We live in hugely exciting times! Unprecedented advances and enhanced application of modern genetic and molecular technologies in fundamental science and health care are driving an explosion set to transform the face of modern medicine. This knowledge is rapidly leading to increased diagnostic power, while translation through to therapeutic benefit and improved health outcomes is progressing at a much slower pace.

Genetic diseases impact more people than AIDS/HIV and cancer combined. There are over 6000 known genetic diseases and every year over 8 million children are born with a genetic disease, 30% of them will not live to see their $5^{th}$ birthday! Most of the current treatment options aim at treating the pathological consequences of the underlying mutations and not at curing the actual genetic defects, which would require correction at the level of the genetic code or delivering a new functional copy of the affected gene.

During the recent decades, gene therapy has become one of the most actively developing and most promising branches of biomedical research. Gene therapy aims to correct disease-causing changes (known as mutations) in the genetic code, process unofficially referred to as “genomic surgery”, or deliver an additional copy of the mutated gene to the affected cells - “genetic prosthetics”. However, there are a number of fundamental obstacles when it comes to treating genetic disorders with viral vectors, the major one being the inability to efficiently and safely deliver genetic material to human cells and tissues inside the human body.

Although number of technologies have been developed to facilitate delivery of genetic payload to target cells in patients, methods based on the use of viral vectors are gaining in popularity due to recent promising results in human trials. This technology is built on the fact that viruses have evolved abilities to infect target cells with his efficiency and specificity, as well as mechanisms to avoid recognition by human immune system or cellular defence mechanisms.

Vectors based on non-pathogenic Adeno-Associated Virus (AAV) have emerged as the leading technology for gene transfer, with over 130 initiated or completed clinical trials and over 2000 patients treated with AAV-based therapeutics to date. In fact, the first AAV-based therapeutic was approved in 2012, paving the way for large number of other AAV therapeutics currently in preclinical and clinical development.

In this project we will screen large pool of novel AAV variants that have the potential to be used for gene therapy targeting genetic disorders of the liver. Furthermore, we will evaluate four available models of human liver in order to identify the model that best recapitulates biological functions of human liver in relation to vector based gene therapy applications. Finally, we will use human hepatocytes to study the intimate relation between AAV vector and human liver, studies that will allows us to better understand fundamental biology of AAV and cell biology of human liver.