HUMAN GENE THERAPY – PRINCIPLES, HISTORY, STATE OF THE ART, CHALLENGES AND APPROACHES FOR MITIGATION

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Since the first proof-of-concept human application in the early 90's, the field of Gene Therapy has now entered a stage of unprecedented revolution for clinical translation and commercialization. The progress of human gene therapy in the past decades has been primarily driven by vector technology platform development. Among the current variety of vectors available for *in vivo* gene therapy, recombinant adeno-associated virus (rAAV) stands out for its high efficiency, stability, and low immunogenicity/toxicity profiles. AAV is a common benign residential virus that can persist in primate tissues for the lifetime of the host without integration into the host genome and pathological consequences, holding great promise for different gene therapy applications. Several recombinant AAV-derived gene therapy drugs have been approved by European and U.S. regulatory authorities for commercialization.

This presentation will provide an overview on the key principles, history, the state-of-art, challenges of human gene therapy and showcase AAV capsid discovery and engineering to modulate target tissue tropism, therapeutic gene expression cassette design and optimization to improve gene delivery efficiency and safety profile, rAAV manufacturability and the next generation of QC pipeline, and examples of AAV gene therapy development: from preclinical proof-of-concept in murine disease models to large animal model and to the first-in-human application.