EMBL INTERDISCIPLINARY POSTDOCS (EIPODS)

SELECTION 2010

Short Title: Rational design of transposon-based genetic tools

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DNA transposons are mobile genetic elements that have the ability to move from one genomic location to another. They can be engineered to carry desired genetic information and offer stable and heritable modifications of a target genome. In vertebrates, the reactivated transposon *Sleeping Beauty* (SB) has recently become a favored genetic tool that is used for multiple applications, including forward mutagenesis screens, discovery of oncogenes and tumor suppressors, identification of gene regulatory landscapes and chromosomal engineering[1]. Moreover, SB has also allowed the first transposon based gene therapy vector to emerge to clinical trials[2].

The reasons of this widespread use of *Sleeping Beauty* lie in its attractive characteristics, notably its high transposition efficiency in somatic and germ cells from various mammals and its random target site selection. Besides, SB activity is known to be influenced by chromatin status, and transposition occurs favorably locally. The mechanistic basis of these features, are unknown and should be further investigated to either improve or exploit them and create novel genetic tools.

The current lack of molecular mechanistic data is greatly hampering the improvement of SB and the design of advanced (e.g. hyperactive or better controlled) transposases. While past approaches in this direction have so far relied on random mutagenesis, we aim to elucidate the transposition mechanism of the SB transposon, and use this information to rationally design a SB-based genetic toolset offering novel applications in mammalian genetics.

The post-doctoral fellow will collect and analyze structural, biochemical and large scale *in vivo* data to better understand the mechanism of SB transposition. Based on these mechanistic insights he/she will modify transposon DNA, transposase or both with the aim of creating a variety of artificial SB transposon cassettes with different properties. He/she will then characterize the activity of these new rationally designed SB cassettes and transposases, biochemically (Barabas lab), as well as in cell culture and in animal models (Spitz lab).

We invite applications from highly motivated candidates with a background in molecular or cellular biology and a strong interest in application driven interdisciplinary basic research. This project will offer training and expertise in a wide range of techniques in biology research from molecular structure determination (X-ray crystallography), through biochemistry, cell culture and animal work. The candidate will be able to build on solid expertise and receive quality training in all of these areas in the two partner labs. In addition, he/she will have the special opportunity to bridge basic research methodology and insights with an application-driven perspective.

1. Ivics, Z. et al. Transposon-mediated genome manipulation in vertebrates. *Nat Methods* **6**, 415-22 (2009).
2. Williams, D.A. Sleeping Beauty vector system moves toward human trials in the United States. *Molecular Therapy* **16**, 1515-1516 (2008).