Plenary Lecture

Plenary Lecture 1

Chair

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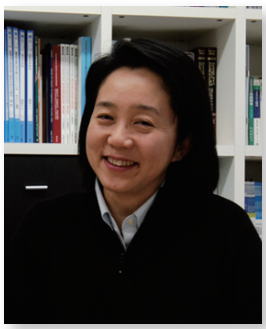

230: PL1

Application of iPS Cells to Retinal Disease

Speaker: Masayo Takahashi [1]
1. Laboratory for Retinal Regeneration, Center for Developmental Biology, RIKEN, Kobe, Hyogo, Japan.

We have started clinical research using iPS cells for Age-related macular degeneration (AMD) and we are now preparing the first patinet's iPSC-derived retinal pigment epithelial (hiPSC-RPE) cell sheets optimized to meet clinical requirements including quality, quantity, consistency, and safety. They have the necessary quality, such as expression of typical RPE markers, tight junction formation, polarized secretion of growth factors and phagocytotic ability. Furthermore, autologous primate iPSC-RPE cell sheets showed no immune rejection or tumor formation after transplantation into the subretinal space of the cynomologus monkeys, while allogeneic transplantation showed immune rejection.
In the clinical research, patients with active wet type AMD after existing treatment such as anti-VEGF drug injection into the eye will be enrolled. The primary endpoint is safety of the treatment. We will follow the patients for more than three years. The efficacy, the secondary endpoint, will be examined one year after the surgery.
Thus, iPS cell-derived retinal cell transplantation is promising. However, the effect of the treatments will be limited for the first decade. We should know precisely about the possibility and the limitation of the therapy.

Commercial Relationships: Masayo Takahashi, None
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Plenary Lecture 2

Chair

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Keio University School of Medicine, Shinjuku, Tokyo, Japan

418: PL2

Sirtuins NAD and Aging

Speaker: Leonard P. Guarente [1]
1. Glenn Laboratory for the Science of Aging, Massachusetts Institute of Technology, Cambridge, MA, United States.

SIR2 and related genes (sirtuins) are NAD-dependent deacetylases that link metabolism, protein acetylation and aging in a variety of species. Sirtuins are also involved in the longevity conferred by dietary or calorie restriction (CR). The mammalian sirtuins SIRT1-7 are involved in changes in stress resistance and metabolism that are triggered by CR, which not only extends life span, but also protects against many diseases of aging, including the major neurodegenerative diseases. In this talk, I will describe how mamamlian SIRT1 impacts tissue maintenance and diseases of aging by deacetyling nuclear transcription factors that govern key physiological pathways. Moreover, I will also describe new data showing the importance of NAD metabolism in aging, and demonstrate that declining NAD during aging may limit health span and life span because it results in sirtuin inactivation. This relies on a new class of mutations in the NAD-binding domain, which may allow Sir2 orthologs to function at sub-optimal NAD levels in cells. Finally, I will also present new data, which demonstrate that SIRT1 in intestinal cells is critical for those cells to respond to dietary signals sent by the niche cells, Paneth cells. This pathway is required for CR mediated responses in the gut, and is mediated by mTOR in Paneth cells (Yilmaz et al., Nature 2012) and SIRT1 in the stem cells.

Commercial Relationships: Leonard Guarente, GSK (C), CHRONOS (C), SEGTERRA (C), ELYSIUM HEALTH (I)
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Plenary Lecture 3

Chair

Yozo Miyake
Aichi Medical University, Nagakute, Aichi, Japan

584: PL3

Gene Polymorphism-based Personalized Patient Care in AMD

Speaker: Nagahisa Yoshimura [1]
1. Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medical Science, Kyoto, Kyoto, Japan.

Age-related macular degeneration (AMD) is a leading cause of blindness in developed countries. Both environmental and genetic factors contribute to the development of AMD and 19 disease-susceptible genes including ARMS2 (age-related maculopathy susceptibility 2) and CFH (complement factor H) have been identified by genome wide association studies (GWAS).

