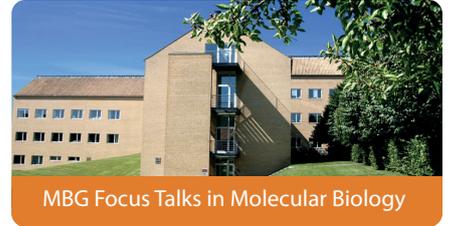


# MBG FOCUS TALK

hosted by Rune Hartmann



**Wednesday 10 October 2018 at 09:15-10:00**

Dept. of Mathematics, Aud. D1 (1531-113)

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## **Evolution of Interferon Lambda 4 and its Impact on Human Health and Disease**

Type III or interferon lambdas (Ls) are critical antiviral signalling proteins that act primarily at barrier tissues and protect against viral infection in lung, gut and liver. One IFNL – IFNL4, is polymorphic in the human population where ~ 50% of people carry a frameshift mutation that prevents its production. However, production of functional IFNL4 is associated with an increased risk of chronic hepatitis C virus (HCV) infection in humans. How an antiviral IFNL seemingly promotes viral infection is unknown & remains a paradox. Motivated to understand this issue, we carried out an in-depth characterisation of human IFNL4 genetic & functional diversity within and between closely related primate species. Through this approach we found that the 'pro-chronic HCV' human IFNL4 has evolved reduced activity following the human-chimpanzee split. Additionally, although very rare, some human populations still carry the ancestral IFNL4 variant conferring greater antiviral activity. Comparative gene expression meta-analyses between humans and chimpanzees infected with HCV suggests that this reduction in IFNL4 activity in humans is associated with lower IFN signalling in vivo in the liver and a worse outcome following HCV infection. The factor(s) have driving the evolution of an IFN with reduced activity in humans remain unknown but likely arose hundreds of thousands – to millions - of years ago. Furthermore, I will present data on the means through which the novel human activity-attenuating mutation acts. Finally, I will discuss evidence for non-redundant role of IFNL4 during antiviral immunity and thus how mutations affecting the protein function might impact health & disease.