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Nucleocytoplasmic trafficking of dengue non-structural protein 5 (NS5) is essential for Dengue infection; Vaccine applications?

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Dengue virus (DENV) is the causative agent of dengue fever, the most prevalent insect-borne viral disease, resulting in >100,000 deaths annually. With 40% of the world's population currently at risk, there is no licensed vaccine or efficacious therapeutic to combat DENV. DENV non-structural protein 5 (NS5) encodes the RNA polymerase and methyltransferase, required for synthesis and capping of nascent viral RNA respectively. Despite both these functions being required in the cytoplasm, NS5 localises strongly in the nucleus during infection, mediated by two nuclear localization signals, and is able to shuttle back to the cytoplasm by means of a nuclear export sequence. Using reverse genetics, we were able to show NS5 nuclear accumulation is essential for DV replication, with one of its key nuclear roles appearing to be to dampen the immune response resulting in higher virus production, and demonstrating the potential of virus with impaired NS5 nuclear import as a potential vaccine candidate. Current work, based on a novel screening approach using Alphascreen® technology, is aimed at identifying specific inhibitors of critical NS5 protein-protein interactions (eg. NS3, Imp-α/β, CRM1). Importantly, inhibitors thus far identified are not cytotoxic, active as inhibitors in live cells, and inhibit virus production. This approach has the potential to identify lead compounds as possible antiviral therapeutics for the much-needed treatment of dengue fever disease.

Biography

Prof. Jans completed his Ph.D at the age of 25 years at the Australian National University (Canberra) and postdoctoral studies at the Friedrich Miescher Institut (Basel, Switzerland) and Max Planck Institut fuer Biophysik (Frankfurt am Main, Germany). He is presently an NHMRC Senior Principal Research Fellow (SPRF1) and Head of the Nuclear Signalling Lab. at Monash University (Melbourne, Australia). He has >240 peer-reviewed publications in eminent journals (> 7000 citations; H-index of 49) and currently serves as an editorial board member of Biochemical Journal (since 2006) and committee member of the International Photodynamic Association (since 2005).