Rare Disease Day: Available Therapies and Searching for New Ones

Online, ZOOM
Friday, February 26, 2021, 12.00

Programme

12.00 Possibilities and limitations of stem cell therapies in rare diseases

Prof dr hab. Józef Dulak, Department of Medical Biotechnology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University

12.30 Terapie w dystrofii mięśniowej Duchenne'a

Dr hab. Agnieszka Łoboda, prof. UJ, Department of Medical Biotechnology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University

13.00 Yeast model in studies of rare diseases and drug development

Dr hab. Joanna Kamińska, Laboratory of Yeast Genetics and Molecular Biology, Institute of Biochemistry and Biophysics PAS

13.30 Whole-exome sequencing in the diagnosis of known and new potentially curable rare diseases

Prof. dr hab. Rafał Płoski, Department of Medical Genetics, Medical University of Warsaw

14.00 Patient organisations in spinal muscular atrophy and their role in the development of new therapies

Kacper Ruciński, Co-founder and Strategy Board Member, SMA Foundation Poland; Board Member, SMA Europe

Exhibition of Photography by Beata Muchowska „Teachers of Love”
Public Donations for SMA Fundation

Possibilities and limitations of stem cell therapies in rare diseases

Józef Dulak

Department of Medical Biotechnology, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Kraków, e-mail: *jozef.dulak@uj.edu.pl*

For several decades, bone marrow and umbilical cord blood transplants containing hematopoietic stem cells have been used in the treatment of blood diseases, including rare diseases. Genetic modification (gene therapy) of such cells enable the treatment of severe complex immunodeficiencies and severe anemias. Limbal stem cells taken from the eye and differentiated to epithelium can regenerate the damaged cornea, and epidermal stem cells help in the treatment of severe burns or some types of hereditary *epidermolysis bullosa*. Promising experimental research is being conducted on other uses for stem cells. However, these are properly selected cells with real differentiation capabilities to cells whose impaired functioning is the cause of the disease (see Dulak J *Stem cells: applications, perspectives, misunderstandings* - Nauka 1/2020; pp. 99-123 - https://journals.pan.pl/Content/115884/PDF/N%23120-06-Dulak.pdf

The therapeutic uses of stem cells have apparently been limited so far (see: EASAC-FEAM report on regenerative medicine, 2nd June 2020; - https://easac.eu/publications/details/challenges-and-potential-in-regenerative-medicine/. Meanwhile, the Internet is full of advertisements for supposedly miraculous treatments for numerous diseases using "stem cells". Stem cells have become the modern synonym for the Holy Grail. A miraculous cup that transforms each drink into an elixir of health, youth, and extremely long life.

Stem cells of known but limited capacity, e.g. hematopoietic stem cells from umbilical cord blood, or cells so named, although not having the proven properties of stem cells, are offered in commercial private clinics as a panacea for autism, cerebral palsy, spina bifida, inherited blindness, amyotrophic lateral sclerosis and dozens other diseases and developmental disorders. Without sufficient biological justification for their action in these conditions, without convincing evidence of safety, but at a high cost.

In the lecture, I will discuss stem cells and the misunderstandings related to often including any type of cell among them. I will highlight the real possibilities and proven uses of stem cells and present the problems, doubts and dangers for patients that accompany "stem cell therapy" offers. I will emphasize the need to comply with appropriate methodological and ethical principles, based on the positions of institutions and scientific societies paying attention to the commercialization of unjustified and potentially treatments.

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Current and future therapies for Duchenne muscular dystrophy

Agnieszka Łoboda

Department of Medical Biotechnology, Faculty of Biochemistry, Biophysics and Biotechnology; Jagiellonian University, Krakow, e-mail: *agnieszka.loboda@uj.edu.pl*

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by the mutation in the dystrophin-encoding gene, *DMD*, which leads to the rapid degeneration of skeletal and cardiac muscles. DMD is still incurable, and its treatment is challenging. Over the last few years, there has been a constant improvement in the gene, cell, and pharmacological experimental therapies aimed at restoring functional dystrophin or to counteract the associated processes contributing to disease progressions like inflammation or fibrosis. Nevertheless, effective therapies that would be amenable for all patients are still missing, and glucocorticoids, exerting many side effects, still serve as a gold standard therapy for patients suffering from DMD. Hence, investigations of innovative therapeutical options at least ameliorating DMD symptoms are undeniably needed.

