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Hepatitis C Virus Vaccine Candidates from Chimeric Hepatitis B Core Virus-like Particles Carrying Different Fragments of HCV Non-structural Protein 3

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Hepatitis C virus (HCV) persists in up to 85% of infected individuals as a chronic infection characterized by liver infiltration of inflammatory cells that can lead to fibrosis, cirrhosis and hepatocellular carcinoma. Chronic HCV infection results from weak or absent T cell responses. Pegulated-interferon-alpha (INF-α) and ribavirin, the standard of care for chronic HCV, have numerous immune effects but are not potent T cell activators. A potent immune activator such as TLR9 agonist CpG oligonucleotide (CpG) may help current treatment approaches. It was shown that vigorous T helper and cytotoxic T cell response to nonstructural protein 3 (NS3) of HCV plays significant role in the clearance of the virus. Therefore the aim of this study was to create unique type of HCV immunogen capable of induction of specific HCV cellular immune response. Chimeric virus-like particles bearing different NS3 regions, containing several CD4+ and CD8+ epitopes, were created on the basis of hepatitits B virus core protein (HBc). To enhance the immunogenicity of these chimeric capsids, immunostimulatory CpG oligonucleotides were packaged into the particles. Such type of HCV immunogen could serve as effective vaccine candidate.

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The Crimean Congo Hemorrhagic Fever European Consortium: Modern Approaches to Diagnostics, Epidemiology, Prevention, Therapy and Preparedness

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Large outbreaks of Crimean Congo Hemorrhagic fever virus (CCHFV) in several European countries and neighbouring areas are on the rise. To date, there is no vaccine available and no selective antiviral drug for the management of the disease. The general knowledge of migration, epidemiology, re-assortment and recombination of the virus is very limited. To fill these gaps, the CCH Fever project proposes to create a multidisciplinary collaborative research environment by bringing together selected competitive advantages such as: operative capacity with appropriate high security research facilities, reference centers and clinical samples from endemic areas and an international network of e xperienced researchers. This multidisciplinary research consortium will facilitate the progress in several key research areas of the field.

This program will mainly focus on (i) developing sensitive and biosafe state-of-art diagnostic tools for CCHFV, (ii) gathering the forces and resources in Europe to build a Biobank of clinical samples, (iii) building a comprehensive database consisting in clinical, laboratory and surveillance data, (iv) taking advantage of unique and state-of art tools to progress towards vaccine candidates and specific antivirals against this bio-treat and (v) disseminating the appropriate knowledge to the health care workers in endemic regions.

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Nitazoxanide is an Indirect Inhibitor of HCV Replication Through Modulation of Cellular Kinase CKI Alpha to Enhance HCV NS5A Hyperphosphorylation

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Nitazoxanide (NTZ, Alinia®, Romark Laboratories, LC) is a licensed thiazolide anti-infective that is currently in advanced stages of clinical development for the treatment of chronic hepatitis C. Previous studies demonstrated that NTZ and its active metabolite, tizoxanide (TIZ), exhibit potent antiviral activity against multiple genotypes of HCV in cell culture, but the antiviral mechanism has remained undetermined. The current investigation sought to provide support for an antiviral mechanism of action. HCV replicon cell lines were treated with NTZ, and the levels and status of viral and specific cellular proteins were followed by Western blot, immunoprecipitation, and *in vitro* assays for enzymatic activities. TIZ was inactive against HCV polymerase, protease, and helicase in enzymatic assays. The overall rate of reduction of HCV proteins in NTZ-treated HCV replicon cell lines was consistent with loss of viral RNA template. Intracellular membrane preparations (where replication of HCV is localized) revealed that 48–72 h of NTZ-treatment induced a 4–6-fold enhancement of hyperphosphorylated HCV NS5A (p58), and a similar reduction in the levels of basally phosphorylated NS5A (p56). The phosphorylation state of NS5A is established as a regulator of the switch from active viral genome replication to packaging and assembly; overproduction of p58 is known to inhibit HCV replication. Casein kinase I-alpha (CKIa), is the cellular kinase responsible for conversion of HCV NS5A p56 to p58. CKI activity in intracellular membrane preparations from NTZ-treated HCV replicon cells was 3–4-fold higher than those from untreated cells, as measured in enzymatic assays. However, TIZ had no direct effect on purified CKIa activity in enzymatic assays, including autophosphorylation. These data provide a primary antiviral mode of action for NTZ against HCV: overproduction of the hyper-phosphorylated form of HCV NS5A, associated with enhancement of the cellular enzyme activity responsible for NS5A hyperphosphorylation. Since TIZ appears to have no direct effect on CK1a in enzymatic assays, we hypothesize the primary cellular target for TIZ is a protein involved in the upstream regulation of CK1a.

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