Abstracts for “Drug Discovery Beyond Borders: Intractable Diseases related Muscle, Bone and Cartilage”

Splicing therapy for inherited heart diseases

Masatoshi Hagiwara

Deep-intronic mutations often distort splicing regulatory motifs and some intronic sequences are retained as exons, which are referred to as pseudo exon. Because of prevailing next-generation sequencing, pseudo exon is now considered a more frequent cause of genetic disease than previously thought. In 2002, A single G→A intronic mutation (IVS4+919G→A) of **α**-galactosidase A (α-Gal A) gene was identified in a patient with cardiac Fabry disease who has the concentric left ventricular hypertrophy. The mutation promotes recognition of intronic 57-nucleotide sequence as a pseud exon in the a-Gal A transcript, which is not translated and subsequently leads to accumulation of globotriaosylceramide (Gb3) in lysosomes of heart. As enzyme replacement therapy is not so effective for the cardiac phenotype, we developed druggable small compounds which can normalize the aberrant splicing of α-Gal A transcript. The splicing therapy with chemical splicing modulators can be applicable for other inherited heart diseases such as several types of long QT syndrome caused by aberrant splicing.

Application of patient-specific iPS cells for intractable skeletal diseases

Junya Toguchida

In the latest version (2019) of Nosology and Classification of Genetic Skeletal Disorders, 461 different diseases were registered and classified into 42 groups based on their clinical, radiographical, and/or molecular phenotypes. Although, the recent progress in the genetic analyses has identified disease-related pathogenic variants in more than 90% of them, there are few instances in which effective treatments are established. One of the reasons is the difficulty for obtaining patients' materials suitable for in vitro analyses. To overcome this issue, iPSCs established from patients will be a powerful tool, which will provide researchers with unlimited materials to be studied. We have applied this approach for several skeletal diseases and successfully recapitulated the disease in a dish. In combination with the drug repurposing approach, we have identified a candidate drug for one intractable disease, fibrodysplasia ossificans progressiva, and proceeded to the stage of clinical trial.

Sarcopenia and muscle regeneration: new therapeutic interventions

Antonio Filareto

Sarcopenia, the age-related loss of skeletal muscle mass and function, is a catastrophic process that reduces the quality of life for individuals, leads to falls and fractures, and requires costly hospitalization and extended rehabilitation. It is estimated that the number of adults over age 65 should increase from 617 million today to over 2 billion by 2050 and they will account for 20% of the world's population. The economic, healthcare, and financial burdens this may place on society are far from trivial. The mechanisms underlying sarcopenia are unclear and the development of effective therapies remains elusive. Impaired muscle regenerative capacity, cellular senescence, and inflammaging (low-grade systemic inflammation) are all key contributors to sarcopenia. The overall focus of this presentation is to provide an up-to-date overview of the biological mechanisms that contribute to the age-related loss of muscle mass and function and a summary of emerging pharmacotherapies.