Our results indicate the protective role of heme oxygenase-1 (HO-1), a cytoprotective enzyme, in ameliorating disease progression. We have shown that HO-1 is an important regulator of many mechanisms related to the pathogenesis of DMD, and its absence aggravates disease progression. Our study performed on the mouse model of the disease, *mdx* mice, show also that targeting specific microRNAs, e.g. miR-378 has the potential to mitigate DMD pathology. Finally, using mouse model as well as human induced pluripotent stem cell-derived endothelial cells, we highlighted the complexity of angiogenesis-related alterations in dystrophic animals, underlying the validity of vascular-based therapies aiming at the restoration of functional angiogenesis to alleviate DMD severity.

Studies performed to better understand the molecular mechanisms of DMD may lead to the development of new treatments for the disease in the future.

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Yeast model in studies of rare diseases and drug development

Joanna Kaminska

Laboratory of Yeast Genetics and Molecular Biology, Institute of Biochemistry and Biophysics PAS, Warsaw, e-mail: *kaminska@ibb.waw.pl*

Neurodegenerative diseases are a growing problem in the aging society. Besides major neurodegenerative diseases, such as Alzheimer's and Parkinson's, there are numerous rare neurodegenerative disorders, many of them vastly neglected by the mainstream of science. These diseases are mostly unknown for physicians and even the proper clinical diagnosis is a problem, not to mention the mechanism of pathogenesis and the search for effective therapy. Research on major neurodegenerative diseases showed that even years of studies and large investments do not result in significant progress in the development of therapy. An additional problem is conducting research on a large scale of thousands patients. To solve the problem we can use model organisms such as the baking yeast *Saccharomyces cerevisiae*. Yeast cells are relatively simple but their biochemical pathways are similar to those of humans and they are easily genetically manipulated. This allows the use of yeast to study the pathogenesis of rare diseases, including neurodegenerative ones, even though they do not have a nervous system. Our research concentrates on recognition of pathology of rare neurodegenerative diseases at the molecular level and finding how it can be overcome. In details we study diseases of the central nervous system caused by mutations in the *VPS13A-D* genes and diseases of the peripheral nervous system of various genetic background, depending on more than 100 genes, including mutations in the *GDAP1* gene. Mutations found in patients are introduced into the yeast model and such mutants are characterized to find a simple phenotype to monitor changes. We found that mutations in the *VPS13* gene result in increased sensitivity to sodium dodecyl sulfate (SDS), a commonly used detergent, and mutations in the *GDAP1* gene change the calcium homeostasis. These phenotypes were used to search the Prestwick drug library, a collection of chemicals accepted for use in human, for those that reverse changes in the functioning of mutant cells. These chemicals are therefore potential drugs for the investigated diseases. Moreover, selected drugs of known effects indicate processes that may become therapeutic targets. Such a strategy indicates not only the way to treat the rare neurodegenerative diseases we are interested in, but also the way to develop treatments for other rare diseases.

Whole-exome sequencing in the diagnosis of known and new potentially curable rare diseases

Rafal Ploski

Department of Medical Genetics, Medical University of Warsaw, e-mail: rploski@wp.pl

In 2012 Department of Medical Genetics (Warsaw Medical University) has acquired Illumina HiSeq 1500 which allowed to establish whole exome sequencing (WES) as method for both research and diagnostic purposes. Since then we have performed > 3000 WES analyses, most of which aimed at finding diagnosis in patients suspected to suffer from rare disorders with a genetic basis. During the lecture, selected results will be presented to illustrate how WES enables, in addition to diagnosis, treatment optimization. In particular, We will present a case of the discovery of a new disease associated with a defect in the *IL6ST* gene, the *in vitro* analysis of which indicated previously unexpected therapeutic possibilities.

Patient organisations in spinal muscular atrophy and their role in the development of new therapies

Kacper Ruciński

Co-founder and Strategy Board Member, SMA Foundation Poland;
Board Member, SMA Europe, e-mail: kacper.rucinski@fsma.pl

Until 2016, spinal muscular atrophy (SMA) was known as the no. 1 genetic killer of infants and small children in the world. That year, on Christmas Eve, US authorities approved the first causative treatment for SMA. Barely two-and-half years later, in May 2019, the world witnessed another breakthrough – the introduction of gene therapy to treat SMA. A third SMA drug was approved six months ago – an orally administered small-molecule drug.

What role did SMA patient organisations play in the development of those treatments? What happened to the hundreds of millions of dollars raised by them to fight the disease? What challenges did clinical trials in SMA face? How did it happen that Poland has one of the most ambitious SMA treatment programmes in the world?

The presentation will take us through the global fight of SMA parents and SMA adults against this deadly disease.