CENTURI
TURING CENTRE
FOR LIVING SYSTEMS

# Contextualisation of signalling fluctuations in resilient versus vulnerable biological systems: an experimental and modelling approach

Lead supervisor: **Flavio MAINA - IBDM**
Co-supervisor 1: **Elisabeth Remy - I2M**
If applicable, name of co-supervisor 2:

**Abstract**
We explore cellular/molecular contexts at the root of resilience versus vulnerability of biological systems. An example we recently identified is how modulation of the stress support pathway switches resilience into vulnerability to WEE1 perturbation, and how this vulnerability is cell type specific (manuscript in prep). This contextualisation (conditioned by cell type and by quantitative stress support) is particularly interesting as WEE1 has distinct modes of action recently emerged, including regulation of an intact dNTP pool, histone levels, epigenetic processes, DNA repair, beside its established implication on cell cycle progression. We propose to use this example of cellular/molecular context to build a logical model combining mathematics with –omics and use this model to predict mechanisms governing the vulnerability versus resilience switch. Quantitative/qualitative approaches will be developed to contextualise the modelled network.

**Keywords:** signalling, cell vulnerability versus resilience, logical mathematical modelling, contextualization

## Objectives

**Aim 1)** Elaborate a logical model recapitulating WEE1 actions in cells, integrating the distinct modes of WEE1 action and highlighting their intersection. **Aim 2)** Analyse and simulate the model to predict signalling nodes and perturbators, which will be experimentally validated through biological/biochemical studies. **Aim 3)** Integrate outcomes to contextualise the modelled network with distinct biological contexts exemplifying resilience versus vulnerability.

## Expected profile

The candidate should preferentially have strong knowledge on biology, particularly on signalling, and must be interested in applying mathematical modelling for qualitative/quantitative approaches. An interdisciplinary experience previously acquired during his/her trainings will be particularly considered. Knowledge on mathematical modelling are not mandatory although desirable.

**Is this project the continuation of an existing project or an entirely new one?** This is an entirely new project at the root of a new collaboration between Remy and Maina teams, based on our recent discussions. This research program reflects a truly synergistic convergence on our main interests on signalling.

---

**Articles related to the project**

- Fan Y., Bazai S.K., Daian F., Arechederra M., Richelme S., Temiz N.A., Yim A., Habermann B.H., Dono R., Largaespada D.A., Maina F. *Evaluating the landscape of gene cooperativity with RTKs in liver tumorigenesis.* **J. of Hepatology,** 70(3): 470-482 (2019). PMID: 30529386.

- Fan Y., Arechederra M., Richelme S., Daian F., Novello C., Caldero J., Di Tommaso L., Morcrette G., Rebouissou S., Donadon M., Morenghi E., Zucman-Rossi J., Roncalli M., Dono R., Maina F. *A Phosphokinome-based screen uncovers new drug synergies for cancer driven by liver-specific gain of non-oncogenic RTKs.* **Hepatology**, 66(5):1644-1661 (2017). PMID: 28586114.

- Fan Y., Richelme S., Avazeri E., Audebert S., Helmbacher F., Dono R., Maina F. *Tissue-specific gain of RTK signalling uncovers selective cell vulnerability during embryogenesis.* **PLoS Genetics**, Sep 22;11(9):e1005533 (2015). PMID: 26393505.

- Katsogiannou M, Boyer JB, Valdeolivas A, Remy E, Calzone L, Audebert S, Rocchi P, Camoin L, Baudot A. *Integrative proteomic and phosphoproteomic profiling of prostate cell lines.* **PLoS One**. 2019 Nov 1;14(11):e0224148. doi: 10.1371/journal.pone.0224148. eCollection 2019. PMID: 31675377.

- Remy E, Rebouissou S, Chaouiya C, Zinovyev A, Radvanyi F, Calzone L. *A Modeling Approach to Explain Mutually Exclusive and Co-Occurring Genetic Alterations in Bladder Tumorigenesis.* **Cancer Res.** 2015 Oct 1;75(19):4042-52. doi: 10.1158/0008-5472.CAN-15-0602. Epub 2015 Aug 3. Erratum in: Cancer Res. 2016 Jan 15;76(2):505. PMID: 26238783.