans are regulated under the Food and Drug Administration's (FDA) regulations governing human cells, tissues, cellular and tissue-based products (HCT/Ps). Depending upon such use and their functional impact within the body, however, they may also be subject to FDA's drug, biologic or medical devices rules. This presentation will provide an overview of FDA's legal authority and regulation governing stem cells products and the criteria that the FDA uses to determine a product's regulatory status, and will offer strategies for mitigating the potential risks associated with the marketing and selling of a stem cell product in the USA. Relying on recent FDA warning letters and court cases, the presenter will identify specific regulatory risks relevant to cellular products and therapies; and discuss methods for controlling such risks.

3.6 REGULATORY PRINCIPLES: SITUATION IN AUSTRALIA

Statement by Marian Sturm

Therapeutic goods are regulated in Australia by the Therapeutic Goods Administration (TGA), a division of the Federal Government's Department of Health and Ageing. Until 2013, regulation of biologicals required compliance with the Code of Good Manufacturing Practice (cGMP), implemented in 2000, as applied to the blood and tissue banking sector. With the emergence and evolution of new biotherapeutic products, this code became outdated and its application proved difficult for both the regulators and manufacturers. After extensive review and in consultation with the sector, a new regulatory framework was implemented in May 2013, with full compliance expected by July 2014. The new biologicals framework, which includes a revised cGMP and Therapeutic Goods Orders (TGOs) detailing specific standards, captures cellular therapies and takes a risk-based approach. The standards have been harmonized as far as possible with international standards, although international standards such as British Pharmacopoia continue to act as default standards.

Products are divided into four classes based on perceived risk, with higher risk products assigned a higher class. Compliance requirements are greater for the higher class products. All products are required to be included on the Australian Register of Therapeutic Goods (ARTG). Products may be declared by legislative order to be a specific class. Biologics declared in the regulation as Class 1 only require a declaration of compliance with the mandatory standards and inclusion on ARTG. Products in Classes 2–4 require preparation and submission of dossiers detailing manufacturing, with the extent of supporting safety and efficacy data increasing with the Class of product. Class 2 products are low-risk products that are minimally processed and for homologous use, for example frozen bone, human heart valves, and corneas. These products must be evaluated for compliance with cGMP and relevant standards. Class 3 biologics are products that have been processed beyond minimal manipulation and may be for homologous use or non-homologous use. Examples are demineralised bone, culture expanded cells, etc. These products must be evaluated for safety, quality and efficacy by the TGA and manufacture must be compliant with cGMP and relevant standards. Class 4 products are those processed in a way to alter their original function and state. They may or may not be for homologous use. This group includes genetically modified cells. Compliance requirements and evaluation by the TGA are similar to that of Class 3 products but a more detailed dossier submission is required for further assessment and analysis of the supporting data. The level and detail in the dossier should correspond to the potential risk that the product poses to the recipient.

3.6 REGULATORY PRINCIPLES: SITUATION IN JAPAN

Statement by Yoji Sato

Regenerative medicine and cell therapy using relevant products derived from engineered human cells/tissues are being keenly anticipated in Japan, in order to compensate for limited human organs and tissues transplantation and to treat various severe diseases that are difficult to cure using existing treatments. At the Summit, I would like to introduce the regulation and development of cell/tissue-based products, and recent important regulatory activities in Japan.

3.6 REGULATORY PRINCIPLES: SITUATION IN JAPAN

Statement by Kazuhiro Takekita

Today, development of cellular and tissue-based products is becoming more and more internationally competitive; therefore it is necessary to update current pharmaceutical regulations by considering characteristics of these products. In order to facilitate the development of cellular and tissue-based products by ensuring safety and efficacy; and also to put them smoothly into Japanese markets, Pharmaceuticals and Medical Devices Agency (PMDA) and the Ministry of Health, Labor and Welfare are planning and implementing various kinds of projects, measures and policies. At this Summit, I will express opinions from the perspective of Japanese regulatory updates and PMDA's efforts on cellular and tissue-based products.

3.6 REGULATORY PRINCIPLES: SITUATION IN SINGAPORE

Statement by Raymond Chua

In Singapore, cellular- and tissue-based therapeutic (CTT) products such as cell therapy products, stem cell products and tissue engineered products are regulated as medicinal products. Currently we have applied a risk-based tiered approach, whereby high-risk CTT products (substantially manipulated, intended for non-homologous use or combined CTT products) are regulated under the Medicines Act, while the regulation for minimally manipulated cells and tissues will be phased in at a later stage under the Health Products Act.

One of the critical challenges faced in the regulation of CTT products is the availability of relevant expertise required for the review of the diverse range of innovative CTT products. Nonetheless, various means have been used to assist the Health Services Agency (HSA) in overcoming this challenge:

1. Regulators' Forum Cell Therapy Group (RFCTG):

    a. Group of CTT regulators from about 12 agencies spanning from North America to Australia/NZ that meets via teleconference three to four times a year, with an annual face-to-face meeting, to understand the current regulatory landscape, discuss issues and challenges and share scientific information.

    b. One of the active groups identified under the International Pharmaceutical Regulators Forum.

2. Network with SwissMedic and Australia TGA:

    a. To discuss cell therapy manufacturing/GMP challenges and information sharing. This was established due to the fact that the majority of the facilities are hospital- or academia-based, where GMP understanding is different.

3. Healthcare manpower development program (HMDP):

    a. Sponsored by our parent Ministry of Health, Singapore.

    b. The experts' visits are geared towards imparting and sharing their knowledge to help improve and upgrade skills amongst healthcare professionals with similar interests in hospitals and institutions across the public healthcare sector.

The second critical challenge is the absence of internationally harmonized guidance documents and consensus standards. The third challenge is product classification and associated regulatory ambiguity; a product could be classified as a medicinal product in one country while it may be regulated as a medical device in a second country or a transplant product in a third country. Currently, under the auspices of Asia-Pacific Economic Cooperation (APEC) Life Science Innovation Forum Regulatory Harmonization, Singapore has been designated as the champion economy leading to the development of a cell therapy roadmap to facilitate the regulatory convergence of approaches and to align best practices, scientific principles and technical requirements. Several partner agencies from both APEC economies and non-APEC regions will be contributing to the roadmap development.

With the above approaches and working in tandem with our stakeholders (that is, academics and industries), it is, therefore, important for HSA as a regulator to facilitate and bring the mind to the market, to advance the field of regenerative medicine and to provide therapeutic options for diseases where options are limited or unavailable.

3.6 REGULATORY PRINCIPLES: SITUATION IN KOREA

Statement by Tae-Gyun Kim

Tissue engineered and regenerative medical (TE/RM) products are involved with innovative therapies that can regenerate lost/damaged tissues or organs and restore function, often being implanted into a patient to make living tissue equivalents. Recently, the advent of stem-cell technology and new biomaterials has stimulated an impetus in the development of more complex and novel products to address unmet medical needs. Through prior experiences for commercialization of a few TE/RM products and approval of ongoing clinical trials, the Korea Ministry of Food and Drug Safety (MFDS) has been challenged by some scientific and regulatory issues on reviewing the safety, efficacy, and quality of the products.

The Korea MFDS is preparing the guidelines entitled 'Points to Consider for Reviewing the TE Products' and plan to release these to the developers in the near future. To assure the quality and safety of the products, it is important for the developer to do testing and characterization, especially including donor eligibility, characterization of cell bank, product potency/performance assay, manufacturing controls/consistency, raw materials/reagents, etc. It is recommended that they can apply the 'Quality by Design' guidance of the International Conference on Harmonization to their products. To obtain validity in the design and conduct pre-clinical studies, it is recommended to choose appropriate animal models of disease relevant to the target of interest for *in vivo* studies. We can accept data using animal analogous cells if the character of the human and animal cells is properly compared. Pharmacokinetic study should be submitted in respect to understand biodistribution and persistency of the products. Tumorigenicity study is necessary for stem cell-derived products. In the early clinical stage, it is better to apply the concept of dose escalation to the clinical protocol, for example TE products can be provided as treatment for patients with small-size defects first and then for patients with large defects. The developers need to communicate with us on the clinical issues, such as patient population and numbers of patients, primary endpoint of study for approval, safety parameters and observation time, etc. The Korea MFDS has recently agreed on the nature and duration of patient follow-up and would like to emphasize that the TE/RM products should show structural and functional effectiveness and safety; thus posing novel challenges to both the developers and us.

3.6 REGULATORY PRINCIPLES: SITUATION IN EUROPE

Statement by David Williams

The features of regulation of regenerative medicine within the European Union represent a microcosm of global issues, where intentions to achieve harmonization of practices at supra-national levels have to be seen in the light of national interests and cultural differences. The European Commission, which has responsibility for the promotion of the principles of the single market within the Union, including the regulation of health care products, has to take into account the primacy of the Member States of the Union with respect to the legal basis of safeguarding human health, enshrined in the Treaty of Rome, even if somewhat modified by the Treaty of Amsterdam. After many years of discussion and negotiation about a Directive on Tissue Engineering Medical Products, to sit alongside directives on pharmaceuticals and medical devices, the Commission approved a regulation, in 2007, on Advanced Therapy Medical Products. A centralized procedure for the scientific evaluation of applications for European marketing authorization was established within the European Medicines Agency (EMA), advised by their Committee for Advanced Therapies (CAT). So far, very few products have received this marketing authorization.

On the other hand, the conduct of clinical trials within the European Union is governed by the Competent Authorities within Member States, such as the Medicines and Healthcare Products Regulatory Agency (MHRA) of the UK, and the Spanish Agency of Medicines and Medical Devices (AEMPS). Each country has its own procedures and advisory committees, and governmental positions on these issues are informed by concerns over patient safety and, conversely, the need to create an industry-friendly environment for the promotion of biotechnology and clinical trials infrastructure. As of 2010, Spain had approved by far the largest number of clinical trials, followed by the UK and Germany. Discussions both within countries and within the European Union center around this dichotomy of balancing speed to market with the public health mandate on the protection of individual patient safety.

3.6 PERSPECTIVES ON GLOBAL REGULATORY ISSUES

Statement by Mime Egami

Considering world scientists' tremendous research efforts and communications in the field of tissue engineering and regenerative medicine (TERM), under special support by governments of various countries, we need to develop proper regulatory platforms and global intelligence to promote safe, effective and efficient TERM to treat sizable numbers of beneficiaries at the bedside, in well-informed environments for all stakeholders, without charging unaffordable prices.

The following are candidate items for session discussion:

1. Autologous cell-based Regenerative Medicine (RM) (including stem cell therapy): regulatory harmonization and re-establishment of new risk/liability sharing agreement by experience among stakeholders (patient, industry, clinical site, regulatory authority): high quality clinical study, conditional approval, outcome data/pharmaeutical vigilance and how to utilize world dialogue on experience?

2. Any scientific 'hottest' regulatory issue to challenge globally (quality for safety and efficacy, tumorgenesity, bio-distribution).

3. Quality control of cell processing: current final product test for 'manually processed' product versus QbD Quality Assurance System by Automated Process Analytical Technology (PAT). How to encourage industry to participate and develop repeatable cell culture technology under traceable environment and enable reasonable cost reduction. How to develop evidence-based tools for product liability as well as regulatory science.

4. Regulatory review for 'single-donor' allogeneic RM (such as finger tissue donated by children of polydactily) versus multi-donor allogeneic RM.

5. New balance of product liability/cost and risk sharing: how regulatory authorities want to manage innovation process under new cooperation.

6. ES cell, iPS cell: what appropriate way to promote global clinical application (competition or convergence?): cooperation in specific needs (disease), science, or full competition among countries.

3.7 MANUFACTURING (1)

Statement by Ken-ichiro Hata

Our first product, J-TEC Autologous Cultured Epidermis (JACE), received a marketing approval in 2007, as the first tissue engineered medicinal product (TEMP) in Japan. JACE is sheet-formed keratinocyte prepared by Professor Green's technique, which has already been used for manufacturing TEMPs for more than 25 years in the USA. In Japan, approved medicinal products are classified into either Drug or Medical Device, and JACE is classified into Medical Device. When we launched the development of JACE in 1999, there was insufficient regulation and understanding of TEMPs in Japan and there was no clear consensus on whether to approve such TEMPs under the Pharmaceutical Affairs Act.

It is unreasonable to supply autologous TEMPs in conformity with the Pharmaceutical Affairs Act, like other medical devices. In the case of TEMPs, patients' own cells as raw materials have various qualities, which makes it difficult to set a simple standard for raw materials. Besides, it is not easy to standardize process management and set a uniform standard for shipping. It may not be appropriate to treat autologous cell cultured tissue transplants in the same way as other traditional medical products.

Under these circumstances, we have accumulated 14 years of research experience on commercialization and have provided our products for more than five years. We have set up ethical consideration on the treatment of human tissues and informed consent. Also, we have established adequate systems for product quality management, maintenance of production environment, instruction to doctors for use of products, smooth supply and evaluation of the product quality. In this session, I would like to provide and overview of these experiences.

