Researcher, Post-doctoral level (15 months)

Research Unit : UMR 8227: Laboratory of Integrative biology of Marine Models
Location: Station Biologique de Roscoff (on the north coast of Brittany, FRANCE)
Function: Structural investigation of RNA : protein interactions
Salary: 2900 €/month (approx.). The grant (SAD) is issued by The Region of Brittany.
The candidate must have worked 12 months (at least) between June 2014 and May 2017 outside France.

The team « Translation, Cell Cycle and Development » investigates the regulation of translation initiation at the early stages of development, mainly in the sea urchin model. We aim to highlight the impact of RNA structural elements on the control of when and where the translation of a specific mRNA is initiated. The role of the future recruit will be to foster the structural approaches required to fully understand the mechanisms by which a messenger RNA is driven to be translated into a protein.

PROJECT
At the core of the translation process is the messenger RNA (mRNA), which beyond its function of code to be translated into a protein, comprises structural elements of variable stability. These are essentially located in the untranslated regions (5'UTR and 3'UTR) and participate to the control of translation. The general mechanism of mRNA activation and loading on the active ribosomes goes through the recognition of the cap structure at the 5'-end, assembly of the preinitiation complex and scanning of the RNA to find the initiation codon (1). This may be influenced by signature sequences, such as the 5' oligopyrimidine (5'TOP) motif, bound by the protein LARP1 to control ribosome biogenesis (2). Another mechanism consists of directly loading the ribosome in the vicinity of the initiation codon. This is the case of viral messengers, where recruitment of the ribosome is achieved thanks to special IRES (Internal Ribosome Entry Site) structures of the RNA (3). Functional IRESs have also been demonstrated in non-infected cells, but only few examples of structural elements (loops, double-stranded regions) of the RNA were given thus far (4), suggesting the participation of RNA-chaperone or RNA-binding proteins in the mechanism (5). Other structures of the mRNA have been shown to be involved in defining where translation takes place, or to coordinate synchronous translation of several mRNAs. This is the case of a stem-loop found in the 5'-UTR of the collagen alpha-1 and alpha-2 mRNAs, which ensures proper stoichiometry of the collagen fiber. It involves the LARP6 protein, which binds the stem-loop and prevents ribosome loading on the initiation codon. Interestingly, the stem-loop and LARP6 are also involved in focusing the translation of collagen at discrete foci of the endoplasmic reticulum (6). These few examples underline that there are many RNA recognition events by which specific (e.g. LARPs) or less specific

RNA-binding proteins (such as translation factors) contribute to the assembly of the initiation machinery.
The Translation, Cell Cycle and Development team wishes to complete current traditional biochemical investigations of complex formation to include structural approaches such as crystallography and SAXS to understand mechanisms of assembly at stake in translation initiation. To lay the foundation for structural work and as a first insight into the type of complexes that assemble on the 5'UTR of mRNAs we propose to tackle complexes involving proteins of the LARP family. Until now, as we have shown in LARP7 (7), the LA-module was known to use its two domains LAM and RRM in a side-by-side configuration to clamp the end of an RNA chain. The LA-module of LARP6 binds the RNA in a different way (8). It involves the interdomain linker to constrain the configuration of LAM and RRM to generate a specific surface to recognize the hairpin structure. In order to establish how this works, and in collaboration with Pr Maria Conte (King's College, London), a crystallographic study of the LARP6 complex with the collagen stem-loop will be attempted in parallel with SAXS investigations. Future research within the structural project will include the new complexes discovered during our investigations on cellular IRESs involved in translation initiation after fertilization in the sea urchins.

COMPETENCES :
The work is at the boundary between biochemistry and structural expertise. Proficiency in RNA biochemistry is required but candidates with basic knowledge of RNA will be considered if their field of expertise in structural investigations (crystallography, SAXS) includes analyses of complexes.

CONTACT
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