

★ Hepatitis C is a major public health issue. **Dr Matthew Albert**, in his 2008 ERC Starting Grant project, aims to provide new insight into the intriguing and at times subversive interplay between virus and host, taken from the perspective of type I Interferons (IFNs) and IFN induced gene products

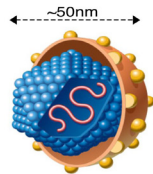
The Great Escape – a true story about hepatitis C and host immunity

The ERC project awarded to Dr Matthew Albert's team tackles a major public health issue, that of hepatitis C (HCV). HCV presents a significant public health problem with approximately 180 million infected people worldwide and challenges immunologists in several ways, as the immune system seems to be effective in clearing the virus in a significant subset of people, yet it is also responsible for much of the morbidity associated with chronic HCV infection. The World Health Organisation has referred to HCV as a 'viral time bomb', as chronically infected individuals are at risk of developing cirrhosis, hepatocellular carcinoma (HCC) and non-Hodgkin's lymphoma. Strikingly, liver inflammation and chronic immune stimulation seem to be entwined in the pathogenesis of these sequelae.

Dr Albert organised his laboratory using a 'bedside-to-bench' approach to translational research. For many reasons, including the significant public health need and the suggested mechanisms involved in viral clearance, he focused on HCV with an interest in better defining the role of the immune system in achieving viral clearance. "HCV offers a unique opportunity to define the immunologic mechanism of action both in patients who spontaneously clear the virus and in chronic patients who successfully respond to the existing treatment interferon and ribavirin," says Dr Albert. "We have a positive control, thus allowing for the definition of true correlates of immunity and providing a tractable strategy for evaluating what is happening in those patients who are refractory to care." His laboratory projects offer a clear vision of this approach.

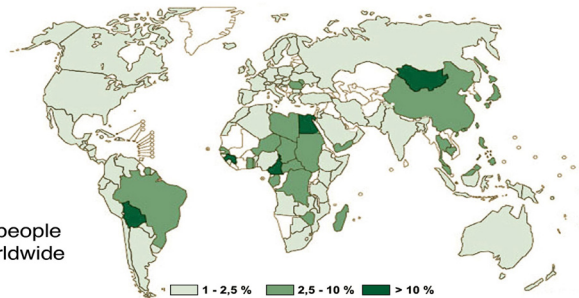
The Egyptian focus

Albert's project offers special attention to Egypt, the country with the most significant epidemic. Among adults, the



- Isolated in 1989, 6 genotypes now identified
- Belongs to the Flavivirus family (dengue, yellow fever...)
- Small RNA+ virus (9.6kb)
- Transmission via exposure to infected blood

180 million people infected worldwide



Source: World Health Organization

Hepatitis C virus (HCV) represented top left is an enveloped RNA virus and is responsible for approximately 180 million infections worldwide. The world map indicates HCV prevalence by country

proportion infected is estimated at 20 per cent in rural areas, and 10 per cent in urban areas, as compared to only 1 per cent of adults that are infected in Western countries. This epidemic is the result of a mass campaign of anti-schistosomiasis

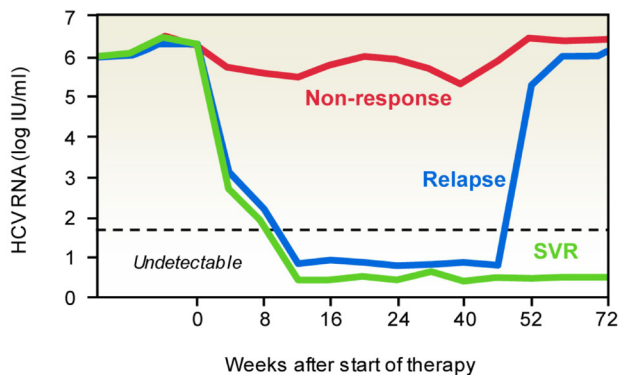
Plot immunity

Contrary to other chronic infections such as HIV, clearance of HCV is possible. Such clearance may occur spontaneously during the acute phase of infection or in response to therapeutic administration of type I

“ **The project will help push forward our understanding of the HCV disease pathogenesis** ”

(bilharziasis) treatment carried out in the 1960s-1970s. During these field campaigns, intravenous injections were given to more than 7 million individuals, allowing HCV (unknown at the time) to spread among the treated individuals as a result of insufficient sterilisation of needles used for injection.

interferon (IFN), typically given in combination with anti-viral agents such as ribavirin. Of note, 50 per cent of HCV genotype 1 or genotype 4 patients clear the virus in response to IFN therapy, but the mechanisms of clearance are not currently understood, nor do researchers yet possess the ability to accurately predict which



The graph indicates possible clinical outcomes for response to treatment of chronic HCV disease. SVR refers to sustained virologic response.

individuals will benefit from treatment.

The ERC project focuses on the virus evading the immune system at two stages: at the early stage of infection by studying the acute phase of the disease and at treatment stage for patients who suffer from persistent infection. Specifically, the ERC project aims to identify key points of immune dysregulation where HCV infection interferes with the generation of viral immunity. Based on prior results from the laboratory and through collaborative clinical partnerships in France and Egypt, the laboratory has focused on the study of the adaptive immune response in HCV infection as well as the search for biomarkers predictive of viral clearance with the hope that this latter approach could help identify, pre-treatment, which individuals will respond to their IFN α / ribavirin therapy.

Specifically, the ERC aims to define the role of IFN and IFN-induced genes in HCV clearance – this is being explored during acute infection and the paradoxical role they play in making chronically infected patients resistant to their exogenous IFN therapy – and to characterise the effect of IFN and IFN-induced gene products in the cross-priming of CD8+ T cells; there is indeed evidence to suggest that HCV-reactive CD8+ T cells are activated by an indirect pathway called cross-presentation

(dendritic cells capturing exogenous viral antigen and presenting it on MHC I) and early results from the ERC grant indicate that IFNs influence this pathway in complex ways.

Thus far, the project has made it possible to identify a novel mechanism of immune regulation that appears to influence a patient's ability to respond to therapy. This observation concerns the disruption of T cell migration, possibly affecting their ability to access the liver and target infected hepatocytes. For Dr Albert, this observation highlights an important matter of regulation and may shed light on why clearance is possible during acute infection but not after chronic inflammatory processes have taken root. In addition, this work would establish a new mechanism of viral escape with potential impact for the understanding of other chronic infections. Perhaps even more important, the observations, if shown to be critical factors in disease pathogenesis, may result in new therapeutic strategies. Indeed, as part of the project, Albert hopes to test his ideas at the bedside of patients with the aim of modulating T cell trafficking in order to improve response to therapy. The project will help push forward our understanding of the HCV disease pathogenesis and lead to the development of new diagnostic tools as well as strategies for improving upon existing therapeutic strategies. ★

HCV PROJECT COLLABORATORS

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At a glance

Full Project Title

The paradoxical role of type I interferons in hepatitis C disease pathogenesis and treatment (HCV-Immunology)

Project Funding

1 million euros

Project Duration

60 months

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Born in New York in 1970, Matthew Albert was trained at Rockefeller University (PhD, Immunology & Clinical Scholar), Cornell University Medical College (MD) and The New York Presbyterian Hospital (Resident in clinical pathology). He is currently heading a mixed INSERM / Institut Pasteur Research Unit. In addition, he is the founder and director of the Center for Human Immunology at the Institut Pasteur, Paris. Matthew Albert was granted the European Starting Independent Investigator Award in 2008.