3.7 MANUFACTURING (2)

Statement by Yuzo Toda

This statement refers to the activities of the Japanese regenerative medicine industry. The Forum for Innovative Regenerative Medicine (FIRM) was established in 2011 to promote the commercialization of regenerative medicine in Japan. Its membership has expanded to more than 50 industry participants. The mission is to pave the way for real, practical breakthroughs in regenerative medicine by pursuing broad, industry-led partnerships with governments, universities, media, and the private sector, for the purpose of building consensus on the commercialization process and the application of new regenerative medicine techniques in the community. Japan is undergoing innovative change in the regulatory environment for regenerative medicine, in order to minimize unnecessary regulatory burden and to promote regenerative medicine. The Act for Promotion of 'Regenerative Medicine', legislation that is expected to become effective within in a couple of years, introduces innovative concepts, such as responsibility for each player, organization of security and other standards, organization of a system for medical institutions outsourcing cells/tissue processing operations to external businesses, and introduction of an early approval system.

FIRM is working with the government, so that the law, when implemented, will work not only to promote industry supporting regenerative medicine, but also to ensure the safety and effectiveness of this technology. This legislation should result in successful commercialization and make regenerative medicine a more feasible and useful option for patients, and thereby make a significant contribution to the quality of life of people worldwide.

3.8 GLOBALIZATION OF R&D

Statement by David Kaplan

The need for new biomaterial strategies to address problems in medicine continues to drive innovation and opportunities. One of these growing options is to develop international partnerships to foster research and development (R&D), as well as education. This option has emerged due to many factors, including the general globalization of R&D, the gradual reversal of the brain drain from developing countries, and, most importantly, from the clinical needs that are in many cases universal among countries. Commercially, globalization has emerged as the norm, which also drives R&D towards a similar outcome. The synergy achievable with such a strategy can be profound, while the challenges along this path continue to be significant.

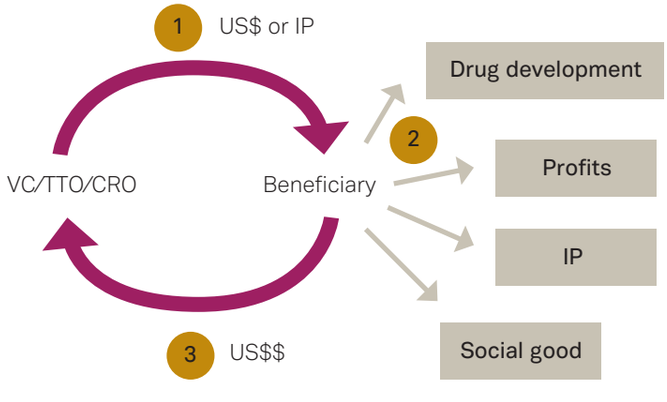
Some of the many challenges to success, particularly from an academic perspective, include how to establish an R&D structure to benefit all parties involved; how to maintain a balance of what is done and where, so that all of those involved can grow, learn and contribute; and how to deal with the logistics of overseas interactions with simple issues of regulatory control and the shipping of biological samples as examples. Additional challenges include language, intellectual property, researcher incentives that are often different in various countries, funding for the enterprise and how this impacts the work, and many related themes. Additional considerations are how to start these new initiatives, how to engage students, faculty and industry at early stages, and how to integrate educational themes into the process. While all of the above issues can be barriers to success, the compelling needs and opportunities to move further into globalization of R&D trumps the barriers to success.

3.9 INTELLECTUAL PROPERTY

Statement by Alan Trounson

Intellectual property (IP) is the core element for the commercialization of discoveries. The patents need to be carefully prepared by IP lawyers who have experience in the prosecution of patents. Care is needed to ensure patent position is not compromised by publication or presentations in conferences and other forums. Experience in protection of patent position and the relative position of other IP needs to be part of the discovery and translation processes. Rights to utilize IP also need to be carefully considered by patent holders and monitored. The right to commercialize is a primary consideration of venture capital institutions and biopharma companies.

VC/TTO/CRO For Profit Model



1. VC/TTO/CRO provides resources to advance the technology.
2. Beneficiaries develop drugs that will generate profits and provide social benefits.
3. Beneficiaries provide a direct return on the initial investment.

VC/TTO/CRO expects direct returns on investments in the form of profits. (Note: VCs generally do not invest in translational research.)

Source: CBT Advisors

The figure on page 37 shows the idealized version of the for-profit model of investing in translation. Venture funds (to the extent that they invest in translation), technology transfer offices and the newcomers, contract research organizations, are putting in money or intellectual property or both, in return for a financial return on investment. Other positive developments usually occur in the process, including the social good that comes from new therapies reaching the market, as well as additional intellectual property. But the main purpose of these models is to generate revenue.

3.10 TRANSLATION FROM ACADEMIA TO INDUSTRY

Statement by Masayuki Yamato

We have applied cell sheet-based therapies to human patients. Japan's regulation allows physicians to perform clinical studies of regenerative medicine with a small number of patients. In 2003, we started a clinical study to treat patients with total corneal epithelial stem-cell deficiencies resulting from alkali burns or diseases, including Stevens-Johnson syndrome, by transplantation of autologous oral mucosal epithelial cell sheets. We then founded a venture company, CellSeed Inc., to promote clinical translation of cell sheet-based therapies. We performed the clinical trial sponsored by the company in Europe. Since 2007, as a clinical study, autologous skeletal myoblast sheets have been used to treat severe heart failure, including dilated cardiomyopathy (DCM) and ischemic heart disease. Recipients of autologous skeletal myoblast sheet transplantation resulted in noticeable improvements: no arrhythmia, discontinued use of a left ventricular assist device (LVAD), and avoidance of cardiac transplantation. Based on this evidence, Terumo Corporation in Japan began a clinical trial to treat patients suffering from severe heart failure due to ischemic heart disease, using transplanted autologous skeletal myoblast sheets. To treat esophageal ulcerations and prevent stenosis, autologous mucosal epithelial cell sheets were transplanted to patients. The clinical study began in 2008, and the treatment has been found to promote wound healing, prevent inflammation and constriction, and improve the patients' post-operative quality of life. Periodontal treatment using periodontal ligament-derived mesenchymal cell sheets has been applied for regenerating damaged periodontal support. The clinical study of this treatment started in October 2011. Autologous chondrocyte sheets have been applied in the treatment of knee cartilage damage. In Tokai University, the clinical study of this treatment, using layered chondrocyte sheets started in November 2011. Now, we are discussing the clinical studies of esophageal and cartilage regenerative medicine with pharmaceutical companies.

From my experience, I believe that a critical point in the transfer from academia to industry would be to understand the differences in culture and ways of thinking, between academia and industry. It is not easy, but working in a coordinated and united forum is important.

3.11 BUSINESS MODELS

Statement by Luke Burnett

The remarkable advances in biomaterials and therapies used in tissue engineering and regenerative medicine have come from the extraordinary efforts of laboratories all over the world. This work has begun to solve complex problems, using biomaterials optimized to their target tissues that leverage porosity, viscosity and architecture; but also biological features such as biocompatibility, degradation profile, cell infiltration capacity and the ability to deliver a variety of drugs, growth factors or cells. Despite the advances in both the science and the production processes for these materials, one of the major limitations for small biotechnology companies trying to commercialize these technologies is business planning and access to capital. Recent uncertainty in the oversight by the US FDA and other international regulatory bodies has resulted in commercialization timelines that are dramatically longer and more expensive than was required even a decade ago. In order to be successful, small companies need to seek operating capital from multiple sources and remain flexible in embracing new opportunities as they become available. Researchers planning on commercializing regenerative medicine technologies

should consider realistic regulatory impacts when planning funding requirements. Additional considerations for successful business plans should address market size, reimbursement strategy (US market), the technology's maturity, government and non-governmental grant funding likelihood, as well as the potential interest by strategic partners, private equity and venture capital. The reality is that, though the total amount of venture capital available in biotechnology has increased in recent years, there has been a corresponding decrease in the number of deals done (more money to fewer companies). These challenges require that business plans be based on solid market analysis, strong pre-clinical safety and efficacy data and realistic regulatory plans, if technologies are to be successful.

3.12 PUBLIC FUNDING MECHANISMS (1)

Statement by Keith McLean

A successful regenerative medicine industry has the potential to generate new, innovative and transformative cell, tissue engineering and regenerative therapies with major health and economic benefits. A successful, and timely regenerative medicine industry will only result from a clear path from 'bench to bedside' and from collaboration between basic scientists, clinicians, investors, manufacturers, commercial entities, regulators and government. Such partnerships are essential as the current model of medical innovation can be considered to be, at best, inefficient and, at worse, broken; exacerbated by the fact that funding for early-stage development has been greatly reduced in the wake of the global financial crisis. While globally it is recognized that public investment in basic research remains a key role for governments through agencies such as NIH, ESPRC, MOST, etc., there is increasingly both a role, and indeed a requirement, for public funding to bridge the gap between research projects and market products and thus assist in translational aspects of regenerative medicine. 'There is a need for public sector support if the promise of the new technology (regenerative medicine) is to be realized' (Head of the EU Unit for Advanced Therapies and Systems Medicine, DG Research and Innovation). This recognition of the need to support the rapid and efficient translation of research has resulted in the establishment of entities such as Californian Institute for Regenerative Medicine (CIRM), Centre for Commercialization of Regenerative Medicine (CCRM); Regenerative Medicine Coalition (RCM), UK Cell Therapy Catapult, Armed Forces Institute for Regenerative Medicine (AFIRM), NIH Centre for Regenerative Medicine, etc., to provide funding as well as to share knowledge, infrastructure and intellectual property, and to accelerate cost-efficient development. In addition, increased government commitments of public funding for regenerative medicine have been seen globally, for example, an additional Yen 100 billion in research support for iPS in Japan in 2013, or the provision of Won 100 billion in South Korea in 2012 to provide a link from basic research to clinical studies and increased funding in China.

While CIRM – created by California's Proposition 71, which authorized it to issue US$ 3 billion in grants, funded by bonds, over ten years for stem cell and other biomedical research – is the best known and largest initiative in this space, other countries also provide examples of innovative use of public funding. The establishment of the Canadian Stem Cell Network played a key role in establishing a multi-disciplinary, high-quality, collaborative research network in stem cell, biomaterials, engineering and clinical science, but the subsequent establishment through public investment in CCRM is now enhancing the potential to commercialize regenerative medicine by providing business leadership to translate breakthrough platforms in conjunction with commercial partners. In addition, CCRM is building global networks to facilitate cooperation and translation and Canada has a public healthcare system suited to clinical trials.

It is well recognized that there is a long and expensive path for regenerative medicine from the laboratory to the clinic, with insufficient scientific understanding; uncertain business models; regulatory, re-imbursement and scale-up issues; and lack of infrastructure all providing barriers to success. Public funding to support basic research and to assist in bridging gaps in translation, either through direct government funding, matched funding, government guarantees or provision of major infrastructure is key to success.

3.12 PUBLIC FUNDING MECHANISMS (2)

Statement by Rui Reis

Tissue engineering and regenerative medicine (TERM) is a rapidly evolving field of research. It is both a rather complex and interdisciplinary area, with many specificities and requirements, and a field where the researchers, governments, policy makers, funding agencies, entrepreneurs and – more importantly – the general public (patients and their relatives and friends, and, consequently, the media) deposit a lot of hopes and expectations.

The research is quite complex, and must link together many areas of expertise. The required research conditions, facilities, equipment and investigation environments have a lot of particularities. But, to be able to really move forward, unique strategies for intellectual property (IP) protection, active interaction with regulatory agencies, specific political moves for translational programs, as well as the possibility to raise the required levels of funding are critical. The area is also quite particular in that, in many cases, it is not as global as other areas of research (although it is one of the areas where more established international collaborations are running and give rise to amazing results), as the legal framework strongly limits/allows for specific categories of research (for instance, in terms of stem cells) and this has a clear influence on funding availability and international networking possibilities.

Several governments in the Americas, the European Union and Asia-Pacific have been setting the path for trying to move forward in this very promising area. Some have been trying to set clear research and networking priorities. Others have tried to catapult some of the very good research results obtained in the laboratories. Some are putting the emphasis on trying to increase IP generation and availability of private venture capital matched with public money. Alternative strategies are focusing on getting funds to speed up regulatory pathways without compromising safety. In addition, top-level networking of companies, universities and state/government to obtain funds are believed to be the way to fulfill the promise of TERM. A more global strategy, which learns from all these very valuable experiences and combines the best of some of them, is clearly needed. TERMIS, as a society with members from more than 80 countries, including most of the relevant players in this field, can play a leading role in moving this area further and faster and in making it much more useful to the general public, without in any way breaching ethical boundaries.

This is the first time that this immensely important subject has been debated on the global stage, and the outcome should have a profound effect on all aspects, including the scientific, ethical, economic, regulatory, clinical and manufacturing arenas.

