

**Master 2 internship project  
Year 2021-2022**

**Laboratory/Institute:** IBS

**Team:** High Throughput Technologies (VRM)

**Director:** W. Weissenhorn

**Head of the team:** Darren Hart

**Name and status of the scientist in charge of the project:** HDR: yes  no

**Address:** IBS, 71 avenue des Martyrs, 38000 Grenoble

**Phone:** 04 57 42 85 86

**e-mail:** darren.hart@ibs.fr

**Program of the Master's degree in Biology:**

- Immunology, Microbiology, Infectious Diseases  Structural Biology of Pathogens  
 Physiology, Epigenetics, Differentiation, Cancer  Neurosciences and Neurobiology

**Title of the project: Directed evolution of Influenza virus inhibitors**

**Objectives:**

We use phage display to evolve high affinity peptide inhibitors of complexes that are essential for influenza virus replication. Hits are analysed by biophysics and X-ray crystallography. This represents a possible future therapeutic approach.

**Abstract:**

This project combines structural biology, synthetic biology and protein engineering on an important human pathogen, influenza. The mature polymerase enzyme of influenza virus is a heterotrimeric complex that interacts with host cell machinery. We identified contact regions within both influenza and host complexes and are targeting these with high affinity synthetic peptides generated using phage display directed evolution (Chemistry Nobel Prize in Chemistry method 2018). We observe that, when added to infected cells or cells expressing polymerase recombinantly, these in vitro evolved high affinity peptides bind competitively and inhibit influenza virus replication.

**Methods:**

Phage Display, Directed Evolution, Molecular Biology, Protein Purification, Interactions using biophysical techniques, crystallisation.

**Up to 3 relevant publications of the team:**

1. Hart DJ & Waldo GS (2013) Library methods for structural biology of challenging proteins and their complexes. *Curr. Opin. Struct. Biol.* 23:403–408.
2. Reich S et al. (2014) Structural insight into cap-snatching and RNA synthesis by influenza polymerase. *Nature* 516:361–366.
3. Thierry E et al. (2016) Influenza Polymerase Can Adopt an Alternative Configuration Involving a Radical Repacking of PB2 Domains. *Mol. Cell* 61:125–137.

**Requested domains of expertise (up to 5 keywords):**

DNA handling, SDS-PAGE, protein purification