Call for applications: Post Doctoral Position

Reseach Topic:

The project is based on a multi-disciplinary integrative approach combining different computational methods directed to deciphering the activating molecular mechanisms of receptor tyrosine kinases (RTKs) drug-resistant mutations. RTKs activate crucial cell signalling pathways and as such, they play pivotal roles in virtually all aspects of cellular physiology [1]. The deregulation of their activity, mainly caused by mutations, is associated with many forms of cancer. Currently, the area of tyrosine kinases (TKs) inhibitors research is facing two major challenges, increasing selectivity/specificity – almost all inhibitors are ATP-competitive, and overcoming resistance [2]. To meet these challenges, we propose an innovative strategy consisting in identifying conformational states specific to oncogenic resistant mutated forms of RTKs and targeting these conformations by small molecules, typically allosteric modulators/inhibitors. The last years have seen the emergence of the definition of pertinent targets together with the accurate description of their dynamical behaviour as an essential strategy of drug discovery projects [3,4].

Job description:

The main objectives are (i) to fully characterize the structural, dynamics and thermodynamics changes induced by oncogenic resistant mutations in RTKs, (ii) to identify putative binding sites in peculiar intermediate conformations between inactive and active sates as suitable targets, (iii) to design a new generation of TKs inhibitors/modulators effective on currently resistant forms.

Combining *in silico* molecular dynamics (MD) studies, binding site mapping, and protein ligands design with *in vitro* functional biological and structural validation, we intend to provide keys defining the determinants of RTKs activation/deactivation processes and molecular recognition of their targets/ligands [5-10]. We ambition to apply this knowledge to identify new potent inhibitors/modulators effective on resistant forms of targets. We believe our work will open an avenue for novel rational strategies for the design and development of new efficient anti-cancer targeted treatments delivered from experimental evidence and theoretical modeling and simulations. Hence it bears a great potential impact on fundamental biology and human health.

The post-doctoral fellow will be in charge of performing molecular modeling and data analysis. He (She) will also work in collaboration with the biological research teams (Molecular Oncology and Pharmacology LBPA, LabEx LERMIT, Research Centre in Cancerology, Marseille), clinicians (Institute of Gustave Roussy, Hospital of Necker), physicians (University of Orleans) and mathematicians/informaticians (FARMAN Institute at ENS de Cachan).

References:

[1] Lemmon M.A., Schlessinger J. (**2010**). *Cell* **141**: 1117-1134
[2] Liu Y., Gray N.S. (**2006**). *Nat. Chem. Biol.* **2**: 358-364.
[3] Laine E., Goncalves C., Karst J.C., Lesnard A., Rault S., Tang W.J., Malliavin T.E., Ladant D., Blondel A. (**2010**). *Proc. Natl. Acad. Sci. U S A* **107**: 11277-11282.
[4] Lee G.M., Craik C.S. (**2009**). *Science* **324**: 213-215.
[5] Laine E., Chauvot de Beauchêne I., Auclair C., Tchertanov L. (**2011**) *PLoS Comput. Biol.,* **7.** e1002068.
[6] Chauvot de Beauchêne I., Laine E., Auclair C., Tchertanov L. (**2011**). *Eur. Biophys. J. Biophys. Lett.* 40:S103.
[7] Laine E., Chauvot de Beauchêne I., Auclair C., Tchertanov L. (**2011**). *Eur. Biophys. J. Biophys. Lett.* 40:S109.
[8] Laine E., Auclair C. & Tchertanov L.(**2012**). *PLoS Comput. Biol.,* (*in press*)
[9] Laine E, Auclair C. & Tchertanov L. **(2012**). *Biophys J.* (*in press*)
[10] Da Silva Figueiredo Celestino P., Laine E., Pascutti P. L. Tchertanov. (**2012**). *Biophys J.* (*in press*)

Qualifications: PhD in a relevant field: Bioinformatics and Molecular modeling or Structural Bioinformatics or Theoretical Physics or Theoretical Chemistry or Biophysics. Track record of published work.

Skills:
Essential: Strong theoretical and practical skills in a least one the following fields: molecular modeling, structural bioinformatics or a background in mathematics/scientific programming applied to molecular computing.
Desirable: Structural biology; Pharmacology

Hiring restrictions: The candidates can be any nationality. ***The position is planned to start as soon as possible*** (1 September or 1 October 2012).

Location: Bioinformatics, Molecular Dynamics and Modeling (BiMoDyM) team (**http://tinyurl.com/tchertanov**), Molecular Oncology and Pharmacology, LBPA, ENS de Cachan, France

Salary: Post doctoral position is founded by OSEO-ISI agency in the frame of the join private/public APAS-ITK program. APAS-ITK is dedicated to the development of new highly specific kinase inhibitors for the treatment of cancer and inflammatory diseases. The funding for this position is initially for 12 months (renewable for the 2nd year) with a salary up to 2 100-2 300 € net according to candidate expirience.

Application process: send you CV to Luba Tchertanov: Luba.Tchertanov@lbpa.ens-cachan.fr
Application should consist on curriculum vitae, list of publications, cover letter explaining why you wish to be considered for the position and how you meet the essential job requirements, and the names of at least two referees who may be approached in advance of interviews.