BIOGRAPHIES

BADYLAK, STEPHEN

Stephen Badylak is a Professor in the Department of Surgery, and Deputy Director of the McGowan Institute for Regenerative Medicine. Dr. Badylak has practiced both veterinary and human medicine, and is now fully engaged in research. Dr. Badylak began his academic career at Purdue University in 1983, and subsequently held a variety of positions, including service as the Director of the Hillenbrand Biomedical Engineering Center from 1995–1998. Dr. Badylak holds over 50 US patents and 200 patents worldwide; and has authored more than 275 scientific publications and 30 book chapters. He has served as the Chair of several study sections at the National Institutes of Health (NIH), and is now a member of the College of Scientific Reviewers for NIH. Dr. Badylak has either chaired or been a member of the Scientific Advisory Board to several major medical device companies. More than four million patients have been treated with bioscaffolds developed in Dr. Badylak's laboratory.

Dr. Badylak is a Fellow of the American Institute for Medical and Biological Engineering, a member of the Society for Biomaterials, a charter member of the Tissue Engineering Society International, immediate Past President of the Tissue Engineering Regenerative Medicine International Society (TERMIS) and a Founding Fellow of TERMIS.

Dr. Badylak's major research interests include: naturally occurring biomaterials, including ECM, biomaterial/tissue interactions, developmental biology and its relationship to regenerative medicine, relationship of the innate immune response to tissue regeneration, biomedical engineering as it relates to device development and biomaterials, and the clinical translation of regenerative medicine.

BULTE, JEFF

Jeff Bulte is Professor and Director of Cellular Imaging at Johns Hopkins University School of Medicine, USA. He obtained BSc and MSc degrees from the Free University of Amsterdam, The Netherlands and PhD in 1991 in Medicine (Immunology) from the University of Groningen, The Netherlands. He was a staff scientist in the Laboratory of Diagnostic Radiology Research at the National Institutes of Health (NIH) and moved to Johns Hopkins University (JHU) in 2001 as Assistant Professor of Radiology. He was appointed Professor of Radiology and Director, Cellular Imaging Section, JHU Institute for Cell Engineering in 2006, Professor of Chemical and Biomolecular Engineering, and Professor of Biomedical Engineering, JHU Whiting School of Engineering in 2007 and Professor of Oncology, JHU School of Medicine in 2012.

Dr. Bulte has been a Fellow of The International Society for Magnetic Resonance in Medicine (ISMRM) since 2008 and Chair of ISMRM Molecular and Cellular Imaging Study Group. He is a Distinguished Investigator, Academy of Radiology Research, Washington DC and has served on

study sections at NIH, DOE, NAS, NMSS, CIRM and on editorial boards of *Magnetic Resonance in Medicine; Current Stem Cell Research and Therapy; Nanomedicine; Contrast Media and Molecular Imaging; Molecular Imaging; Journal of Magnetic Resonance Imaging.*

Dr. Bulte has been active in the field of molecular and cellular MRI for over 20 years and has developed several techniques for non-invasive cell labeling and tracking *in vivo* using nanoparticles and MRI reporter genes. Dr. Bulte has experience with translating new tumor imaging techniques from 'the bench to the bedside', and has been part of the first clinical study using magnetically labeled cancer vaccines.

BURNETT, LUKE

Luke Burnett currently serves as the Chief Science Officer of the biomaterials company KeraNetics, located in Winston-Salem, North Carolina, and is Adjunct Assistant Professor in the Department of Orthopedic Surgery at the Wake Forest School of Medicine. Dr. Burnett leads a team of 18 scientists and technicians at KeraNetics, working on the pre-clinical and clinical development of various keratin-based biomaterial products in the fields of trauma, regenerative medicine and skin care. He currently leads or participates in nine US government funded research contracts/grants that total over US$ 14 million and has raised an additional US$ 15 million in private equity. Dr. Burnett has extensive experience with animal models and has worked with all research species from rodents to primates, including leading several surgical teams using pig burn and bone trauma models. Additionally, Dr. Burnett is a Lieutenant Colonel in the US Army National Guard with 23 years of experience, including two tours in Iraq, giving him unique insights into the medical needs of battlefield trauma casualties.

CANCEDDA, RANIERI

Ranieri Cancedda is Professor of Cell Biology and Dean of the Biotechnology School at the University of Genova, Italy. He also serves as Head of the Laboratory of Regenerative Medicine of the IRCCS AOU San Martino-IST National Cancer Research Institute, Genova. A 1969 magna cum laude graduate of the University of Genova Medical School, Professor Cancedda went on to complete postdoctoral training in Nigeria and in the USA. He was Associate Professor of General Biology and Chair, Department of Cellular and Molecular Biochemistry, 2nd Faculty of Medicine, University of Naples, Italy. In the middle of the 1980s, he moved to Genova, where he has been Professor of General Biology, Dental School, University of Genova and Vice Scientific Director of the National Cancer Institute from 2001 to 2004. He is Affiliate Member of the McGowan Institute for Regenerative Medicine, Pittsburgh University, USA and Fellow of the Tissue Engineering and Regenerative Medicine International Society (TERMIS).

CAO, YILIN

Yilin Cao is Professor of Plastic Surgery at Shanghai 9th People's Hospital affiliated to Shanghai Jiao Tong University School of Medicine and President of Beijing Plastic Surgery Hospital. His major contribution is the creation of cartilage in the shape of a human ear in a nude mouse, for which he received the James Barrett Brown Award in 1998 at the meeting of American Association of Plastic Surgeons. Dr. Cao is the Chief Scientist of National Tissue Engineering Research Project. His major contributions in this field are the tissue constructions of bone, cartilage, tendon and skin in large animal models with translation into clinical application. Currently, Dr. Cao is the President of the Chinese Society of Tissue Engineering, Director of National Tissue Engineering Center of China, Vice President of Chinese Society of Biomaterials, and Immediate Past President of Chinese Society of Plastic Surgery. Dr. Cao is Chapter Chair of TERMIS-AP. Dr. Cao has given more than 30 invited speeches at various international conferences. He currently serves as Associate Editor of *Biomaterials*, editorial board member of *Journal of Biomaterial Research; Plastic and Reconstructive Surgery; International Journal of Plastic, Reconstructive and Aesthetic Surgery*. Dr. Cao was also elected as a Founding Fellow of TERMIS. He has published 50 research papers in international academic journals and contributed chapters to several international textbooks.

CAPLAN, ARNOLD

Arnold Caplan is Professor of Biology and Director of the Skeletal Research Center at Case Western Reserve University, USA. He received his PhD from the Johns Hopkins University School of Medicine. Dr. Caplan is a national and international scholar focusing on experimentation in the area of musculoskeletal and skin development. He has published over 390 papers and manuscripts and has long been supported by the National Institutes of Health (NIH) and other non-profit and for-profit agencies for his efforts in trying to understand the development, maturation and aging of cartilage, bone, skin and other mesenchymal tissues; and for his pioneering research on mesenchymal stem cells.

CHUA, RAYMOND

Raymond Chua began his medical career after graduating from the Faculty of Medicine in National University of Singapore in 1997. He was assigned to numerous medical and surgical postings in the public sector hospitals until October 2000. Associate Professor Chua then began his public health training with the Ministry of Health, Singapore, before he became certified as a registered Public Health Specialist and Fellow with the Academy of Medicine, Singapore in 2007. He was awarded a scholarship by the Ministry of Health to take up an MSc in Public Health with the London School of Hygiene and Tropical Medicine, University of London, in 2002. Asst. Prof. Chua also holds an MBA degree from the University of Nottingham and obtained a Graduate Diploma in Change Management, Institute of Public Administration and Management, Singapore in 2007.

Asst. Prof. Chua left the public service to join Eisai Co., Ltd in June 2007 as the Managing Director of Eisai Clinical Research, Singapore, to oversee, execute and manage the development and operations of the global and regional clinical research activities within Asia-Pacific and Middle East. In 2010, he joined Shire Pharmaceuticals as their International Medical Director, to oversee the growth and development of Shire's products in Asia-Pacific. In 2011, Asst. Prof. Chua joined Health Sciences Authority (HSA) and was designated as Group Director of the Health Products Regulation Group (HPRG) in 2012. He oversees and provides strategic directions to the HPRG – as a national professional pre- and post-market regulatory body – of all health-related products, including drugs, medical devices, complementary health products and tobacco; taking into account the wider context of regional and international regulatory advances, in alignment with the vision and mission of HSA.

Asst. Prof. Chua holds other appointments as Council Member of the Singapore Medical Council and Adjunct Assistant Professor in the Saw Swee Hock School of Public Health in the National University of Singapore. In addition, he is an appointed member of the International Committee, Faculty of Pharmaceutical Physicians, London; Fellow of the Royal College of Physicians and Surgeons (Glasgow); and Fellow of the Royal College of Public Health (London).

COOL, SIMON

Simon Cool was awarded his PhD by the University of Queensland, Australia in 1996 and subsequently joined the School of Biomedical Sciences at the University of Queensland. In 2003, he moved to Singapore as a Principal Investigator at A*STAR, first with the Institute of Molecular and Cell Biology, then with the Institute of Medical Biology, where he currently co-heads a research program focused on developing novel heparan sulfate glycosaminoglycans for bone, cartilage, blood vessel and skin regeneration. His team has made important discoveries as to how unique heparan sulfate variants bind to particular growth factors of therapeutic interest. Dr. Cool is also co-founder of SMC Biotechnology Inc., a US-based regenerative medicine company focused on the clinical applications of these carbohydrates.

DAI, JIANWU

Jianwu Dai is Professor and Associate Director, State Key Laboratory of Molecular Development Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences. He is also Joint Professor and Director, Nanomedicine Division, Suzhou Institute of Nano-tech and Nano-bionics, Chinese Academy of Sciences.

Dr. Dai graduated from Wuhan University with a BSc in Cell Biology and then obtained a MSc in Biophysics from Beijing Medical University. He then studied in the United States and obtained a PhD degree from Duke University Medical Center. After two years' postdoctoral training in animal genetics and stem cell biology at Harvard Medical School, he went to work in a US-based biotech company for biomaterial- based product development. He returned to work at the Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, in 2003. Dr. Dai has established a tissue engineering laboratory at the Chinese Academy of Sciences and for the past ten years he has been working on collagen-based functional biomaterials for tissue regeneration, with a special interest in spinal cord injury repair. His group has invented a method to produce collagen binding human growth factors and has developed a line of collagen-based medical device products by modifying collagen scaffolds with recombinant collagen binding human growth factors. The first product in this line is an active bone induction product by combining collagen containing material with collagen binding human BMP2. A spinal cord injury repair device of collagen fiber with collagen binding human BNDF has gone through the test of several rodent spinal cord injury models and two rounds of dog spinal cord injury models with the removal of several millimeters of spinal cord tissues. This device actively induced neuronal regeneration in all the animal models and improved the animal functional recovery in the dog models.

DAI, KERONG

Kerong Dai graduated from Shanghai First Medical College in 1955, and worked in the Mayo Clinic, USA, as Research Fellow. Afterwards, he served as Superintendent of Ninth People's Hospital, Shanghai Second Medical University (SSMU); Dean of Ninth People's Hospital Medical School; and Director of the Department of Orthopedics, Ninth People's Hospital, SSMU. He is now Director of Clinical Translational Center of Stem Cell and Regenerative Medicine, Shanghai Jiao Tong University School of Medicine; Director of Shanghai Medical Center of Joint Surgery; Director of Bone and Joint Research Institute, Shanghai Jiao Tong University School of Medicine; and Director of Engineering Research Center of Digital Medicine and Clinical Translation, Ministry of Education.

In recent years, he has engaged himself in the field of bone and cartilage regeneration, orthopedic biomechanics, biomaterials, bone metabolism and osteoporosis, design and development of computer assisted customized joint prosthesis, etc. His contributions have been honored with more than 30 prizes, including the Chinese National Invention Prize and the National Science and Technology Prize. He has been President of the World Chinese-Speaking Orthopedic Society and Asia-Pacific Arthroplasty Society, a Trustee of AO/ASIF Foundation and Vice President of the World Interdisciplinary Research Association on Biomaterials, as well as the Chair or Vice Chair of more than ten national academic associations. In 2002, Professor Dai was awarded *Doctorat Honoris Causa* of the Mediterranean University in Marseilles, with the approval of the French Ministry of Foreign Affairs and Ministry of Public Health, and in 2007, he was given the title of Raine Visiting Professor of University of Western Australia. Professor Dai is Academician of the Chinese Academy of Engineering.

DIERICKX, KRIS

Kris Dierickx is full Professor of Biomedical Ethics and a staff member of the Centre for Biomedical Ethics and Law, Faculty of Medicine, KU Leuven, Belgium. His research and publications focus on ethics in genetics, research ethics, regenerative medicine and biobanks. Professor Dierickx was also the coordinator of the European Commission-funded FP6 project named GeneBanC: Genetic bio and dataBanking: Confidentiality and protection of data: Towards a European harmonization and policy. He was and is a partner in several national and international research consortia, including EuroPHEN, GeneBanC, EuroCareCF, STEPS, Eurogentest and Disk Regeneration. Kris Dierickx is member of several ethics committees, editorial boards, and acts as an ethics reviewer for FP7 projects and European Research Council grants.

EGAMI, MIME

Mime Egami is Chief Medical Innovation Officer and Visiting Professor, Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University.

