3C*-based Visual Recovery for the Aging Society (*3Cs: Cell, Circuit, and Cognition)

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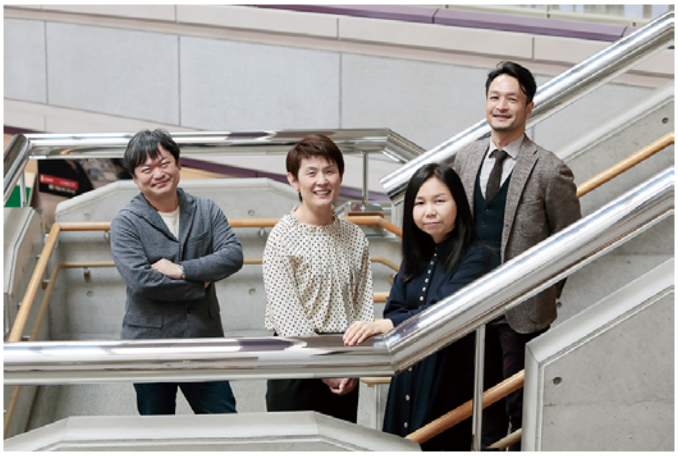


Establishing a retinal evaluation system and complementary tools useful for the recovery of natural vision through regenerative medicine

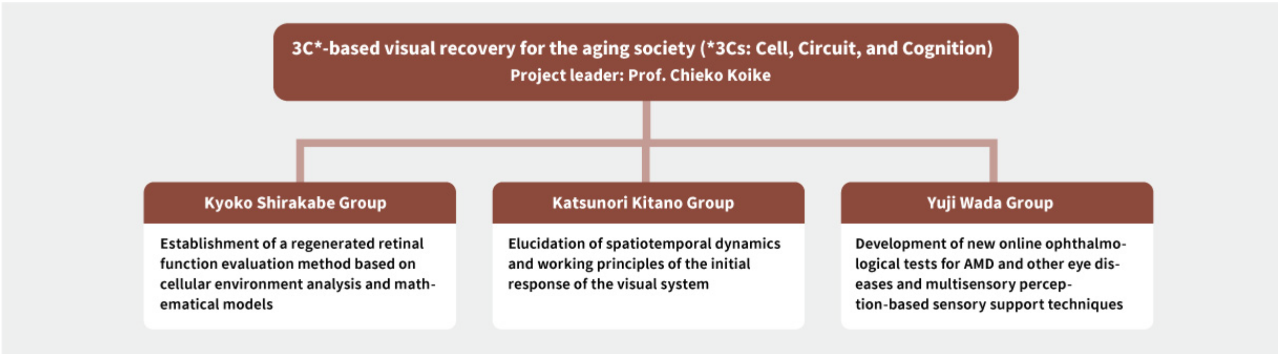
Tackling obstacles to the recovery of natural vision ahead of the coming era of genuine visual recovery

In October 2020, the world's first clinical transplant operation using a regenerated retina deriving from iPS cells was performed at Kobe City Eye Hospital. While regaining eyesight even to the extent of being able to vaguely distinguish the shapes of objects would already considerably improve the quality of life of blind patients, nearly full recovery of natural vision may become possible in the not-so-distant future. To meet this future, in which we anticipate the recovery of natural vision within the context of a personalized and custom-tailored medical care system, our research project aims to construct a quantitative evaluation system for regenerated retinas and to develop vision-complementing approaches that leverage multisensory perception.

When visual recovery technology is established by regenerative medicine, several obstacles will still have to be overcome before its general use can be realized to benefit many people. The absence of an effective retina simulator is one such obstacle. Simulation is essential to predict suitability and to ensure a regeneration of the retina that is optimal for each individual, and to do so in a highly-efficient way. However, no research group in the world has yet succeeded in constructing a retina simulator. Meanwhile, it is known thathumans visually recognize what they see by mobilizing not only the sense of sight but also other sensory cognitive functions such as the senses of hearing, touch, and taste, and therefore, the recovery of natural sight does not depend solely on a healthy retina. That is to say, visual recovery can be aided if external stimuli are addressed to other senses in addition to sight. Therefore, even in the domain of regenerative medicine, complementary tools making use of multisensory perception can be useful for more natural visual recovery. Therefore, the focal themes of our project are these two: a retinal evaluation system and multisensory visual complementation tools.

