EuroSciCon

17th Edition of International Conference and Exhibition on

Pharmaceutics and Novel Drug Delivery Systems

October 04-06, 2018
Moscow, Russia

Ruth Belostotsky, Int J Drug Dev & Res 2018, Volume 10
DOI: 10.21767/0975-9344-C1-002

New approaches to drug design and drug delivery for the treatment of primary hyperoxaluria

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Primary hyperoxaluria type 1 (PH1) is a rare, autosomal recessive metabolic disorder caused by mutations in the hepatic alanine-glyoxylate aminotransferase (AGT). Defective AGT results in excessive oxalate synthesis that induces urolithiasis, nephrocalcinosis and progressive kidney failure leading to end-stage renal disease. Combined liver-kidney transplantation is currently the only curative treatment approach, but is associated with significant morbidity, mortality and costs. Transplantation requires a medical infrastructure which is not available to most patients suffering from PH1 worldwide. Thus, there is an urgent need for new therapies besides transplantation. The following strategies for molecular therapy of PH1 are currently being developed: proteostasis regulation therapy by targeting pharmacoperones; adeno-associated virus (AAV)-mediated gene therapy with liver-specific AAV vectors for *in vivo* genome editing; cell therapy by hepatocyte transplantation; substrate reduction therapy through suppression activity of different enzymes from the glyoxylate pathway. This includes high-throughput screening for small molecules inhibitors as well as development of synthetic siRNAs targeting the endogenous mRNA transcript of a given gene, leading to its cleavage and subsequent depletion of the substrate for oxalate synthesis and; Enzyme replacement therapy by delivery of polymer-conjugated AGT proteins into the peroxisomal compartment. In this speech, the author will address the advantages and challenges of these strategies and the ways of treatment delivery applicable to individual approaches. We believe that coupling small molecule chaperones and inhibitors with protein-, cell-, and gene-based therapies may decrease excessive oxalate production. Effective treatment of this devastating inborn error of metabolism will become available in the near foreseeable future.

Biography

Ruth Belostotsky acquired BA and MSc degrees in Chemistry from the Chemical Department of the Moscow State University, MSc in Molecular Biology in the Department of Biology, Technion, Haifa, Israel and PhD in Molecular Biology at the Hebrew University School of Medicine, Jerusalem, Israel. She did her Postdoctoral research in the laboratory of Professor Haya Lorberboum-Galski at the Hebrew University School of Medicine. Currently she is the Head of Pediatric Nephrology Lab at the Shaare Zedek Medical Center in Jerusalem. Among her latest accomplishments are finding that mutations in: a previously uncharacterized gene, *HOGA1* cause primary hyperoxaluria type 3, unrevealing the biochemical mechanisms of glyoxylate metabolism, discovering that mutations in the gene encoding mitochondrial seryl-tRNA synthetase cause HUPRA syndrome and others. Her laboratory is currently investigating the biochemical and cellular aspects of the primary hyperoxaluria and searching for approaches to treatment of this group of disorders, as well as looking for novel genes critical for normal kidney function.

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