Professor Egami studied International Finance and Economy at Hitotsubashi University. Between 1984 and 2005 she worked in corporate finance at the Tokyo office of Citi Bank (Mergers and Acquisitions and Structured Finance), Prudential Securities (Director and Head of Global Funding), CIBC Wood Gundy (Executive Director of Financial Products Department) and then ABN AMRO Bank, Tokyo (Director and Head of Healthcare and Life Science Advisory). She has been Strategy Advisor at TUBERO (SCOE) and Visiting Professor at Tohoku University; and is now Visiting Professor at Tokyo Women's Medical University and Visiting Research Teacher at Waseda University in the Regulatory Science Doctor Program.

Professor Egami has served on the Ministry of Education, Culture, Sports, Science and Technology (MEXT) Science and Technology Academia Committee, the Japan Patent Office Regenerative Medicine Patent Committee, the Council of the Japan Society of Regenerative Medicine and the Policy Committee of Engineering Academy of Japan. She is Treasurer of the TERMIS-AP, and Japanese Chief Representative at the Regulatory Affairs Professionals' Society. She has received the Most Outstanding Researcher 2009 Award (Field of Project, Industry Alliance and International Research Collaboration) of the National Institute of Science and Technology Policy, MEXT; and the Innovation Coordinator Award, 2010, by Japan Science and Technology Agency.

EL HAJ, ALICIA

Alicia El Haj is Director of the Institute of Science and Technology in Medicine (ISTM) and Chair of Cell Engineering at Keele University, UK. She has been involved in bringing together interdisciplinary groups interested in aspects of cell and tissue engineering within biomedicine, physical sciences and engineering. She has been a founder Director of ISTM, which is rated highly in UK research assessments.

Professor El Haj is the Research Director of an Engineering and Physical Sciences research Council (EPSRC) Doctoral Training Centre in Regenerative Medicine, one of the Co-Directors of the new EPSRC Centre for Innovative Manufacturing Centre in Regenerative Medicine and a collaborator in the new Arthritis Research UK Tissue Engineering Centre. She has published over a hundred publications with an emphasis on engineering solutions for controlling stem cell behaviour and new orthopedic repair strategies using novel enabling technology approaches with funding from Engineering and Physical Sciences Research Council (EPSRC), Biotechnology and Biological Sciences Research Council (BBSRC), Welcome Trust, Arthritis Research UK and EU Framework Programs.

Professor El Haj is Chair of the European Council of TERMIS, a member of the UK National Stem Cell Advisory Board, the International Federation for Medical and Biological Engineering

(IFMBE) Working Group for Cellular Engineering, and the Institute of Physics and Engineering in Medicine (IPEM) Academic Advisory board. She is on the editorial board of the *Journal of Tissue Engineering and Regenerative Medicine (JTERM)* and *Tissue Engineering* and is currently serving as a member of the Medical Research Council's Developmental Pathway Funding Scheme (DPFS) Panel and the Higher Education Funding Council General Engineering 2014 Review Panel.

GU, XIAOSONG

Xiaosong Gu works as Director of the Jiangsu Key Laboratory of Neuroregeneration of Nantong University. He is Vice President of the Chinese Society for Anatomical Sciences (CSAS) and Director of the Regenerative Medicine Branch of CSAS. As a founding member of the World Society for Reconstructive Microsurgery, Dr. Gu focuses his research on the development and application of tissue engineered nerve, as well as molecular mechanisms underlining neural regeneration. So far, he has published over a hundred academic articles in SCI-indexed journals such as *Brain, Biomaterials, Progress in Neurobiology, Science* (supplement), *Nucleic Acids Research, Journal of Cell Science, Nature Cell Biology and Stem Cells*. As one of the main inventors, he has several Chinese patents and, in addition, international patents for his innovative research have been granted.

GULDBERG, ROBERT

Robert Guldberg is the Petit Director's Chair in Bioengineering and Bioscience; Executive Director, Parker H. Petit Institute for Bioengineering and Bioscience; and Professor, George W. Woodruff School of Mechanical Engineering, Georgia Institute of Technology, USA.

Dr. Guldberg received his degrees in Mechanical Engineering and Bioengineering from the University of Michigan. In 2009, he was appointed Executive Director of the Petit Institute for Bioengineering and Bioscience (IBB) at Georgia Tech after serving as Associate Director since 2004. Dr. Guldberg's research interests focus on musculoskeletal growth and development, functional regeneration following traumatic injury, and degenerative diseases, including skeletal fragility and osteoarthritis. His research is supported by the NIH, NSF, DoD, and several biotechnology companies and has resulted in over 160 book chapters and publications. Dr. Guldberg is a Fellow of the American Institute for Medical and Biological Engineering (AIMBE) and holds several national leadership positions, including Chair of the Americas Chapter of the Tissue Engineering and Regenerative Medicine International Society (TERMIS-AM).

HATA, KEN-ICHIRO

Ken-ichiro Hata was trained as an oral surgeon and is a specialist in the multidisciplinary treatment of jaw deformity and cleft palate and translational research to regenerative medicine. He worked at the Department of Oral Surgery, Nagoya University Graduate School of Medicine and contributed to basic and clinical researches on the reconstruction of intraoral tissues, using cultured oral mucosal cells, followed by the research and development of regenerative medicine on various tissues such as bone, peripheral nerve and cardiovascular system.

Dr. Hata left Nagoya University to engage in the research and development and management of a biotech company, J-TEC, focusing on the development of regenerative medicine in Japan. In 2009, J-TEC launched the first product of regenerative medicine in Japan, autologous cultured epidermis. In 2013, J-TEC launched another product, autologous cultured cartilage to use for the cartilage regeneration. Now J-TEC is working on the research and development of cultured corneal epithelium.

HOLLISTER, SCOTT

Scott Hollister is a Professor of Biomedical and Mechanical Engineering at the University of Michigan, in addition to being an Associate Professor of Surgery. He is a fellow of the American Institute of Medical and Biological Engineering (AIMBE). Dr. Hollister directs the Scaffold Tissue Engineering Group at the University of Michigan, whose research focuses on the computational design, fabrication and testing of biomaterial platform systems for tissue reconstruction. His work with Dr. Glenn Green on the design and 3D printing of a new splint device to save the life of a child with severe tracheobronchial malacia was recently published in the *New England Journal of Medicine* and received worldwide media coverage: *Today Show, CBS Morning News, USA Today, Associated Press, New York Times, National Public Radio, US News and World Report* and the *Guardian*. He is also a co-founder of the start-up company Tissue Regeneration Systems, which focuses on the development of resorbable devices for skeletal reconstruction.

HUBBELL, JEFFREY

Jeffrey Hubbell is Professor in the Institute of Bioengineering and the Institute of Chemical Sciences and Engineering of the Ecole Polytechnique Fédérale de Lausanne (EPFL). Prior to moving to Lausanne, he was on the faculty at the Swiss Federal Institute of Technology, Zurich and University of Zurich (Medical Faculty); at the California Institute of Technology; and at the University of Texas in Austin. He holds a BSc from Kansas State University and a PhD from Rice University; both degrees being in Chemical Engineering. He was elected to the US National Academy of Engineering in 2010.

Dr. Hubbell uses biomaterials and protein engineering approaches to investigate topics in regenerative medicine and immunotherapeutics. In regenerative medicine, he focuses on biomaterial matrices that mimic the extracellular matrix, and on growth factor–extracellular matrix interactions, working in a variety of animal models of regenerative medicine. In immunotherapeutics, he focuses on nanomaterials in vaccines that target lymphoid-resident antigen presenting cells and on protein engineering approaches to deliver antigen to the spleen and liver to inverse vaccines, to induce tolerance to protein drugs and in autoimmunity. His interests are both basic and translational, having founded or co-founded three biomedical companies based on his technology: Focal Inc., in Boston, acquired by Genzyme; Kuros Biosurgery AG, in Zurich, in the domain of regenerative medicine; and Anokion SA, in Lausanne, in the domain of immunological tolerance.

At EPFL, he founded the Institute of Bioengineering, which he has grown to a present team of approximately 30 professors appointed in the School of Life Sciences and the School of Engineering. He served as the Founding Director of the Center for Neuroprosthetics and he coordinates the Bertarelli Program in Translational Neuroscience and Neuroengineering. He is currently Dean *ad interim* of EPFL's School of Life Sciences.

JIN, YAN

Yan Jin graduated from the Fourth Military Medical University, Xi'an, China in 1985 and was awarded a PhD degree in 1991. He is the Professor and Director of the Tissue Engineering Center of the Fourth Military Medical University (FMMU). He was offered the position of Professorship of the Chang Jiang Scholars' Program and was awarded National Distinguished Young Scientists Grant of the National Natural Science Foundation of China. He is the Chief Scientist of 973 Project.

Professor Jin is a Council Member of the Asia-Pacific Chapter of TERMIS; Chair-Elect of the Tissue Engineering and Regenerative Medicine branch of the Chinese Society of Biomedical Engineering; Council President of the Chinese Collaborative Innovation Center of Tissue Engineering and Regenerative Medicine; Standing Committee Member of the Chinese Biomaterials Association; Vice Chair of the Chinese Society of Oral Pathology; and Vice Chair of the Chinese Society of Oral Biomedicine.

He has published 120 papers in various journals, for example, *Stem Cells, The Journal of Biological Chemistry, Biomaterials, Journal of Bone and Mineral Research, Journal of Control Release, Tissue Engineering* and so on. He has studied the development and regeneration of skin, tooth, cornea, bone and peripheral nerve, concentrating on mesenchymal stem cells and the use of multipotent stem cells with target inductive differentiation, trans-differentiation and application in tissue regeneration. His research group has successfully developed products of tissue engineering skin (including the first tissue engineering Chinese FDA-approved product in China), the cornea and other reparative medical products.

JOHNSON, PETER

Peter Johnson is a graduate of the University of Notre Dame and SUNY Upstate Medical University. After training in general and plastic surgery, Dr. Johnson practiced reconstructive surgery for ten years at the University of Pittsburgh, where he founded and was the first President of the Pittsburgh Tissue Engineering Initiative. Subsequent roles were co-founder/ Chief Executive Officer of Tissue Informatics; Executive Vice President of Life Sciences; Chief Medical Officer of Icoria; and Executive Vice President, Entegrion, Inc. He presently serves as the Vice President, Research and Development and Medical Affairs of Vancive Medical Technologies, an Avery Dennison business. He was Chair of the Plastic Surgery Research Council; President of the Pennsylvania Biotechnology Association and the Tissue Engineering Society, International; and is presently the Co-Editor-in-Chief of the three-part journal, *Tissue Engineering*. He serves on the Industry Committee of TERMIS, on the Board of Trustees of the Pittsburgh Tissue Engineering Initiative and on the University of North Carolina Medical Foundation. He serves as an Adjunct Professor of Business, Bioengineering and Surgery at the University of North Carolina at Chapel Hill, of Bioengineering at North Carolina State University and of Regenerative Medicine at Wake Forest University School of Medicine.

KAPLAN, DAVID

David Kaplan holds an Endowed Chair, the Stern Family Professor of Engineering, at Tufts University, USA. He is Professor and Chair of the Department of Biomedical Engineering and also holds faculty appointments in the School of Medicine, the School of Dental Medicine, Department of Chemistry and the Department of Chemical and Biological Engineering. His research focus is on biopolymer engineering to understand structure-function relationships, with an emphasis on studies related to self-assembly, biomaterials engineering and functional tissue engineering. He has published over five hundred papers and edited eight books. He directs the National Institutes of Health (NIH) P41 Tissue Engineering Resource Center (TERC) that involves Tufts University and Columbia University. He serves on the editorial boards of numerous journals and is Associate Editor for the journal *Biomacromolecules*. He has received a number of awards for teaching, was elected Fellow at the American Institute of Medical and Biological Engineering and received the Columbus Discovery Medal and Society for Biomaterials Clemson Award for contributions to the literature.

KATAOKA, KAZUNORI

Kazunori Kataoka is Professor of Biomaterials at the Graduate School of Engineering, University of Tokyo, Japan. Since 2004, he has been appointed to the joint positions of Professor (Graduate School of Medicine, University of Tokyo) and Chair (Division of Clinical Biotechnology, Center for Disease Biology and Integrative Medicine). He also serves as Director of the Center for NanoBio Integration at the University of Tokyo, an interdisciplinary initiative sponsored by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

Professor Kataoka received a BEng (1974) in Organic Chemistry, an MEng (1976) and a PhD (1979) in Polymer Chemistry from the University of Tokyo. He has held positions at the Institute of Biomedical Engineering, Tokyo Women's Medical College (1979–1989) and the Department of Materials Engineering at Tokyo University of Science (1989–1998) before joining the medical faculty at the University of Tokyo in 1998. He was a Visiting Professor at the University of Paris XIII, France (1992, 1996); Tohoku University, Sendai, Japan (2007); and Ludwig-Maximillians University (LMU), Munich, Germany (2008). He served as the Adjunct Director of the Biomaterials Center at the National Institute for Materials Science (NIMS), Japan from 2001–2004. Professor Kataoka is President of the Society of Polymer Science, Japan; Vice President of the Controlled Release Society; Fellow of the American Institute of Medical and Biological Engineering (AIMBE) and Fellow of Biomaterials Science and Engineering (FBSE).

