



**The objectives of FragNet are to (a) train a cohort of ESRs across FBLD methods and (b) develop individual skills in research into either new methods in FBLD or to apply FBLD to interrogate biological systems.**

We are looking for highly motivated and talented students with a MSc degree who are interested in an ambitious multidisciplinary project on Fragment-Based Lead Discovery (FBLD).

**At this moment we have 15 vacancies**



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### **ESR13: Fragment-based assessment of new antibiotic**

**Host:** University of York, UK

**Academic supervisors:** Prof. dr. Peter O'Brien and Prof. dr. Rod Hubbard (University of York)

**Industrial Supervisor:** Dr Laurent-Michel Vuillard (Servier)

### **Synopsis**

Fragment-based approaches will interrogate protein targets and identify potential drug targets.

### **Objectives**

1. To use computational screening methods to characterise a set of proteins from the bacterial DNA replication machinery.
2. To over-express, purify and characterise protein for at least two such targets, determining crystal structures.
3. Conduct screening against the targets, identifying and characterising fragment hits.
4. SAR by catalogue and limited chemical synthesis to optimise the fragment hits and assess in bacterial replication assays.

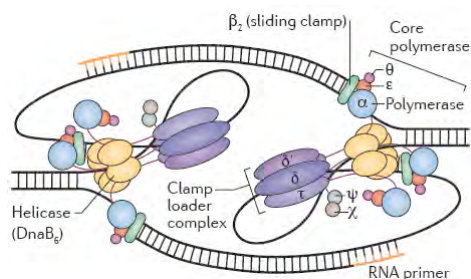
### **Approach**

The student will use the methods of fragment-based discovery[1] to assess which of the proteins in the bacterial replisome are potential targets for antibiotics. The bacterial replisome consists of some 15 proteins which together replicate DNA within a bacterial cell. The McGlynn group is one of the few in the world that can reconstitute this molecular machine in the test tube. The aim of this project is to use fragment-based methods to assess whether any of the proteins (or the complexes they make) are suitable targets for the development of new classes of antibiotics. The crystal structures for many of the proteins are already available

and another laboratory has already identified fragments and optimised compounds for one of the proteins (the  $\beta$  sliding clamp)[2]. Preliminary screening of the York fragment library is planned for Summer 2016 and the outcomes of these screens will inform the precise direction of the project. There are multiple assays available to characterise the effect of any inhibitory fragments on the functionality of the entire replisome, subcomponents and individual enzymes[3-5]. The project will focus on fragment hits for a number of different targets, characterise binding using biophysical methods such as NMR, SPR and ITC, determine crystal structures of the fragment-enzyme complexes and explore preliminary optimisation of the compounds by purchase of similar compounds. In addition, there will be opportunities for computational work centred on identifying potential inhibitor binding sites within individual replisome components using molecular docking calculations.

### **Qualifications**

The skills required are an interest in protein structure and function and an aptitude for the methods of characterising biomolecular interactions.





### Key publications

1. Hubbard *et al.* *Methods Enzymol*, **2011**, 493, 509-31.
2. Yin *et al.* *J. Med. Chem.* **2014**, 57, 2799-806.
3. Gupta *et al.* *J Biol Chem.* **2010**, 285, 979-87.
4. Gupta *et al.* *Proc Natl Acad Sci U S A*, **2013**, 110, 7252-7.
5. McGlynn *et al.* *J Mol Biol*, **2008**, 381, 249-55.



#### FragNet offers:

- Generously funded positions (duration 36 months) for 15 Early stage researchers (ESRs)
- High profile research projects in an Innovative European Training Network Program
- Excellent facilities for research and education
- Research training in both academic and industrial settings
- Training in state-of-the-art scientific and transferable skills
- Intensive contacts with international collaborators & secondments in other research laboratories

#### FragNet is looking for candidates that:

- are highly motivated and talented
- are able to work in a multidisciplinary team
- are keen on intra-European mobility to perform PhD research abroad
- have good communication skills

#### Selection criteria of the candidate:

- fulfil the eligibility criteria (ESR, international mobility) for Marie Skłodowska-Curie Innovative Training Networks (Horizon 2020)
- have a MSc degree in Life Sciences or obtain a MSc degree by September 2016
- have completed a research internship with relevant expertise
- have obtained high grades during his/her studies
- be fluent in English

#### Application procedure:

1. Send your application mentioning the **ESR number** in the subject line to [hrm@fragnet.eu](mailto:hrm@fragnet.eu).
2. **Deadline for applications: 31 January 2016.**
3. Please send all the necessary information as **one pdf file** to [hrm@fragnet.eu](mailto:hrm@fragnet.eu).
  - Detailed **CV** (include information on your BSc and MSc studies, languages, achievements, expertise)
  - **Motivation letter**, addressed to the FragNet selection committee, explaining your motivation why you apply with us. You have to indicate which FragNet ESR project(s) you are interested in (please motivate your selection and indicate which has your preference).
  - Provide contact details of at least 2 references (names, addresses, emails).
  - **Reference letter** from one of the enlisted references
  - Copies of your key educational certificates
  - **Transcript of Records** (i.e. documents enlisting your performance as BSc and MSc student over time by listing the course units or modules taken, credits gained and the grades awarded). If you have not completed your MSc degree yet include all grades obtained so far.
4. You may apply to more than one ESR position. If you do, submit a separate and dedicated application file for each position.
5. If applicable provide a language certificate Application is OPEN 3. The applications will be assessed by the FragNet selection committee, in which all group leaders are represented. Candidates are in particular evaluated on creativity, originality, intellectual capacity and quality of CV and motivation letter. The selection committee also takes into account interdisciplinary and gender balance.
6. Potential (Skype) interviews will be arranged with the group leaders associated with the ESR projects.
7. The ultimate starting date for the ESR projects is: **1st September 2016**, as the complete Fragnet ESR cohort will participate in the first Fragnet workshop that will be organized in York, UK in September 2016.

For other FragNet related questions please contact: [info@fragnet.eu](mailto:info@fragnet.eu)

#### Eligibility criteria

Eligibility criteria of Marie Curie Initial Training Networks apply. Only applicants who comply to the following conditions will be considered:

#### Conditions of experience (ESR)

Candidates must be, at the time of recruitment by the host organisation, in the first four years (full-time equivalent) of their research careers and have not yet been awarded a doctoral degree. This is measured from the date when they obtained the MSc degree which would formally entitle them to embark on a doctorate.

#### Conditions of international mobility

Eligible candidates may be of any nationality but must not, at the time of recruitment have resided or carried out their main activity (work, studies, etc.) in the country of their host organisation for more than 12 months in the 3 last years immediately prior to the reference date.



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