

## INTERNSHIP PROPOSAL

**Institute and Group: IBS (Virus Replication Machines)**

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**Research project title:**

***Directed evolution of peptide inhibitors against influenza virus***

**5 Keywords to describe the project:**

***Protein engineering, phage display, viral enzymes, activity assays, synthetic biology***

### **Description of the project:**

*Aims:* Influenza epidemics and pandemics are a serious health risk. Vaccination is important, but not always effective, so antiviral drugs are necessary. Peptides that block interactions between subunits in a complex provide an alternative strategy to small molecule inhibitors targeting active sites. We are using phage display directed evolution (2018 Nobel prize method), to identify peptides that mimic natural regions of the influenza polymerase and interfere with enzyme assembly. Information from crystal structures is used to design the random phage display library and hits are characterised initially in the lab, and then in cell-based assays (collaboration).

*Experimental techniques:* Phage display of large random libraries ( $\leq 10^8$  variants), ELISA, biophysical methods (ITC, Biacore), X-ray crystallography.

*Recommended background:* Interest in virology, protein engineering, molecular biology and technology development.

### **Justification that the internship's subject fits with the general theme of GRAL (3 lines):**

This new project fits *host-pathogen interactions* and *method development* themes. It will build on preliminary phage-display results from our Fondation de Recherche Medicale (FRM) project. Collaborations with IBS and EMBL teams are envisaged.

### **Relevant publications of the team (3 max):**

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. Thierry E, Guilligay D, Kosinski J, Bock T, Gaudon S, Round A, Pflug A, Hengrung N, Omari K, Baudin F, Hart DJ, Beck M, Cusack S (2016) Influenza Polymerase Can Adopt an Alternative Configuration Involving a Radical Repacking of PB2 Domains. *Mol. Cell.* 61:125-137.
3. Delaforge E, Milles S, Bouvignies G, Bouvier D, Boivin S, Salvi N, Maurin D, Martel A, Round A, Lemke EA, Ringkjøbing Jensen M, Hart DJ\*, Blackledge M\* (2015) Large-Scale Conformational Dynamics Control H5N1 Influenza Polymerase PB2 Binding to Importin  $\alpha$ . *J. Am. Chem. Soc.* 137:15122–15134.