Grenoble Alliance for Integrated Structural & Cell Biology

INTERNSHIP PROPOSAL

Institute and Group: IBS (Virus Replication Machines)

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Research project title:

Directed evolution of peptide inhibitors of influenza virus

5 Keywords to describe the project:

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

Description of the project:

Aims: Many host-pathogen functions are performed by multi-protein complexes. Inhibiting their activities requires small molecules that normally target binding or catalytic sites. Such complexes also possess protein:protein interaction interfaces that, if blocked by competing molecules, may inhibit complex assembly and function; however, design of small molecule inhibitors of protein interactions is notoriously difficult. We will use influenza polymerase structures to identify interacting linear peptide regions (20-30 aa) and use these as the basis for blocking complex assembly.

Experimental techniques: Phage display of large random libraries ($\leq 10^8$ variants) of 20-30 aa linear peptides will be "panned" to identify those that bind their target with high affinity. These will be characterised by biophysical and structural methods e.g. Biacore, ITC, X-ray crystallography.

Recommended background: The student should be interested 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 establish phage-display and directed evolution-type approaches for use in other projects. Collaborations with IBS and EMBL teams is 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* in press.
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 α. *J. Am. Chem. Soc.* 137:15122–15134.