

TRI

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Translational Research Informatics Center (TRI) takes the initiative to reduce disability through Japanese academic research

The Translational Research Informatics Center (TRI) was founded in 2002 by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) and Kobe city as the first academic data centre for clinical research in Japan. Since its establishment, the TRI has led academic translational research and conducted clinical studies (<http://www.tri-kobe.org/>). The TRI has succeeded in forming the Academic Research Organization with 14 active translational research centres. The TRI supports the whole spectrum of clinical trials and clinical studies, from phase 1 to phase 4, including many mega-trials and large cohort studies. Our vision is to increase and promote biomedical innovation, and to accelerate the formation of a global alliance network. (For more, see <http://www.nature.com/naturejobs/science/articles/10.1038/nj0417>)

The scientific revolution

The scientific revolution that began with Galileo radically transformed society through numerous advances that began with the development of a methodology for the mathematical description of nature by observation and experimentation. Ultimately, it gave rise to the civilization we live in today. We are currently in the middle of an unprecedented scientific revolution that will undoubtedly prove to be the biggest paradigm shift in history¹. Scientists are embracing fields such as information technology and artificial intelligence (AI), genomics and molecular immunology, cybernetics and robotics, and nanotechnology and stem-cell medicine. Ray Kurzweil predicts that we will reach the singularity², the point when AI surpasses human intelligence, around 2045. But because this singularity is likely to come as a massive wave that integrates innovative technologies in AI as well as in other fields, we may reach it faster than Kurzweil has predicted. To ascertain the true essence of this extraordinary scientific revolution we require a profound understanding of the structure and principles of such revolutions³. To that end, six axioms of life can aid understanding. These are integrity, homeostasis,

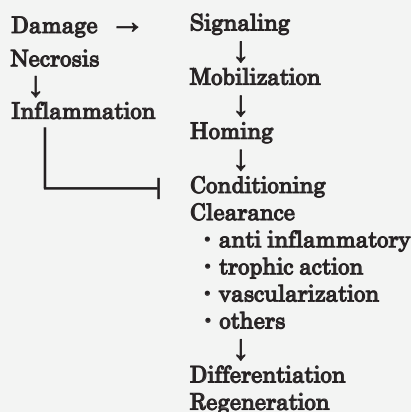


Figure 1. Cellular processes at the foundation of stem-cell physiology and pathology.

self-organization, field theory, symbiosis and resonance/synchrony. From these axioms we can get to the root of the three fundamental mysteries of life: origin and evolution, lifespan and consciousness. With these axioms in mind, we should be able to develop a better understanding of the true essence of the revolution in stem-cell medicine.

Stem-cell physiology and pathology

A deeper understanding of the physiology and pathology of stem cells will facilitate and pave the way for their clinical application. In order to maintain homeostasis at an individual level, multicellular organisms must routinely eliminate not only dead cells, but also bacteria, viruses, infected cells and tumour cells. Innate immunity has a central role in this process. Removal of foreign bodies and abnormal cells by immune cells such as natural killer (NK) cells and phagocytes is a well-known mechanism. Recent studies have shown that innate immunity is also involved in tissue regeneration³. Furthermore, when the body detects abnormalities such as tissue damage, adult stem cells are mobilized from their niches to the site of damage at which a range of cellular activities occur to correct the abnormality. The suppression of excessive inflammatory responses has been shown to be

a major function of mesenchymal stem cells⁴, for example. The tissue is then regenerated and repaired. This action in particular is attributed to muse cells, which were first reported by Mari Dezawa of Tohoku University⁵. Tissue regeneration and clearance of abnormal cells maintain homeostasis in the adult body (Figs 1 and 2). A series of recent discoveries has been made concerning the molecular entities involved in the cellular processes of stem-cell physiology and pathology. The technology for repairing injuries and promoting cellular differentiation and long-term regeneration using stem cells is unlike organ transplantation — tissue is regenerated, rather than introduced. An understanding of the body's intrinsic mechanisms for maintaining optimum health is revolutionizing the treatment of intractable diseases.

In summary, regenerative medicine using adult stem cells is an axiomatic technology in the sense that it exploits natural healing mechanisms that are intrinsic to the body and that have been well conserved throughout evolution, and it has the potential to become a fundamental curative therapy.

Status of clinical trials and development in regenerative medicine

In Japan, the Pharmaceutical Affairs Law (PAL) was amended and enforced in 2014, to include a review system for the consideration of the special characteristics of cellular and gene-therapy products. This system accelerated regulatory approval for products with proven safety and presumed efficacy, even if this had been shown in a small number of patients, provided that the product is later tested in additional patients and another application for approval is submitted within a set period of time. Autologous human skeletal myoblast sheets, developed by Yoshiki Sawa of Osaka University, were approved through this system. At around the same time, an allogeneic human bone marrow mesenchymal stem cell (BM-MSC) product was also approved under the amended law — the first allogeneic cellular product.

