

2013 ACTERIA Early Research Prize – Final Report

Nicolas Manel – 8 September 2016

DECRYPTING THE INNATE SENSING OF HIV BY DENDRITIC CELLS AND ITS IMPACT ON IMMUNE RESPONSES

The goal of the 3-year funded ACTERIA project was to decipher how innate sensing of HIV by dendritic cells operates at the molecular level, and to determine how it impacts the overall immune response. Through the study of HIV innate sensing, we identified a critical new player in the replication of HIV, the protein SUN2 that is located in the nuclear envelope (Cell Reports, 2016, doi:10.1016/j.celrep.2016.03.074). This work opens a fascinating avenue of research to understand how the nuclear envelope functions, as a critical barrier that the virus must overcome to reach the cellular DNA for its replication. We also discovered that viral particles of HIV can package and transport the small molecule 2'3'-cGAMP, a second messenger that activates antiviral immunity. This establishes that the immune system can use viruses as Trojan horses to disseminate immune activation signals between cells (Science, 2015, doi:10.1126/science.aab3628). This work additionally unveiled new exciting opportunities to develop vaccines and immunotherapies based on this mechanism. The results that we obtained also enabled us to engage in active collaborations, and we made essential contributions to the study of functional flexibility of CD4⁺ T lymphocytes (Nature Communications, 2014, doi:10.1038/ncomms4987), to the identification of pathogenic human mutations in the innate sensor STING (The Journal of Clinical Investigation, 2014, doi:10.1172/JCI79100) and to the discovery that the nuclear envelope of normal cells can rupture in interphase due to mechanical constriction of the nucleus that occurs during migration (Science, 2015, doi: 10.1126/science.aad7611). Finally, we published three review articles on HIV sensing (Current Opinion in Immunology, 2015, doi:10.1016/j.coi.2014.12.003; Current Opinion in Virology, 2015, doi: 10.1016/j.coviro.2015.01.013; Nature Reviews Immunology, 2015, doi:10.1038/nri3850). ACTERIA funding played a critical role in enabling these contributions, and unlocking new research directions.

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