Three-layered approach to cells, circuits, and cognition to elucidate the functions and mechanisms of the retina

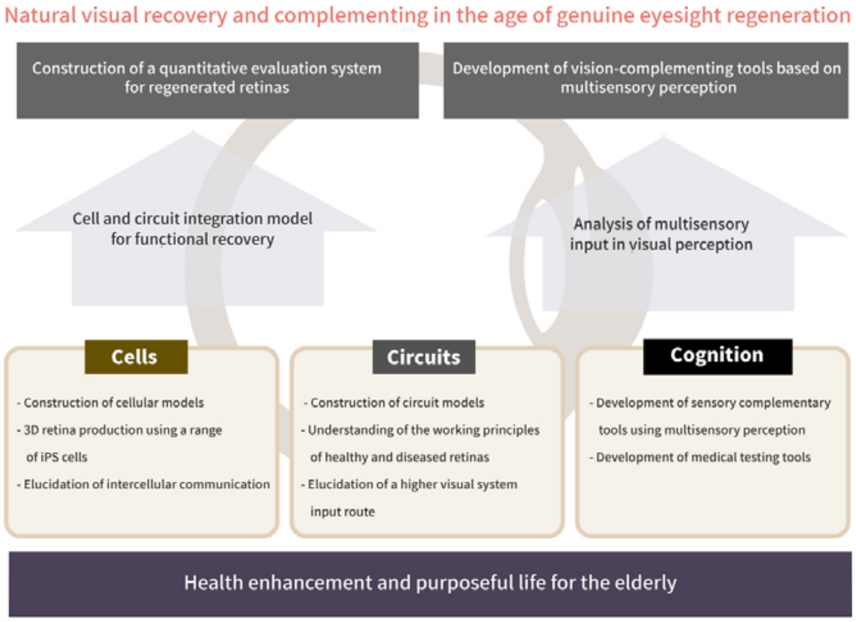
This research project is conducted by three groups, each working at one of three levels: cells, circuits, and cognition. The Shirakabe Group, which works on cells, oversees elucidating the cellular-level functions of the retinal tissue, in which many different types of neurons form complex circuits. The group’s first focus is 3D retina production, which involves generating high-quality iPS cells that serve as seeds for growing these retinas-in-a-culture-dish. Data obtained by analyzing these 3D retinas will be the basis for constructing a



system for evaluating retinal functions. The group's second focus is on remodeling, the process by which unhealthy neurons and neuronal connections are removed and replaced with new healthy neurons and connections. The "shedding" of cell membrane proteins plays an important role in the molecular mechanism of phagocytosis, the process by which dead cells are "eaten" and removed and neuronal contacts are disassembled. The shedding/phagocytosis mechanism will be analyzed for an accurate understanding of the dynamic wiring in the retina, which will be useful in developing control technology, since membrane proteins are expected to contribute to cellular generation, death, motility, and differentiation during 3D retina generation using iPS cells. Based on data on these experimental systems, we will attempt to build a cellular mathematical model for the evaluation of regenerated retinal function. We will try to establish a method to evaluate the degree of cell maturity from the components of cell membrane ionic currents, using information obtained by the electrophysiological analysis of cells.