He has received several awards, including the Award of the Japanese Society for Biomaterials; Outstanding Paper Award of the Controlled Release Society; Award of the Society of Polymer Science, Japan; Clemson Award in Basic Research, Society for Biomaterials, USA; Barre Award, University of Montreal; Founder's Award of Controlled Release Society; NIMS Award, National Institute of Materials Science, Japan; and the Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, Japan (MEXT). He has more than four hundred publications and is on the editorial board of twelve international journals. He is Editor of *Journal of Biomaterials Science, Polymer Edition,* Associate Editor of *Biomacromolecules (American Chemical Society),* and Associate Editor of *Biomaterials*. His current major research interests include supramolecular materials for nanobiotechnology and focusing on gene and drug delivery.

KELLATHUR, SRINIVASAN

Srinivasan Kellathur received a BSc in Biochemistry from the PSG College of Arts and Sciences, Coimbatore, India (1991); an MSc (1992) and an MPhil (1996) from the Annamalai University, Chidambaram, India; and a PhD from the Department of Anatomy/Biochemistry, National University of Singapore (2001). He was Postdoctoral Fellow, Venom and Toxin Research Program, Department of Anatomy, Faculty of Medicine, National University of Singapore (2001–2003), and then Postdoctoral Fellow, Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine and Division of Biomedical Sciences, Johns Hopkins, Singapore (2004–2006). He was a Senior Regulatory Specialist, Advanced Therapeutic Products Unit, Health Products Regulation Group, Health Sciences Authority (2007–March 2013); then becoming Head and Regulatory Consultant, Advanced Therapy Products Unit, Pre-marketing, Health Products Regulation Group, Health Sciences Authority.

As Team Leader, Cell and Tissue Therapy, he has been involved in the development of policies, guidelines, processes and framework for regulation of human cell- and tissue-based therapeutic products. The team comprises specialists from Pharmaceuticals and Biologics, Clinical Trials, Pharmacovigilance, GMP Audit and Compliance and Medical Devices Branch. He has been a member of HSA-MOH Cell and Tissue Therapy Workgroup, responsible for drafting guidelines for the regulation of cell and therapy products in Singapore.

KIM, TAE-GYUN

Tae-Gyun Kim is Deputy Director of the Cell and Gene Therapy Product Division in Korea Ministry of Food and Drug Safety (formerly KFDA). In 1996, he entered the KFDA and has been working in the field of review and regulation of advanced therapy products such as cell and gene therapy products and tissue engineered products. He received his PhD in medical biotechnology at the Korea University (completing a thesis on gene therapy) and had postdoctoral training in the Department of Anatomy at the University of Wisconsin-Madison, USA (2003–2005).

KIRKPATRICK, JAMES

James Kirkpatrick has a triple doctorate in science and medicine (MD, PhD, DSc) from the Queen's University of Belfast, Northern Ireland, UK and, since 1993, has been Professor of Pathology and Chair of the Institute of Pathology at the University Medical Center of the Johannes Gutenberg University in Mainz, Germany. Previous academic appointments were in pathology, at the University of Ulm, Manchester and the RWTH Aachen University, Germany.

His principal research interests are in biomaterials in tissue engineering and regenerative medicine, with a special focus on the development of human cell culture techniques, especially in co-culture systems in three dimensions. He is author/co-author of 430 articles in peer-reviewed journals and has made more than 1 230 presentations to scientific meetings worldwide. He is former President of both the German Society for Biomaterials (2001–2005) and the European Society for Biomaterials (2002–2007) He was presented with the George Winter Award of the European Society for Biomaterials (ESB) in 2008 and the Chapman Medal from the Institute of Materials, Minerals and Mining, London, UK in 2010. He is an Honorary Professor at the Peking Union Medical College in Beijing and the Sichuan University in Chengdu, China and a Visiting Professor at the South China University of Technology in Guangzhou and the Nanyang Technological University in Singapore.

He is a former Associate Editor of the *Journal of Pathology* (2001–2006) and a current Associate Editor of *Biomaterials* (since 2002) as well as a member of the editorial advisory boards of several journals in the biomaterials and regenerative medicine fields. He is a member of the scientific advisory boards of a number of research institutes, centers of excellence and companies in biomaterials and regenerative medicine in Europe, as well as the Medical Technology Committee, Federal Ministry of Education and Research in Germany and the German Federal Institute for Drugs and Medical Devices. He is a Fellow of Biomaterials Science and Engineering (FBSE) of the International Union of Societies for Biomaterials Science and Engineering (IUS-BSE) (1996), Fellow of European Alliance of Medical and Biological Engineering and Science (EAMBES) (2012), and Fellow of Tissue Engineering and Regenerative Medicine (FTERM) of the Tissue Engineering and Regenerative Medicine International Society (2012).

LEE, BUMSUP

Bumsup Lee is Vice President and Chief Technology Officer at Kolon Life Science, Inc. He has acquired his expertise in drug development for more than a decade through his previous tenures at biotech and pharmaceutical companies Mitokor, Syrrx and Takeda Pharmaceuticals in USA, where he advanced multiple drug candidates to clinical stages and commercialization in the areas of diabetes, arthritis and cancers. He obtained his BSc and MSc degrees at Seoul National University, Korea and his PhD from Iowa State University, USA. He was a postdoctoral fellow at State University of New York at Buffalo.

LEE, ENG HIN

Eng Hin Lee is Professor of Orthopedic Surgery at the National University of Singapore and the Program Leader of the NUS Tissue Engineering Program (NUSTEP). He also holds appointments as Senior Advisor, Division of Graduate Medical Studies, National University of Singapore; Emeritus Consultant in Orthopedic Surgery at the National University Hospital; and Senior Consultant in the Department of Orthopedic Surgery at KK Women's and Children's Hospital. He was a past Dean of the Faculty of Medicine, National University of Singapore. Dr. Lee received his medical and postgraduate medical training in Canada and specializes in pediatric orthopedics. He is known internationally for his research on stem cells and tissue engineering in the musculoskeletal system. His research has twice won him the Best Scientific Paper Award by the Pediatric Orthopedic Society of North America. He won the Outstanding Researcher Award from the National University of Singapore (2006) and the Outstanding Clinician Mentor Award from the Ministry of Health (2008). He was given the Lee Foundation/National Healthcare Group Lifetime Achievement Award (2008). He is a member of the editorial boards of several international refereed journals in orthopedic surgery and pediatric orthopedics and reviews regularly for high-impact journals in orthopedics, stem cells and tissue engineering. He has over 150 publications in refereed journals and over three hundred conference papers. He has co-authored a book entitled *Stem Cells: From Bench to Bedside,* which is used by many international centers as a reference and textbook for stem cell courses.

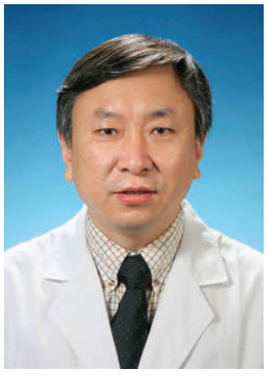
LI, XIAOGUANG

Xiaoguang Li graduated from Bethune Medical University in 1984. From 1991 to 1993, he studied in the University of Kyoto, Japan. His major research direction is the mechanism and clinical application of tissue engineering methods to repair nervous system injury, which includes the repair of brain injury, spinal cord injury, and peripheral nervous system injury. He has obtained the approval of the State Food and Drug Administration for clinical research on the use of spinal cord reconstruction tubes, the first of their kind in China. He is Professor at Capital Medical University School of Basic Medical Sciences and of the School of Biological Science and Medical Engineering, Beihang University, both in Beijing.

LIM, JEONG OK-GRACE

Grace Lim received her BSc in Korea, MSc in Polymers at Cornell University, a PhD in Polymer Science at the University of Massachusetts Lowell in 1993, and took a postdoctoral fellowship at Dr. Langer's laboratory at MIT and Harvard Medical School. She was Assistant Professor at the Wake Forest Institute for Regenerative Medicine (WFIRM) from 2004 to 2006. She was an affiliated faculty member of the Virginia Tech-Wake Forest University School of Biomedical Engineering and Sciences. Currently she is Professor at Kyungpook National University School of Medicine in Korea and Adjunct Professor at Wake Forest Institute of Regenerative Medicine. She has recently organized an international center; the Joint Institute for Regenerative Medicine.

Dr. Lim's interests are in research areas in biomedical applications of biomaterials, such as controlled drug delivery systems, tissue engineering, cell therapy, regenerative medicine and novel diagnostic system using cell chip technology.



LIU, WEI

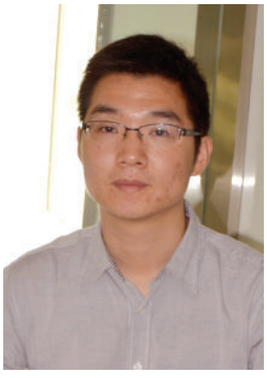
Wei Liu received his MD from Shanghai Second Medical University in 1983 and his PhD from University of Arkansas for Medical Science in 1998, followed by two years' postdoctoral training at New York University. He has been a plastic surgeon since 1983 and now is a full time researcher, after his return to China in 2000. Currently, he is a Professor of Plastic Surgery of Shanghai Jiao Tong University School of Medicine, Associate Director of Shanghai Tissue Engineering Center and Shanghai Institute of Plastic and Reconstructive Surgery and Associate Director of the National Tissue Engineering Center of China. Dr. Liu is the principal investigator of four national key projects of tissue engineering research sponsored by the Chinese Ministry of Science and Technology. He is a standing committee member of the Chinese Society of Biomaterials and the Chinese Society of Tissue Engineering. Dr. Liu is the author of more than a hundred original articles published in international journals and the contributor to several international tissue engineering text books. Dr. Liu is an editorial member of *Biomaterials*, Editor of *Emerging Issues* and Clinical Council Member of *Tissue Engineering*. He has presented more than 30 invited speeches at various international conferences, including TERMIS-AP and TERMIS-EU chapter meetings and TERMIS-World Congresses. Dr. Liu was the organizer of the 8th TESI Annual meeting and for the 2013 TERMIS-AP meeting, is a Member-at-Large of TERMIS-AP and a Member of the International Union of Societies of Biomaterials Science and Engineering (IUSBSE).

LU, SHIBI

Shibi Lu is Director of the Orthopedic Research Institute of the Chinese PLA General Hospital (301 Hospital), China. Professor Lu has practiced medicine, mostly in orthopedics, for more than 40 years. He was the first person to design and develop cemented and cementless prosthesis, which has been widely used in China for total joint replacement. He is also in charge of many national research projects, including the 863 Projects, National Natural Science Foundation of China, and projects of '8–5', '9–5', and '10–5'. In 1995, he won the National Award of the Guanghua Foundation for Science and Technology, and in 1996, he was awarded the Great Contribution of the First Award of China Military Science and Technology, and the Advanced Award of Ho Leung Ho Lee Foundation for Science and Technology, Hong Kong. In 2008, he was awarded Famous Generation Teacher by the General Logistics Department of PLA and named National Outstanding Communist Party Member. In 2010, he was given the honorary title of Exemplary Medical Expert by the Central Military Commission. The orthopedic research institute under his leadership was approved as the National Key Laboratory of China in 2002, the Key War Traumatic Laboratory of PLA in 2010 and Key Laboratory of Beijing in 2012. Professor Lu became an academician member of the Chinese Academy of Engineering in 1996.

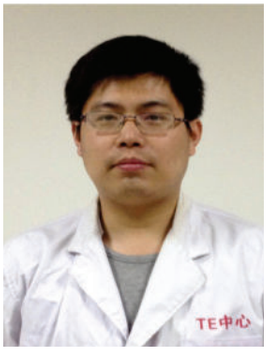
LU, SHI-JIANG

Shi-Jiang Lu is currently the Senior Director for Research, Advanced Cell Technology. Dr. Lu has more than 17 years of experience in stem cell research, focusing on specific differentiation of human embryonic stem cells and induced pluripotent stem cells toward mesoderm lineages including vascular and mesenchymal cells, and blood cells, especially red blood cells and megakaryocytes/platelets. Dr. Lu was the Senior Director of Stem Cell and Regenerative Medicine International, a joint venture between Advanced Cell Technology and Cha Biotech of Korea, and Director and Senior Scientist of Advanced Cell Technology. Prior to joining Advanced Cell Technology, Dr. Lu was Director of Stem Cell Research, Dept. of Pediatrics, University of Illinois at Chicago, where he led a team to investigate the hematopoietic differentiation of non-human primate rhesus and human embryonic stem cells. Dr. Lu received his BSc in Biochemistry from Wuhan University, Master of Medicine from Peking Union Medical College, MPH from Columbia University in New York and PhD in Molecular Biology from University of Toronto. He has more than 50 scientific publications.



LU, YONGBO

Yongbo Lu graduated from Sichuan University in 2009 and then joined Xi'an Institute of Tissue Engineering and Regenerative Medicine for skin tissue engineering research. He was offered the position of Senior Engineer in the Institute and placed in charge of the research and development of *in vitro* Skin Test Model, which has been well applied for cosmetic and chemical companies like Johnson & Johnson. He has published several scientific papers in journals such as *Biomaterials, Burns* and so on. He focuses on the interaction between dermal and epidermal cells. Dr. Lu has performed research on the change of skin homeostasis in the conditions of skin aging and disease. He has also performed studies on the reconstruction and establishment of *in vitro* models representing various *in vivo* conditions. A comprehensive testing platform was successfully established, providing testing of toxicological and skin efficacy endpoints.