Self-preservation ability

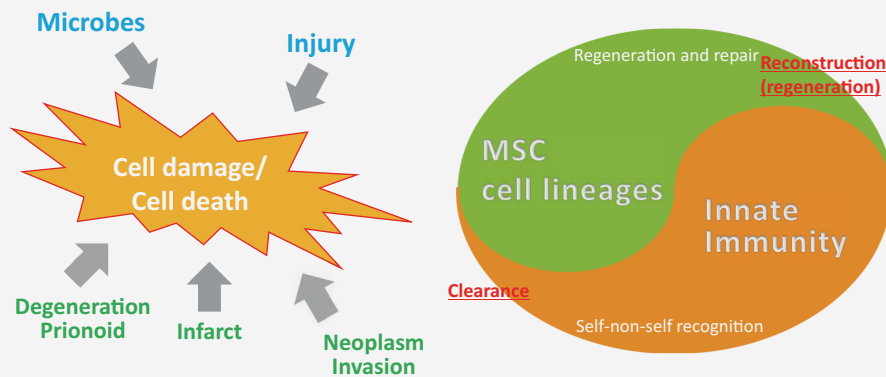


Figure 2. Mechanisms regulating maintenance of normal functioning of multicellular symbiotic systems.

To further accelerate product development, the Japanese government started the SAKIGAKE designation system in 2015 (ref. 6), which is similar to the US Food and Drug Administration's Fast Track. This system cuts the review time for breakthrough drugs and devices in half by designating products for priority handling at the early stages of the consultation and review process. This has enabled the country to quickly deliver cutting-edge treatments to patients. Currently, three cellular and gene-therapy products have been designated through the SAKIGAKE system. All of these were promising technologies developed from basic research conducted in academia. Autologous BM-MSK to treat spinal cord injury, developed by Osamu Honmou⁷, is included in such products. These products could potentially obtain regulatory approval within a few years.

This is a typical example of disruptive innovation⁸. Autologous stem-cell therapy is a biological treatment that is completely different from conventional small molecule drugs; stem-cell therapy exploits principles of the body's natural healing and regeneration processes and has upended conventional treatment concepts. Another example of disruptive innovation is the use of the interactive biofeedback principle for the robot suit HAL⁹. This was developed by Yoshiyuki Sankai of University of Tsukuba and Takashi Nakajima of Niigata National Hospital have conducted a multicenter clinical trial (JMA-IIA00156) for HAL to improve motor neuron function. This accomplishment, as part of the Rare/Intractable Disease Project of the Ministry of Health, Labour and Welfare was realized by unraveling the principles of the reciprocal physiological interaction between the brain and muscles, which helped the researchers to reconstruct the connectivity of neurons and represent plasticity¹⁰. In other words, interactive biofeedback can drastically change conventional methods for functional

recovery and rehabilitation. The therapeutic effects of BM-MSK in animal models of stroke also suggests neuronal plasticity. Thus, stem cells and interactive biofeedback are both mechanisms that govern the body as a unit and as a multicellular complex system; they are also the fundamental systems for maintaining homeostasis and the integrity that is intrinsic to the body, which has evolved great precision. The approach of exploiting optimum regulation of the overall system is now at medicine's disposal. This approach was pioneered by stem-cell therapy and the robot suit HAL — developments that will undoubtedly lead to a radical revolution in medicine. These two technologies could substantially reduce the number of people who are confined to bed or using a wheelchair within five to ten years.

The path towards reducing disability

Advances in stem-cell physiology are sparking discoveries about how the body repairs and regenerates itself after injury and what cells are involved in that process. Regenerative-medicine clinical trials based on research at academic institutions using adult stem cells are steadily progressing, and the day is approaching when these products will become the first-line treatment for their indications. Japan is at the forefront of this field of research, and preparations are being made for clinical development abroad after regulatory approval within the country. The establishment of investigator-initiated IND-registered trials, regulatory strategy consultations and the SAKIGAKE designation system were needed to support the development of promising technologies based on basic science conducted at academic institutions. This is Japan's new road for generating innovation in health and medicine, and it has made it possible to develop products for approval more efficiently.

The fact that we are now seeing dramatic recoveries in those treated with stem-cell therapy, even in patients with severe conditions who were otherwise unlikely to make a recovery, such as those with a spinal cord injury or cerebral infarction, has overturned preconceptions. This disruptive innovation will supplant conventional technologies and result in the fundamental transformation not only of treatments, but also of research and development of pharmaceutical products and medical devices, as well as research in regenerative medicine and biology.

Pharmaceutical companies have invested vast amounts of money and resources in the development of many pharmaceutical products to treat disease. We have now entered an era of treatment that uses cellular mechanisms hidden within our own bodies. We are fast approaching a day when disruptive innovation in stem-cell medicine turns conventional medical concepts and values on their heads.

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