Project 1.4 N-DRC proteins in cilia beating regulation and primary ciliary dyskinesia etiology

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Background:

Cilia are microtubule-based hair-like cell projections that play crucial sensory and/or locomotory functions. Their lack or defects result in multi-symptom disorders called ciliopathies. Basically, there are two types of cilia, immotile sensory and motile.
In humans, motile cilia are assembled by epithelial cells lining airways, brain ventricles, oviduct, and embryonic node. Coordinated ciliary beating is required for mucociliary clearance of airways, circulation of the cerebrospinal fluid, transport of oocytes and early embryos into the uterus, and motility of sperm cells as well as the proper arrangement of the main body organs during embryo development. Defects in the structure or function of motile cilia, cause so-called primary ciliary dyskinesia, PCD, that affects one per 15-30 000 individuals. In about 30-40% of cases, the genetic background of PCD remains unknown.

Despite numerous studies that have been carried out during the last years, the knowledge regarding motile cilia protein composition and molecular mechanisms controlling their assembly and motion is still fragmentary. Such partial knowledge impedes the diagnosis of many PCD cases and the development of the therapy.
Nexin-dynein regulatory complex (N-DRC) is a major hub regulating and coordinating ciliary multiprotein complexes in order to translate their activity into cilia motion. Till now, mutations in three out of 11 N-DRC subunits (DRC proteins) were shown to cause PCD.

Aim:

The goal of the project is to dissect the role of DRC proteins in the transduction of signals that regulate cilia motion. Moreover, we want to uncover how PCD-causative mutations in DRC genes affect this process. Because cilia are highly evolutionarily conserved from protists to humans we will use simple models (according to 3R roles) to address this goal, ciliate Tetrahymena thermophila and mouse cell lines.

The implementation of the project will require, among others, analyses of the significance of DRCs' functional domains, analyses of proteins interactions, engineering cells with knocked-out DRC genes or expressing mutated DRCs (point mutations including PCD-causative mutations, truncation of the functional domains), and analyses how such alterations affect cilia motility.

During the Ph.D. course, the successful applicants will use a broad range of techniques, including cell biology, biochemistry, and molecular biology techniques.

Requirements:

- some experience in molecular and cell biology or biochemical methods are preferred but not obligatory
- passion for discovery and knowledge and scientific curiosity
- willingness to learn and take new challenges,
- ability to work independently and analytical thinking
- good interpersonal skills and a collaborative attitude.
- fluency in English