LUO, HAILANG

Hailang Luo graduated from the Central South University in 2008 and then joined Xi'an Institute of Tissue Engineering and Regenerative Medicine for nerve and cornea tissue engineering research. He was offered the position of Senior Engineer in the Institute and placed in charge of the research and development of tissue engineered cornea, which has completed multi-center randomized clinical trials. He has focused on the construction and engineering of cornea and peripheral nerve tissue. Dr. Luo performed research on the application of mesenchymal stem cells in defect corneal and nerve tissue repair and regeneration. He performed studies on the preparation of tissue engineered peripheral nerve and corneal scaffold using various biomaterials. Some products prepared by him were successfully applied in the clinic in China.

MACCHIARINI, PAOLO

Paolo Macchiarini earned his medical degree at the Pisa University School of Medicine, Italy, in 1986. After completing postgraduate training in general surgery in Italy, he completed a two-year clinical fellowship at the University of Alabama at Birmingham, under the supervision of Dr. Richard McElvein and Dr. John Kirklin. Dr. Macchiarini then trained in general thoracic and vascular surgery, and heart-lung transplantation and research at the Centre Chirurgical Marie-Lannelongue (CCML) in Paris under the supervision of Professor Philippe Dartevelle. He was a consultant at the CCML until 1998, during which time he earned his PhD in organ and tissue transplantation at the Franche-Compte University in France. In 1999, Dr. Macchiarini became Chair of the Department of General Thoracic and Vascular Surgery at the Heidehaus Hospital, and Professor of Surgery at the Hannover Medical School in Germany. He then became Chair of the Department of General Thoracic Surgery at the Hospital Clinic in Barcelona, Spain. In 2010, he joined the Karolinska Institutet in Stockholm, Sweden, where he is currently Professor of Regenerative Surgery and Director of the European Airway Institute of Advanced Center of Translational Regenerative Medicine. Dr. Macchiarini's clinical interests include adult and pediatric surgery for complex tracheal, lung, esophageal and mediastinal diseases, as well as intrathoracic, non-cardiac transplantation (lung, heart-lung and airways). He has contributed to more than 150 articles in peer-reviewed journals and 40 book chapters. He has received numerous awards and is Visiting or Honorary Professor at several leading academic institutions worldwide. In 2008 in Barcelona, Dr. Macchiarini made transplant history by using stem cells to help achieve the world's first successful in-human transplantation of a tissue-engineered organ (windpipe) without immunosuppression. In 2011 in Stockholm, Dr. Macchiarini transplanted the world's first bio-artificial windpipe using a completely artificial, laboratory-made nanocomposite.

MARTIN, IVAN

Ivan Martin studied Biomedical Engineering at the University of Genova, Italy, where he obtained his PhD under the mentorship of Professor Ranieri Cancedda in 1996. After three years as a postdoctoral Associate in the group of Professor Robert Langer at the Harvard/MIT Division of Health Sciences and Technologies in Cambridge, Massachusetts, he joined the Departments of Surgery and Biomedicine at the University Hospital of Basel, Switzerland, as Director of the Tissue Engineering research group.

Ivan Martin's group includes scientists from the biological, engineering and clinical fields, dedicated to develop a solid scientific basis for innovative translational strategies in regenerative medicine. His findings have advanced understanding on how to control the differentiation of mesenchymal cells towards functional tissue development and have pioneered innovative bioreactor-based strategies to streamline manufacturing of cell-based grafts. He is author of more than 150 peer-reviewed papers published in international journals and inventor on over ten patent applications. The developments in science and technology have been translated into the establishment of three clinical trials in the field of cell-based cartilage and bone repair – which are currently ongoing at the University Hospital Basel – and into the founding of a spin-out company from his group, Cellec Biotek AG, for which he is President of the Board of Directors.

Ivan Martin has been a member of the Executive Editorial Board of the journal *Tissue Engineering*; is currently part of the editorial boards of five international journals, including the top-ranked *Biomaterials;* and sits on the review panels of prestigious organizations (for example, the European Research Council and the Research Review Commission of the AO Foundation). In 2012, the TERMIS Governing Board awarded him the title of Founding Fellow for his 'formative role in shaping the tissue engineering and regenerative medicine field and TERMIS'.

MCLEAN, KEITH

Keith McLean obtained a PhD from the University of Aberdeen, Scotland, and is currently the Theme Leader for Biomedical Materials and Devices in the Commonwealth Scientific and Industrial Research Organization's (CSIRO) Division of Materials Science and Engineering and an Adjunct Professor at Monash University's Australian Regenerative Medicine Institute. He leads a 75-member team of polymer, protein and surface chemists and biologists developing materials for tissue engineering, stem cell propagation and medical device applications. Over the past 20 years the Biomedical Materials Group within CSIRO has developed biomaterials in pre-clinical, clinical or commercial application, including: Ciba Vision's extended wear contact lens; biostable and biodegradable polyurethanes (Aortech Biomaterials (Pty) Ltd and Polynovo Biomaterials (Pty) Ltd); and drug delivery materials (Polyactiva (Pty) Ltd). Dr. McLean is Past President of the Australasian Society for Biomaterials and Tissue Engineering (ASBTE) and is currently Secretary to the International Union of Societies of Biomaterials Science and Engineering.

NAKAMURA, NORIMASA

Norimasa Nakamura is Professor of the Institute for Medical Science in Sports at Osaka Health Science University and the Center for the Advanced Medical Engineering and Informatics at Osaka University. He is an orthopedic surgeon at the Osaka University Hospital, Osaka, Japan, specializing in arthroscopic surgery. He received his MD at the Osaka University in 1988, completed a specialization in orthopedics in 1992, and received a PhD in 1994. In 1995, he became Assistant Professor of Orthopedics at the Osaka University and in 2009 he moved to his current position. Norimasa Nakamura's research has been focused on joint tissue repair, with the main focus on the regeneration of cartilage, ligament, and meniscus with stem cells. Currently, the main interest is the development of three-dimensional osteochondral bio-implant, using pluripotent stem cells in combination with biomaterials, in collaboration with the Center for iPS Cell Research and Application, Kyoto University, and the Division of Tissue Engineering, University of Tokyo. Norimasa Nakamura serves as the Vice President of the International Cartilage Repair Society (ICRS) and also as the Chair of the Scientific Committee of the International Society of Arthroscopy, Knee, and Orthopedic Sports Medicine (ISAKOS).

NAUGHTON, GAIL

Gail Naughton founded Histogen, Inc., a regenerative medicine company, in 2007, and serves as its Chief Executive Officer and Chair of the Board. She was the founder of Advanced Tissue Sciences Inc. and has spent more than 25 years extensively researching the tissue engineering process; holds more than 95 US and foreign patents; and has been extensively published in the field. She served as Dean for the College of Business Administration at San Diego State University from 2002–2011. In 2000, Dr. Naughton received the National Inventor of the Year Award from the Intellectual Property Owners' Association, in honor of her pioneering work in tissue engineering.

NOBERT, KARL

Karl Nobert is a Food and Drug Regulatory Attorney with Squire Sanders (US) LLP in Washington, DC. His legal practice focuses on the US Food and Drug Administration's regulation of prescription and over-the-counter drug products; biologics, including cellular and tissue products; medical devices; and veterinary products. He has considerable experience working with clients on the design and adoption of FDA regulatory strategies covering the manufacturing, marketing and sale of both human and veterinary regenerative products. He frequently writes and presents on these topics.

O'DONNELL, PEGGY

Peggy O'Donnell is Managing Partner of Morgan and Masterson, a consulting firm that focuses on global healthcare issues, providing scientific support for top-level corporate strategic decisions relating to new medical technologies, product liability and risk management and health economics; particularly in the areas of biomaterials, medical devices, tissue engineering and regenerative medicine.

A dual national of the US and Belgium, Ms O'Donnell lived and worked in Europe for 25 years, specializing in the representation of multinationals, event organization and medical information science. She holds a BA from Boston College and Master's Degree in Library and Information Sciences from the University of Wales, Aberystwyth. She was Director of European Operations for Regulatory Affairs Professionals Society (RAPS), a non-profit American organization involved in continuing education of healthcare industry professionals, and set up its first overseas operation. This included the establishment of a Brussels representative office, the development and implementation of core curricula, the organization of symposia and conferences, as well as the production of relevant publications. She worked extensively with the American Chamber of Commerce in the European Union, as well as national chambers. She has served as Managing Editor of *Biomaterials*, the pre-eminent journal in the field of Materials Science, since 2001.

OKANO, TERUO

Teruo Okano obtained his BSc in Applied Chemistry in 1974, an MSc in Polymer Chemistry in 1976 and his PhD in 1979, all at Waseda University, Tokyo, Japan. From 1994 to 2000 he was Professor, Institute of Biomedical Engineering at Tokyo Women's Medical University. He is currently Vice President and Professor, Tokyo Women's Medical University; and Director, Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University. Since 1994, he has been Adjunct Professor in the Department of Pharmaceutics and Center for Controlled Chemical Delivery, University of Utah, USA.

Professor Okano is currently President, Japanese Society for Regenerative Medicine and has been President, Japanese Society for Drug Delivery System; President, Tissue Engineering and Regenerative Medicine International Society (Asia-Pacific); President, Japanese Society for Biomaterials; Board of Governors, Controlled Release Society; and Board Member, Japanese Society for Biomaterials.

Professor Okano has research interests in microdomain structured polymers, stimuli-responsive polymers, hydrogels, polymeric micelles, modulated drug release, targetable drug carriers, blood compatible polymers, cell engineering, tissue engineering and artificial organs. In recognition of his research, he has been made Fellow, Tissue Engineering and Regenerative Medicine International Society and Fellow, Controlled Release Society. He is Fellow, International Union of Societies for Biomaterials Science and Engineering, Fellow, American Institute of Medical and Biological Engineering, and Fellow, Science Council of Japan. He has received the Founders Award of the Controlled Release Society and the Yamazaki-Teiichi Prize and has been awarded the Emperor's Medal with Purple Ribbon (National Meritorious Achievement Award) and the Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology.

ORLANDO, GIUSEPPE

Giuseppe Orlando is a transplant surgeon scientist, specializing in kidney and pancreas transplantation, as well as abdominal organ bioengineering and regeneration. Dr. Orlando is currently Assistant Professor in Surgery and Attending Transplant Surgeon at the Wake Forest University School of Medicine in Winston-Salem, USA. In addition, he has a joint appointment at the Wake Forest Institute of Regenerative Medicine and is a Marie Curie Fellow.

Dr. Orlando's main fields of investigation are: renal, endocrine pancreas, and small bowel bioengineering; the regenerative medicine approach to clinical tolerance; biomarkers of kidney repair and regeneration; and minimal immunosuppression and clinical operational tolerance after abdominal organ transplantations. His main achievements have been in the fields of steroid-free immunosuppression, immunosuppression minimization, clinical tolerance after liver transplantation, and the development of platforms for renal bioengineering and regeneration research. The main goals of the investigations during the years to come are to bioengineer and implant into humans renal organoids that are able to exert the proper physiological renal function, as well as insulin-producing cells to treat diabetes. The ability to produce kidneys or insulin-producing cells from patient's own cells will enable us to address the two most urgent needs in organ transplantation, namely, a new inexhaustible source of organs and immunosuppression-free transplantation. This will revolutionize transplant medicine.

Dr. Orlando has been involved in clinical and basic science research and is an author and co-author of more than 140 research papers, review articles, books and book chapters. He has been a member of numerous transplant-oriented societies and is on the editorial boards of a number of relevant journals, as well as acting as a regular reviewer for them.

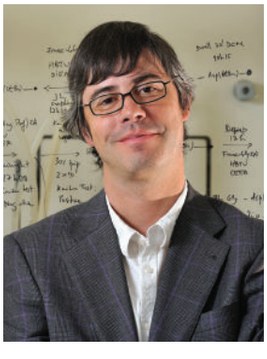
PILEGGI, ANTONELLO

Antonello Pileggi is a physician-scientist and academic with experience in multi-disciplinary basic, translational and clinical research. He is Associate Professor at the Division of Cellular Transplantation of the Department of Surgery (primary), and the Departments of Microbiology and Immunology, and Biomedical Engineering at the University of Miami. Since 2003, he is Director of the Preclinical Cell Processing and Translational Models Program at the Cell Transplant Center of the Diabetes Research Institute.

Dr. Pileggi received his MD and PhD degrees from the University of Pavia Medical School in Italy. Focusing primarily on the restoration of beta-cell function in insulin-requiring diabetes and transplant immunobiology, he is a strong advocate of effective collaborative research, bridging multiple scientific disciplines to foster synergy and acceleration of innovative, patient-focused biomedical research. He is co-inventor for innovative biomedical approaches, and a co-founder and Advisory Board Member of two spinoff biotech companies at the University of Miami (Converge Biotech, Inc. and NEVA Scientific, LLC).

