

## ABSTRACT

cGAS-STING signalling pathway plays the key role in the host immune defence in diverse pathologies including, autoimmune and autoinflammatory diseases, cancer, senescence and ageing, pathogen infection, i.e., bacterial, viral infection, such as hepatitis B (HBV). HBV infection can result in either an acute or a chronic type (CHB), both of wide range of immune invading mechanism potentially leading to liver cirrhosis, steatosis, or hepatocellular carcinoma. Currently, two available CHB therapies are approved, both of which rarely result in the complete cure and often require life-long application.

The development and validation of novel CHB therapeutics relies on suitable CHB animal models. The main goal of this thesis was to develop a mouse model reflecting CHB based on hydrodynamic injection suitable for robust preclinical testing of novel CHB therapeutics. Two delivery systems were compared, adeno-associated plasmid vector (pAAV) and minicircle construct, encoding HBV genomes of two genotypes (A or D) with introduced point mutation in the START codon of the polymerase in two immunocompetent mouse strains, C57Bl/6 and C3H/HeN. Persisting expression of viral antigens was observed only in the C3H/HeN mice when using pAAV construct encoding HBV genome of genotype A with introduced T2308C point mutation in the START codon of the polymerase preventing formation of viral progeny. Developed mouse model reflecting CHB was used to study and identify the most effective CHB therapeutics based on natural cyclic dinucleotide - STING interaction and activation together with immune response induction. Our lead compound chosen based on *in vitro* screening from a large library of novel STING agonists exclusively prepared at the Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences showed outstanding results in CHB mouse model as monotherapy which makes it interesting for clinical studies.