Profile N° (à remplir par VAS) **Funding Planned** MRT Non fléché **Obtained**

Sheet Abstract of thesis 2011 Disciplinary Fields Biologie fondamentale et Autres

Thesis Title : (1-2 lines)
Mitotic spindle centering and orientation in nematode embryo: an approach combining molecular cell biology and biophysics modeling

Unit/Team of framing : (1-2 lines)
UMR 6061, IGDR / group: CeDRE (reverse engineering cell division)

Name of the scientific director and co-director : (1 line)
Jacques Pécréaux (supervisor)

Contact : (1 line)
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Socio-economic and scientific context : (10 lines)

Cell division is an essential process and dysfunctions in its mechanism or regulation has deleterious effect on heath. Thus, a broad variety of approaches were adopted to decipher its regulation and molecular mechanism: molecular biology, biochemistry and biophysics in vitro already provides a vast knowledge of individual molecules; cell biology qualitatively describes mitosis events, while simulations and theoretical approaches propose qualitative understanding at cell scale. However, to quantitatively connect these micro- and macroscopic scales, a bottom-up, engineering approach is yet to be built. Avaialbility of these data, combined with microsopy and imaging technique developement make the moment just right for a reverse engineering, integrative approach. Spin-offs are manifold: e.g. fostering targetted cancer therapeutics developement, pinpoint peculiarities of cancerous cell division or stem cell research through studying asymmetric division.

Topic

Assumptions and questions (8 lines)
(see pecreaux.openwetware.org)
In the C. elegans one-cell embryo aymetric division, the spindle is oriented in response to polarity cues. It is also centered until anaphase onset, when it starts elongating but also moving towards the posterior and oscillating transversely. Positioning and orientation are key to successful division. Furthermore, orientation of the spindle is connected to the balance proliferation/differentiation (e.g. in brain development). From biophysics point of view, centering is extremely accurate. Several clues suggest that pulling forces exerted on centrosomes through microtubules may not be the centering mechanism. In a broader perspective, how biological systems can perform tasks with such an extraordinary fidelity and robustness despite their complexity and variability?

The main steps of the thesis and demarche (10-12 lines)
To address such questions, the team has developed microscopy and image processing tools to finely quantify spindle positioning. Furthermore, a mini-screen on 15 proteins, one per category/pathway putatively involved, is currently performed. The project will be broken into 5 steps: (1) By a simplified systems approach (collab.) combined with mini-screen, identify the putative pathways involved. (2) Hypothetizing a model (elaborated by Jacques Pécréaux and collab.), run-down identified players (RNAi, mutants,…) and challenge the model. (3) microtubule dynamics will likely be essential, thus we will measure it upon running-down proteins involved in centering. (4) Adress the question of orientation: is it the same mechanism than centering. Are pulling forces orienting the spindle ? is it a third mechanism. (5) The result will be merged with spindle centering model. (6) depending scientific interests and professional goals of the student, different ways will be possible: either (a) Compare with fly SOP (in coll. with a postdoc, HFSP funding already requested), or (b) merge the orientation/centering model with spindle mechanics (an other PhD student), or (c) highlight the role of dynein in centering (collab. Postdoc currently recruited), or (d) preliminary investigation of link with cancer.

Methodological and technical approaches considered (4-6 lines)
Approach combine experiments in vivo, (2) biophysics modeling and simulations, and (3) advanced quantification techniques. The PhD student is expected to work on (1): e.g. breed nematodes, RNAi proteins (feeding and injection, prepare dsRNA), cross fluorescently lines with mutants (genetics, PCR, DNA gels, sequencing), quantifying proteins (western blots), phenotype (image embryo by microscopy)…

Scientific and technical skills required by the candidate (2-4 lines)

(1) Molecular cell biology and to a lower extend genetics. (2) Knowledge in microscopy is a plus. Interest / knowledge in systems biology (bioinformatics) is advantageous. (3) An interest for biophysics and image processing is required though no education in these field is required.