Dr. Pileggi is member of several international professional organizations, including the American Diabetes Association, the American Society of Transplant Surgeons, the Association for Academic Surgery, the Cell Transplantation Society, the International Pancreas and Islet Transplantation Association, the International Xenotransplantation Association, the Transplantation Society and the Cure Alliance. He is a member of the University of Miami's Embryonic Stem Cell Research Oversight Committee. He served as Reviewer for the National Institute of Health, USA, the American Diabetes Association, the Italian Republic's Ministry of Health, Diabetes UK, the Biomedical Research Council and the National Medical Research Council, Singapore.

Dr. Pileggi has authored twenty scientific book chapters/monographs and over three hundred peer-reviewed scientific publications in the field of diabetes, transplantation immunobiology and regenerative medicine. His research has been funded by National Institute of Health, Juvenile Diabetes Research Foundation, Helmsley Charitable Trust, American Diabetes Association, Diabetes Research Institute Foundation, University of Miami and industry.



REIS, RUI

Rui Reis is both the Director of the 3B's Research Group and of the ICVS/3B's PT Government Associate Laboratory at the University of Minho, Portugal. He is also the Chief Executive Officer of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine and the President and Chief Scientific Officer of the company Stemmatters. He is an elected member of the General Council of the University of Minho. In addition, he is the Global President-Elect of TERMIS and the Editor-in-Chief of the *Journal of Tissue Engineering and Regenerative Medicine*.

He is the co-author of 708 Information Sciences Institute listed publications, around two hundred book chapters, 25 patents and six books. He is Principal Investigator of many projects, including the European Research Council (ERC) Advanced Grant. He has been awarded several major national and international scientific and innovation awards, including both the Jean Leray and George Winter Awards from the European Society for Biomaterials (ESB). He was also awarded an *Honoris Causa* degree by the University of Granada, Spain.

RUSSELL, ALAN

Alan Russell obtained his PhD in Biological Chemistry, 1987, from the Imperial College of Science and Technology, University of London. He was Distinguished University Professor of Surgery and the Founding Director of the McGowan Institute for Regenerative Medicine at the University of Pittsburgh, with positions as Professor in the departments of Bioengineering, Chemical Engineering and Rehabilitation Science and Technology. In addition, Dr. Russell was the Executive Director of the Pittsburgh Tissue Engineering Initiative, Inc.

Since 2012, he has been the Highmark Distinguished Career Professor at Carnegie-Mellon University, Pittsburgh, with appointments in the Institute of Complex Engineered Systems and in the Department of Biomedical Engineering. His emphasis is on a disruptive health technology initiative, increasing the simplicity, affordability, and accessibility of healthcare through science and engineering. He has founded three biotechnology companies: ICX Agentase LLC, NanoSembly LLC and O2Cyte LLC; and was also the Founding President of the Tissue Engineering and Regenerative Medicine International Society.

Within the scientific community, Dr. Russell has participated on 24 advisory boards. Since the outset of his career, he has received numerous prestigious awards for his contributions to research, teaching and public service. These awards include: R&D 100 Award (*R&D Magazine*); three Carnegie Science Center Awards for Excellence; the Gilbreth lectureship from the National Academy of Engineering; the Cockroft Rutherford lectureship from the University of Manchester (2007); the Outstanding Alumnus Award from the University of Manchester; and the American Chemical Society's Pittsburgh Award. He was number 32 on the *Rolling Stone*'s list of 'Top 100 People who are Changing America' in 2009. He has contributed significantly to the interface between the fields of chemistry, biology and material science. He has given more than 250 national and international invited lectures; has published over 140 articles in refereed journals, one book and ten book chapters; and holds 14 patents, with 23 additional pending patents. Dr. Russell served as Chair of the College of Fellows for the American Institute for Medical and Biological Engineering for 2012 and is a current member of the FDA's Science Board. He is the Editor of the new journal *Disruptive Science and Technology*.

RUSSELL, JOHN

John Russell is Senior Founding Partner, Managing Director and Senior Strategic Advisor of North Head Communications Inc, based in Beijing, China. He has over 25 years' experience in public relations, public affairs and government relations, covering four continents. Prior to establishing North Head, he was Executive Vice President, Asia Pacific, at Weber Shandwick. Before moving to China, he was Chief Executive Officer of Weber Shandwick's operations in Brussels; before which he was Executive Director of the American Chamber of Commerce to the European Union. He has operated at the highest level of corporate and government public affairs matters, for example, advising the Japanese Ministry of Foreign Affairs on their chairing of the G8. He is on the Advisory Board of the Chinese International Business Leader's Forum at Remnin University, Beijing and is a board member of *PublicAffairsAsia*.

SATO, YOJI

Yoji Sato is Head of the Division of Cellular and Gene Therapy Products, National Institute of Health Sciences at Tokyo, and an Adjunct Professor of the Department of Quality Assurance Science for Pharmaceuticals, Graduate School of Pharmaceutical Sciences, Nagoya City University. Dr. Sato is also a Guest Professor of the Graduate School of Pharmaceutical Sciences, Osaka University. He is an alumnus of the University of Tokyo and received his PhD in Pharmaceutical Science (Toxicology and Pharmacology) from the University of Tokyo in 1995. While a post-doctoral fellow at the University of Cincinnati College of Medicine, he succeeded in establishing a variety of useful transgenic animal models to elucidate mechanisms of cardiac excitation-contraction coupling and heart failure. His current research is in the field of regulatory science for the evaluation of quality and safety of cellular and gene therapy products. His research team develops *in vitro*/*in vivo* methods highly sensitive in detecting residual undifferentiated/tumorigenic cells in cellular therapy products, especially critical for the clinical use of those derived from ES/iPS cells. Since 2011, Dr. Sato has been serving as a member of technical committees; Panel on Science and Technology; Health Science Council; and the Ministry of Health, Labor and Welfare.

SHOICHET, MOLLY

Molly Shoichet received her BSc from the Massachusetts Institute of Technology in Chemistry (1987) and her PhD from the University of Massachusetts, Amherst in Polymer Science and Engineering (1992). She now holds the Tier 1 Canada Research Chair in Tissue Engineering and is Professor of Chemical Engineering and Applied Chemistry, Chemistry and Biomaterials and Biomedical Engineering at the University of Toronto. Dr. Shoichet has published over 450 papers, patents and abstracts and has given over 275 lectures worldwide. She currently leads a laboratory of 25 researchers and has graduated 115 researchers over the past 18 years. She founded two spin-off companies from research in her laboratory and is actively engaged in translational research. Dr. Shoichet is the only person to be a Fellow of Canada's three National Academies: the Canadian Academy of Sciences of the Royal Society of Canada, the Canadian Academy of Engineering and the Canadian Academy of Health Sciences. She is the recipient of many prestigious distinctions, including: the Canada Council for the Arts' Killam Research Fellowship; Natural Sciences and Engineering Research Council of Canada's (NSERC) Steacie Fellowship; Young Explorer's Award (to the top 20 scientists under 40 years old in Canada); Canada's Top 40 under 40™; the Society for Biomaterials' Clemson Award; and International Fellows of Tissue Engineering and Regenerative Medicine. In 2011, Dr. Shoichet was appointed to the Order of Ontario, Ontario's highest honour, and recognized as a Fellow of the American Association for the Advancement of Science. In 2013, Dr. Shoichet's contributions to Canada's innovation agenda and the advancement of knowledge were recognized with the QEII Diamond Jubilee Award. Before being recruited to the University of Toronto in 1995, Dr. Shoichet worked at CytoTherapeutics Inc. on encapsulated cell therapy.

SPENCER, STUART

Stuart Spencer is Executive Editor of *The Lancet*. He joined T*he Lancet* in 1999 and throughout his time there has led the Fast Track team that aims to select, review and publish prestigious manuscripts within four weeks of receipt. Although dealing with all areas of research, he deals with most of the cardiology submissions.

Prior to joining *The Lancet* he was a successful researcher for 25 years. His research resulted in many papers on topics ranging from fetal growth to neuroendocrinology and from immunology to molecular biology, and he has also published a number of papers on bioethics. Stuart started research at the Brompton Hospital, London, looking at spinal curvature in children, before moving to the Veterinary School site at Bristol University. During this period he was invited to work on secondment in The Netherlands for a year, setting up a research unit. Later, he spent a year in Switzerland to set up a research team for a major pharmaceutical company. He then spent nine years as Senior Researcher in New Zealand. He has also had two senior research fellowships at Leuven University, Belgium, and visiting professorships at King's College, London and Hong Kong University.

STUPP, SAMUEL

Samuel Stupp obtained his BSc in Chemistry at the University of California at Los Angeles, and his PhD in Materials Science from Northwestern University. He spent 18 years at the University of Illinois at Urbana-Champaign, where he was the Swanlund Professor of Materials Science, Chemistry and Bioengineering. In 1999, he joined the faculty at Northwestern as Board of Trustees Professor of Materials Science, Chemistry, and Medicine, and later was appointed Director of Northwestern's Institute for BioNanotechnology in Medicine. He is Director, Louis A Simpson and Kimberly K Querrey Center for Regenerative Nanomedicine at Northwestern University.

Professor Stupp is a member of the National Academy of Engineering, the American Academy of Arts and Sciences, and the Spanish Royal Academy. He is also a Fellow of the American Physical Society, the Materials Research Society, the American Association for the Advancement of Science, the World Technology Network and the World Biomaterials

Congress. His awards include: the Department of Energy Prize for Outstanding Achievement in Materials Chemistry; Humboldt Senior Award; the Materials Research Society Medal Award; the American Chemical Society Award in Polymer Chemistry; the Sir Edward Youde Memorial Award in Hong Kong; and the American Chemical Society Ronald Breslow Award for Achievement in Biomimetic Chemistry. He has held the appointments of Joliot Curie Professor at Ecole Supérieure de Physique et de Chemie in Paris, Merck-Karl Pfister Visiting Professor in Organic Chemistry at MIT and Visiting Professor at the Institut de Science et d'Ingenierie Supramoléculaires in Strasbourg; and is currently Distinguished Professor of Eindhoven University of Technology in the Netherlands. He also received an honorary doctorate from Eindhoven University for revolutionary research in complex molecular systems and, in 2011, an honorary doctorate from the National University of Costa Rica. His research is focused on self-assembly and supramolecular materials for regenerative medicine and energy.

STURM, MARIAN

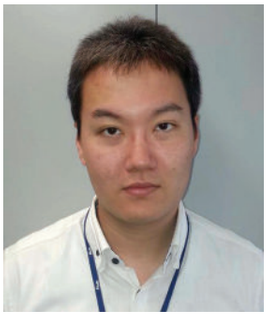
Marian Sturm has worked for the Australian public health sector for more than 30 years, both in a research capacity and in the manufacture of clinical products for transplantation. She is currently Principal Scientist of the Ray & Bill Dobney Cell and Tissue Therapies WA (CTTWA) facility at Royal Perth Hospital in Perth, Western Australia; Adjunct Senior Lecturer with the Department of Pathology and Laboratory Medicine, University of Western Australia; and Member the Therapeutic Goods Administration (TGA) Advisory Committee on Biologicals. She manages CTTWA, a TGA-licensed manufacturing facility producing a range of biotherapeutic products, and is actively involved in the development of emerging biotherapies and their translation to the clinical setting. Her main research interest is in bone marrow-derived mesenchymal stromal cells and she is involved in many clinical trials using this cell therapy. She is an active committee member of a number of relevant associations.

SUNG, HSING-WEN

Hsing-Wen Sung is Tsing Hua Chair Professor, Department of Chemical Engineering and Deputy Dean, Research and Development Office at National Tsing Hua University. He received his PhD from Biomedical Engineering Center, Georgia Institute of Technology in 1988. His research interests are nanobiomaterials, nanomedicine, drug/gene delivery, and tissue engineering. Professor Sung has received numerous awards, such as Fellow of American Institute for Medical and Biological Engineering, Fellow of International Union of Societies for Biomaterials Science and Engineering, Ho Chin Tui Outstanding Research Award, National Science Council Outstanding Research Award and Professor Tsai-The Lai Award. He has published 210 scientific papers and received 55 international patents.

TABATA, YASUHIKO

Yasuhiko Tabata is the Professor and Chair of the Department of Biomaterials at the Institute for Frontier Medical Sciences, Kyoto University and serves as Adjunctive Professor at 14 different universities. He received his BD in Polymer Chemistry (1981), PhD in Technology (1988), DMedSc (2002), and DPharm (2003); all at Kyoto University. Amongst the awards he has received are: the Young Investigator Award (1990); the Scientific Award from the Japanese Society for Biomaterials (2002) and the Scientific Award from the Japan Society of Drug Delivery Systems (2011). He has published 1 080 scientific papers, including 120 book chapters and review articles, and has 130 patents. Dr. Tabata is the Board Governor of five Japanese Academic Societies and is Associate Member of the Science Council of Japan, Cabinet Office and serves on the editorial boards of seven scientific journals. Specific research interests include biomaterials, drug delivery system (DDS), tissue engineering, stem cell technology, and medical diagnostics.



