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From virus-host interactomics to perspectives in terms of drugability of protein-protein interactions

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This presentation fall within the scope of an emerging discipline at the convergence of virology and systems biology. Since the completion of the human genome, it is commonly admitted that identifying protein interaction network (interactomes) gives key clues to understand how parts work together and thus to reach to a mechanistic understanding of the cell. Similarly, interactomes are also susceptible to provide a support to conceptualize the intricate relationships between virus-host proteins. We performed pioneering analyses to decipher virus-host interactomes (virhostomes), using high-throughput innovative approaches. In order to identify specific signatures, correlating interaction datasets, protein sequences and structural informations with pathogenic traits, we have developed a new strategy based on comparative interactomics which was applied to a broad spectrum of viruses from HPVs, HCV to Influenza virus. These interactomic datasets were generated by combining two orthogonal strategies: yeast two-hybrid and a newly designed high-throughput Gaussia princeps luciferase-based protein fragment complementation assay which can be declined in vivo on human cells as well as in vitro. Integrative analyses of the resulting virhostomes have highlighted a viral singularity characterized by a strong tendency to target highly central and interconnected cellular proteins. These "hubs" and "bottlenecks" proteins are enriched in essential proteins involved in critical cellular processes such as cell cycle control, cellular innate immunity, apoptosis, ubiquitin-proteasome pathway and cellular transport machinery. Furthermore, in order to monitor virus-host protein interaction in the course of infection, we adapted our split-luciferase assay to a transfection-infection or an infection only setting. This later approach was applied to influenza viruses with promising perspectives to identify new therapeutics.

Biography

Yves Jacob, MD, PhD is group leader in virus-host interactomics in the Molecular Genetics of RNA Viruses Unit in the Department of Virology, Pasteur Institute Paris. He has received a MD from Lariboisière-St Louis School of Medicine, Paris University in 1983 (mentor Prof Jean Dausset, awarded Nobel Prize 1980), and after a three years residency/clinicat in Necker Hospital in Paris, he joined the Pasteur Institute and received a PhD in Philosophy from the Denis Diderot University in 1992. Since 2001, after completing his postdoctoral training in virology, his is senior scientist in the Department of Virology at Pasteur Institute in Paris. The main line of investigation of his team concerns virus/host interactomics with pioneering analyses using high-throughput innovative approaches combining a yeast two-hybrid pipeline with an orthogonal assay performed in human based on complementation of a split-luciferase. Since several years, a close collaboration was also established with the Center for Cancer Systems Biology (CCSB, Harvard Medical School), a center of excellence which has generated first-draft models of the human interactome. By plugging virus interactomics datasets onto these models, the main goal of his team is to answer questions such as how perturbations in complex networks induced by viral hijacking lead to pathogeny. Since 2012, Dr Jacob shared time between Pasteur Institute in Paris and CCSB in Boston.

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