With development of modern imaging modalities, occurrence of AMD subtypes and racial differences in AMD subtypes are known; Asians have more polypoidal choroidal vasculopathy and less retinal angiomatous proliferation than in Caucasians. Such differences can be explained by genetic differences but information on racial differences is rather limited. Our data show that ARMS2 A69S SNP plays an important role in the development of all subtypes of exudative AMD but with different importance. Also, some genetic differences was found in patients of recently proposed pachychoroid neovasculopathy that may be more common in Asians. Currently, an Asian Consortium (GAMA) to discover Asian-specific disease susceptible genes is established, and hopefully such genes will be found in near future.

From clinician's viewpoint, it may be more important to know whether disease-susceptible genes also play a role in the determination of clinical pictures or treatment responses. If we can find genes that modify clinical course of AMD or response to anti-VEGF treatment, such information is useful to develop personalized medical care of AMD patients. Our candidate gene approach and GWAS revealed that ARMS2 A69S SNP was associated with second-eye involvement of exudative AMD and with the period between first- and second-eye involvements. Also, ARMS2 A69S together with MMP20 polymorphism was associated with the lesion size by our GWAS analysis. So, ARMS2 A69S polymorphism is really important not only in the development of exudative AMD but also clinical presentations of the disease. On the other hand, whether this SNP can be used as a marker of treatment outcome is controversial. Results from two important prospective studies (CATT or IVAN) are negative for the association of treatment outcome and this SNP. Because these studies use candidate gene approach and the number of cases is rather small for genetic analyses, a large cohort study with GWAS is needed to draw a conclusion whether gene polymorphism-based personalized medicine for AMD can become practical in the future.

Commercial Relationships: Nagahisa Yoshimura, Santen (F), Santen (R), Senju (F), Senju (R), Ohtsuka (F), Ohtsuka (R), Alcon Japan (F), Alcon Japan (R), Novartis Japan (F), Novartis Japan (R), Pfizer Japan (F), Pfizer Japan (R), MSD (F), MSD (R), Kowa (F), Kowa (R), Wakamoto (F), Wakamoto (R)
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Plenary Lecture 4

Chair

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676: PL4

Recent Progress in iPS Cell Research and Application

Speaker: Shinya Yamanaka [1, 2]
1. Center for iPS Cell Research and Application, Kyoto University, Kyorto, Kyoto, Japan. 2. The J. David Gladstone Institutes, Gladstone Institute of Cardiovascular Disease, and L.K. Whittier Foundation Investigator in Stem Cell Biology, San Francisco, CA, United States.

The appeal of induced pluripotent stem cells (iPSCs) is that they can proliferate almost indefinitely and differentiate into multiple lineages. Although originally generated from fibroblasts, they can be made from various somatic cells, which significantly expands their medical application. As a result, cell-based therapies, disease mechanisms and new drug development are being studied worldwide using iPSCs.

We are establishing safe and efficient technologies for iPSC generation towards medical applications in accordance with GMP. The original iPSCs were made from the retroviral transduction of four genes, *Oct3/4, Sox2, c-Myc* and *Klf4*. We have since reported an integration-free method using episomal vectors that does not cause chromosomal damage. Furthermore, we proposed the use of L-Myc as an alternative to c-Myc to reduce the risk of tumorigenicity. To avoid the need for conventional feeder cells or culture materials from different species and to make iPSCs more suitable for the GMP setting, feeder cells were replaced with a recombinant laminin-based matrix and a culture medium free of animal-derived constituents (xeno-free) was developed. Regarding quality control, some marker genes for neural differentiation-defective clones have been identified, suggesting we can separate high-quality iPSCs before use for regenerative medicine.

In September 2014, the world's first clinical study using iPSCs was reported. This study involved the transplantation of iPSC-derived retinal pigment epithelium sheets for age-related macular degeneration. In addition, iPSC studies have shown major progress in corneal diseases, blood diseases and Parkinson's disease, suggesting iPSC-based human regenerative medicine in the near future. From a broader perspective, we are proceeding with an iPSC stock project in which iPSC clones are being established from donors with homologous HLA haplotypes, which is associated with decreased immune response, to provide quality-assured iPSCs for cell transplantation.

iPSCs can also be applied to drug screening, toxicity studies and the elucidation of disease mechanisms by using disease-specific iPSCs from patients with intractable diseases. In addition, using individual iPSCs may make it possible to predict the patient condition and provide a preemptive therapeutic approach or personalized medicine. Moreover, iPSCs are also leading the way for drug repositioning.

Commercial Relationships: Shinya Yamanaka, None
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