TAKEKITA, KAZUHIRO

Kazuhiro Takekita received a Master's degree from the Nara Institute of Science and Technology, Japan, and joined Osaka University Graduate School of Medicine as Research Fellow (2005–2007). He joined the Pharmaceuticals and Medical Devices Agency (PMDA) in 2008 and was assigned to the Office of Biologics II. He was seconded as an officer of the Research and Development Division, Ministry of Health, Labor and Welfare, and was the Secretary for the Review Board for Clinical Research and Translational Research Grants (April 2010–June 2011). He was assigned to the Office of Biologics II in PMDA in the beginning of July, 2011 and is currently a Reviewer in the Office of Cellular and Tissue-Based Products.

TODA, YUZO

Yuzo Toda received a MSc degree in the Graduate School of Engineering from Chiba University, Japan in 1973. He has worked for over 20 years in the Fujifilm Corporation, including positions as Corporate Vice President and General Manager, Life Sciences Products Division; then Director, Senior Vice President of the Pharmaceutical Products Division and, from 2013, Senior Vice President of Regenerative Medicine. He is Director of Fujifilm Kyowa Biologics Co. Ltd and is Chair of the Forum for Innovative Regenerative Medicine, Japan.

TROUNSON, ALAN

Alan Trounson led a team to discover human embryonic stem cells and directed their differentiation into nerve and other tissue cells, with the results being published in 2000. He was appointed Director of the Monash Centre for Early Human Development (1985–2002) and founding Deputy Director/Director of the Institute for Reproductive Biology (1990–2002). He founded the first Australian Biotechnology Centre of Excellence, Australian Stem Cell Centre, in 2003 and was the founding Chief Executive Officer. He established the Monash Immunology and Stem Cell Laboratories (MISCL) (2004–2007). In January 2008 he was appointed President of the California Institute for Regenerative Medicine (CIRM), responsible for the management of the US$ 3 billion fund for stem cell research in California. He has overseen the extraordinary development of basic science, which has led to more than 1 000 publications in peer-reviewed journals in the four years of his tenure as President. These studies are revolutionizing the development and clinical applications of stem cell science.

TUAN, ROCKY

Rocky Tuan received his PhD in 1977 from the Rockefeller University in New York. His postdoctoral research fellowship was at Harvard Medical School in Boston; first in the Department of Orthopedic Surgery at the Children's Hospital, and then in the Developmental Biology Laboratory at the Massachusetts General Hospital. In 1980, Dr. Tuan was appointed as Assistant Professor in the Department of Biology, University of Pennsylvania in Philadelphia, and was promoted to Associate Professor in 1986. In 1988, Dr. Tuan joined Thomas Jefferson University, Philadelphia, as Professor and Vice Chair in the Department of Orthopedic Surgery; with a joint appointment in the Department of Biochemistry and Molecular Biology. From 1992–1995, Dr. Tuan was the Academic Director of the MD/PhD program at Jefferson, and, in 1997, he established the USA's first cell and tissue engineering PhD program at Jefferson, with the mission of training the next generation of 'cross-cultural' biomedical scientists committed to regenerative medicine and the development of functional tissue substitutes.

In 2001, Dr. Tuan joined the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Health, as Chief of the newly created Cartilage Biology and Orthopedics Branch. In 2004, Dr. Tuan received the Marshall Urist Award for Excellence in Tissue Regeneration Research of the Orthopedic Research Society. In 2009, Dr. Tuan was recruited by the University of Pittsburgh School of Medicine to be the Founding Director of the Center for Cellular and Molecular Engineering, and as Arthur

J Rooney, Senior Professor and Executive Vice Chair of the Department of Orthopedic Surgery, with a joint appointment as Professor in the Department of Bioengineering. Dr. Tuan is currently Co-Director of the Wake Forest University/University of Pittsburgh Consortium of the Armed Forces Institute of Regenerative Medicine, a multi-institutional consortium, funded by the Department of Defense, focused on developing regenerative therapies for battlefield injuries. He is also Associate Director of the McGowan Institute for Regenerative Medicine and Founding Director of the Center for Military Medicine; both at the University of Pittsburgh.

Dr. Tuan has published over four hundred research papers, has lectured extensively, and is currently Editor of the developmental biology journal, *Birth Defects Research Part C: Embryo Today* and the Founding Editor-in-Chief of *Stem Cell Research and Therapy*. Dr. Tuan directs a multidisciplinary research program that focuses on orthopedic research as a study of the biological activities that are important for the development, growth, function and health of musculoskeletal tissues, and the utilization of this knowledge to develop technologies that will regenerate and/or restore function to diseased and damaged skeletal tissues.

WILLIAMS, DAVID

David Williams was trained as a metallurgist, at the University of Birmingham, UK; receiving degrees of BSc, PhD and DSc. When Professor Williams started his career in 1967, at the University of Liverpool, there were few biomaterials in clinical use. He worked alongside the pioneers in implant surgery, and wrote the first monograph on this subject in 1973. He developed systems to explore biocompatibility, polymer biodegradation, physiological metallic corrosion and the role of the immune response. He has received major awards of all biomaterials-based societies, and is a Fellow of the Royal Academy of Engineering. In 2012 he received the Gold Medal of the Acta Biomaterialia Group. In Liverpool he established the Department of Clinical Engineering and became Senior Pro Vice Chancellor of the University and Director of the Liverpool-Manchester UK Center for Tissue Engineering and Scientific Director of the EU STEPS program. He left the UK in 2007 and has positions in several countries, principally at the Wake Forest Institute of Regenerative Medicine in the USA, with Visiting Professorships in China, Australia, South Africa and Singapore. His recent publications on the nature of biomaterials and the mechanisms of biocompatibility are already seen as seminal works. His primary focus in recent years has involved his role as Editor-in-Chief of the journal *Biomaterials*, which he has taken to the top position in the world's journals. In the pursuit of the globalization of excellence in biomaterials research, he has been elected to the position of President of TERMIS. He has just finished a single-author book, *Essential Biomaterials Science,* to be published by Cambridge University Press. He is also Founding Director and Chair of a new South African company Strait Access Technologies (Pty) Ltd (SAT), where, working with co-founder Professor Peter Zilla, a new technology for the treatment of young individuals suffering from rheumatic heart disease is being developed.

YAMATO, MASAYUKI

Masayuki Yamato was originally trained with a background in cell biology and biochemistry. Over the past decade, his research interests have been focused on the regeneration of various tissues and organs, such as the cornea, using cell sheets, instead of traditional tissue engineering approaches using cells seeded into biodegradable scaffolds. In particular, his work with both corneal and oral mucosal epithelial cell sheets has already been applied to human patients suffering from ocular surface dysfunctions. Presently, he is engaged in research collaborations with doctors from various medical departments, such as ophthalmology, cardiology, gastroenterology, urology, and thoracic surgery; with the aim of taking regenerative medicine using cell sheets from the level of basic laboratory science including stem cell biology, biomaterials and nanobiotechnology to clinical applications.

Dr. Yamato has received several awards from the Japanese Society for Artificial Organs, the Japanese Society for Biomaterials and the US Society for Biomaterials. In 2009 he received the Yamazaki Teiichi Award and in 2010 the Society Award of the Japanese Society for Biomaterials. He is a Board Member of the Japanese Society for Biomaterials and the Japanese Society for Regenerative Medicine. He is on the editorial boards of several international journals.

YASHIRO, YOSHIMI

Yoshimi Yashiro is an Associate Professor in the Uehiro Research Division of the Center for iPS Cell Research and Application, Kyoto University. He earned a PhD in Medical Science from the University of Tokyo in 2009. He was originally trained with a background in stem cell biology. He has researched the anti-aging system of the hematopoietic stem cell under Professor Hiromitsu Nakauchi at graduate school. Dr. Yashiro started his academic career in 2009 at the Keio University and then at the Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University and he moved to Kyoto University in 2013. After he had finished graduate school, his research interests have focused on the ethics and social acceptance of stem cell science and regenerative medicine. He has been a member of the Ethics Committee of the Japanese Society for Regenerative Medicine from 2010 to 2013.

ZHANG, YONGJIE

Yongjie Zhang graduated from the Fourth Military Medical University in 1996 and was awarded his PhD in 2006. He is Vice Director of Tissue Engineering Center of 4th Military Medical University (FMMU). As a senior engineer, he participated in researching, developing production processes, clinical testing, submitting for signature and industrialization work of Tissue Engineered Skin, which is the first tissue engineered product in China. He has published several scientific papers in relevant journals, such as *Biomaterials*, *Journal of Tissue Engineering* and so on. His research focuses on tissue regeneration, especially for tissue engineered skin and peripheral nerve. He has accumulated rich experience in researching, developing and industrialization of tissue engineered skin. He also successfully developed the tissue engineered nerve to repair peripheral nerve defect.

ZHANG, XINGDONG

Xingdong Zhang is Professor at the National Engineering Research Center for Biomaterials, Sichuan University; President of the Chinese Society for Biomaterials; and a member of the Chinese Academy of Engineering. He is Director of both the National Technical Committee on Dental Materials and Devices of Standardization Administration of China and the National Technical Committee on Biological Evaluation on Medical Device of Standardization Administration of China. Professor Zhang has initiated and organized over 20 international biomaterials conferences, such as Asian Symposium on Biomaterials and China-European Symposium on Biomaterials. He is a Council Member of Tissue Engineering and Regenerative Medicine International Society, Asia-Pacific Region. He was President of the International Society for Ceramics in Medicine and a member of the international advisory committee of IUSBSE. Professor Zhang was also President of the 9th World Biomaterials Congress held in Chengdu in 2012.

Professor Zhang's research focuses on biomaterials and tissue engineering for the musculoskeletal system. He is the author of over four hundred journal articles, the inventor of 17 Chinese patents, and has edited and co-edited 12 books. He has won numerous awards, including Science and Technology Progress Awards at the ministry/provincial level, the National Science and Technology Progress Award of China and the Hashiguchi Lungi Fund Award. He is a Fellow of Biomaterials Science and Engineering, granted by IUSBSE; Life Member, granted by the Society for Biomaterials and Artificial Organs, India; and Honorary Member of Council, granted by the Chinese Materials Research Society.

ZILLA, PETER

Peter Zilla received academic qualifications from the Universities of Vienna (Austria), Zurich (Switzerland) and Cape Town (South Africa) and his clinical qualifications from the Austrian Physician's Board and the College of Medicine of South Africa.

After graduating as a medical doctor from the University of Vienna, Austria in 1980 he obtained a DMed from the University of Zurich in 1983, a PhD from the University of Vienna and a separate PhD from the University of Cape Town in 1990. Clinically, he was initially registered as a specialist general surgeon with the Austrian Physicians Board in 1988, followed by his registration as a specialist vascular surgeon. After passing the fellowship examinations of the South African College of Medicine, he was registered as a specialist cardiothoracic surgeon in South Africa in 1992.

Aiming to be a clinician scientist, he spent his early postgraduate years in basic science. This included a period as a lecturer at the Neurobiology Division of the Anatomical Institute of the University of Zurich, Switzerland, from 1981 to 1983, after which he established his own research laboratories in Vienna. In 1987 he was invited to set up a tissue engineering laboratory in the Chris Barnard Department in Cape Town and perform preclinical trials with his method of *in vitro* endothelialization. After successfully demonstrating its clinical feasibility, he headed the tissue engineering program at the University of Zurich, from 1989. When clinical implementation of *in vitro* endothelialization commenced in Austria, he joined the program from its start until early 1992 and remained its scientific advisor for almost two decades. With the undertaking of a major American corporation to fund plans for a similar research program for developing countries, he established the Cardiovascular Research Unit at the University of Cape Town in 1992, where he continues as Director.

He became Head of the Chris Barnard Department in Cape Town in 2000 and is in charge of cardiothoracic surgery at Groote Schuur Hospital and Red Cross Children's Hospital, which have become leading training institutions for cardiothoracic surgeons from other African countries.

Professor Zilla's main research foci continue to be in the fields of tissue engineering and prosthetic cardiovascular implants. He has authored 150 peer-reviewed full papers, is the inventor on 26 patents, has been the editor on five books and has authored 24 book chapters. He was President of the International Society for Cardiovascular Biology (ISACB) from 1994–1998, is a regular reviewer of the 18 top journals, is on the editorial board of four major international journals and is Associate Editor of *Biomaterials*. He has been awarded the Theodor Billroth Award (Austrian Surgical Society), Alexis Carrel Award (German Society of Vascular Surgery), Goetz Award (South African Cardiac Society), Eiselsberg Award (Austrian Physicians Association) and Alain Carpentier Award (International Society Heart Valve Disease).

In 2007, together with David Williams, Professor Zilla founded the company Strait Access Technologies (Pty) Ltd (SAT), whose goal it is to provide heart valve technologies to the millions of young patients in developing countries who are suffering from rheumatic heart disease and who have no access to cardiac surgery. He is the company's Chief Executive Officer and has obtained funding from the South African government and private investors. SAT has a staff of 17 and has patented five unique concepts for self-homing, non-occlusive deployment devices, as well as the stent-based, synthetic aortic valve prostheses and mitral valve repair clips these devices deliver.

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