The Kitano Group oversees the elucidation of circuit-level functions and mechanisms. To this end, the group will first attempt to identify the working principles of healthy retina and the dynamic state of diseased retina. The retina contains unique neuronal circuits that are optimized for visual information processing. These circuits are refined by visual stimuli during the postnatal period through processes that persist in a latent state after mature wiring is achieved in the adult. When the retina is damaged or diseased in the adult, these dynamic processes can reactivate, but reactivation results in aberrant rewiring and electrical oscillations in the context of an unhealthy retina. In previously conducted research, the group has succeeded in highlighting important circuit systems and the characteristics of their fluctuations in healthy and diseased conditions separately. Drawing on this knowledge as well as multi-neural activity measurements by various methods, the group will gauge the spatiotemporal dynamics of the retina, clarifying working principles in both healthy and diseased conditions. Secondly, the group will examine information transmission from the retina to the visual cortex. Visual information processed in the retina is then sent to the primary visual field, which is at the beginning of the visual cortex, for further processing before it is visually perceived. The group's research involves measuring this output response from the retina to the visual cortex to identify the optimal retinal output pattern. In the long run, the group hopes to use such research findings to predict information processing in the connection of optic nerves during regenerated retina transplant operations. The group's third focus is the construction of a mathematical retinal circuit model for quantitative evaluation of retinal information processing based on experimentally obtained data. To evaluate the functions of a regenerated retina and verify its equivalency to a healthy retina, it is essential to have a retinal circuit model as its blueprint, but nobody has yet succeeded in producing one. With the development of a mathematical model, it would be possible to envisage the predictability of factors that are essential for the retina to adapt to environmental changes.

The Wada Group takes two approaches in its cognition-level research. Firstly, the group is trying to develop a visual function test built on a completely new paradigm. Visual information sent from the eyes to the brain is selected, processed, and complemented by the brain so that the person can "see." That is to say, the absence of photosensitive cells in the portion of the visual field called the blind spot is compensated with other types of information sent to the brain. In the case of a person with a retinal degenerative disease that has damaged the visual field, a similar mechanism of compensation comes into play, thanks to the plasticity of the brain, thus making it difficult for the affected person to notice the ailment. The group will examine this mechanism and use research findings, including knowledge related to optical illusions, to develop the new testing method. The Wada Group's second research focus is the development of post-retinal transplant rehabilitation tools



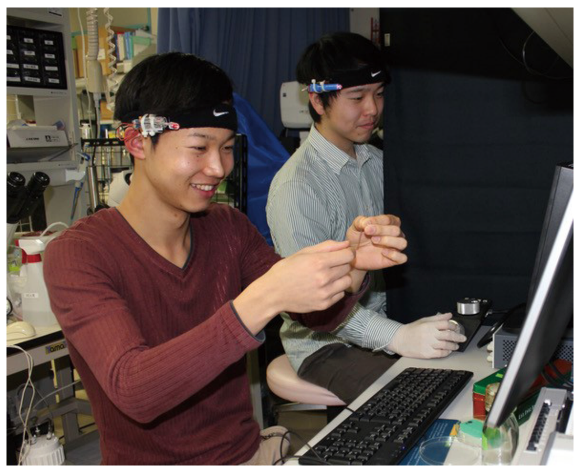
Research results envisaged in this project

that help visual recovery drawing on multisensory perception. As mentioned above, humans maintain their eyesight not only through the visual sense but also by mobilizing various other sensory cognitive functions. The group will explore and apply this mechanism of multisensory perception to develop vision-complementing tools.

Improving retinal regeneration to help people enhance their health and lead a purposeful life in the rapidly aging society

This research project is characterized by the participation of researchers from various domains, including information, science and engineering, biology, and psychology, who have worked together for a total of some 10 years to establish a solid interdisciplinary research program with the Center for Systems Vision Science of Ritsumeikan University as its nucleus. The unique strength of the project lies in its execution, comprising a dual focus on experimental analysis and theoretical reconstruction using mathematical models.

Moreover, in addition to the research per se, we are also making serious efforts through this project to train young researchers specializing in regenerative medicine and ophthalmology. We attach great importance to human resource development for future advancement in these two fields through research and inter-sector networking and collaboration. We implement them, for example, by working with Vision Care Inc., a Kobe-based company engaged in R&D and commercialization of regenerative medicine in ophthalmology. We send young researchers to the Vision Care as interns.



Analyzing electrophysiological response in retinas by the patch-clamp method

Since human beings depend on eyesight for an overwhelming 80% or more of their sensory information from the outside world, visual impairment and disease considerably reduce people' s quality of life (QOL). As the population continues to age, the prevalence of eye diseases in society is bound to rise, and this will inevitably lead to increasingly enormous and serious societal costs in multiple aspects. Our research targeting improvement in retinal regeneration technology will be an important way to reduce these costs. Supporting the progress of regenerative medicine in this way, we hope to help bring as much comfort and enrichment as possible to a rapidly aging society.

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