PAUL SCHERRER INSTITUT

PSI

Wir schaffen Wissen – heute für morgen

Paul Scherrer Institut

Aurélien Rizk

Trafficking and Signaling of Receptor

Advisory Board Meeting

Personal Background

•2001-2004 : Preparatory classes in mathematics and physics for the French Grandes Écoles selective exams

•2004-2007 : Predoctoral diploma in computer science at École Normale Supérieure de Cachan

•2007-2011: PhD in systems biology at INRIA Paris-Rocquencourt, France

-developed tools for the development and analysis of chemical reaction networks

-application to the modeling of the angiotensin receptor signaling

•2011-2012: Postdoc at the Paul Scherrer Institute and at ETH Zürich

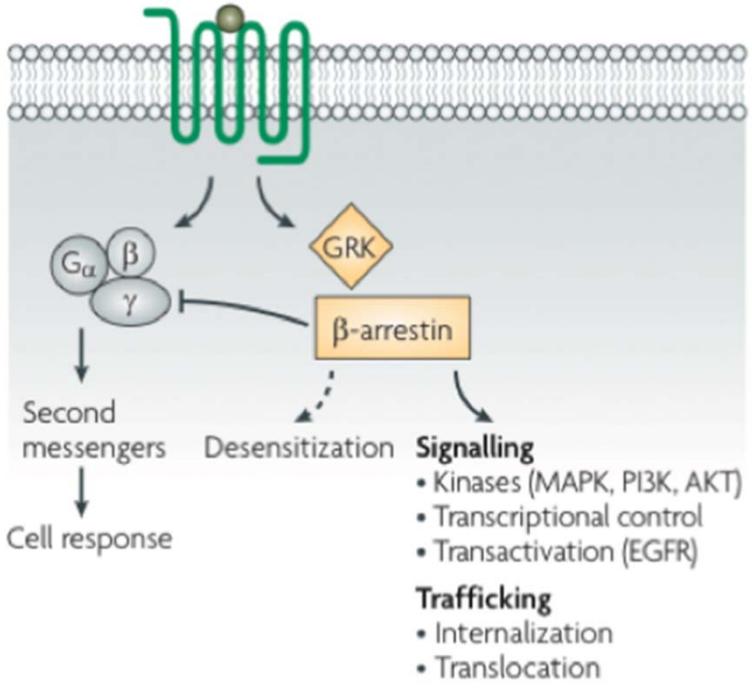
-developed an automatic workflow for the segmentation and colocalization of subcellular objects in fluorescence microscopy images (SystemsX IPP project)

January 2013 : PSI fellow on the trafficking and signaling of receptors

PSI-Fellow Project Scientific Background

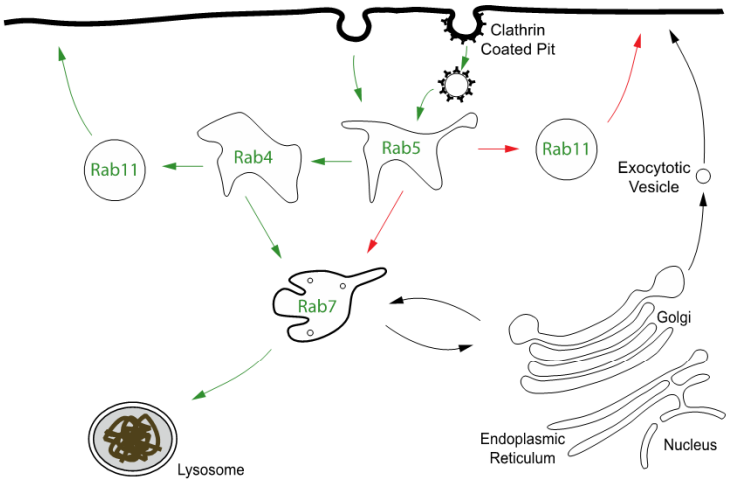
G protein coupled receptors (GPCRs) are **major pharmaceutical targets** (30% of all drugs).

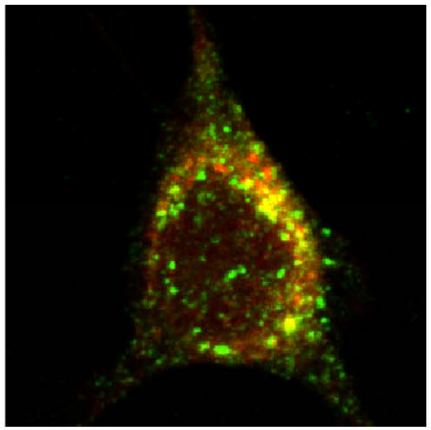
- GPCRs undergo conformational change upon ligand binding leading to activation of G protein
- phosphorylation allows **internalization** and activation of other signaling molecules
- development of drugs with specific action requires unveiling selective pathway activation mechanisms: **biased signaling**



Project: Study interplay between serotonin receptor 5HT2c **signaling** and the **trafficking** machinery. Combine signaling and fluorescence microscopy localization data into dynamic biochemical reaction and transport model.

First Results

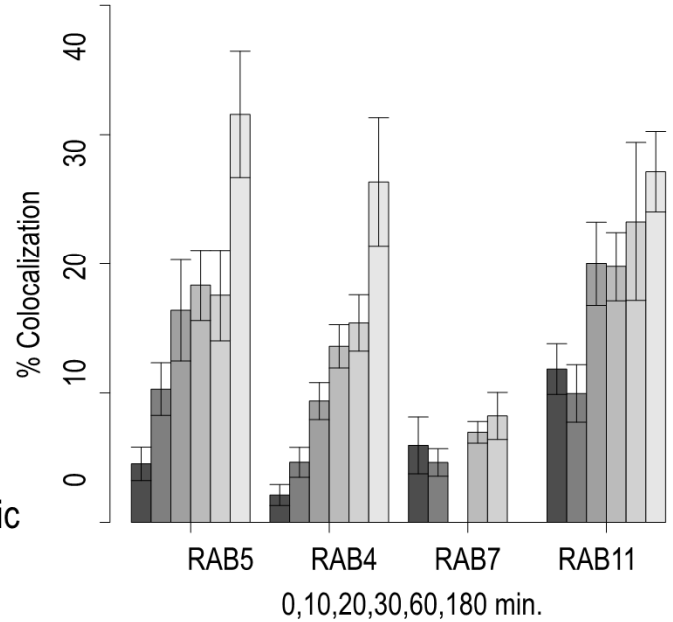




5HT2c receptor (green), RAB11 (red)
180 min after activation (z-projection)

500 3D confocal microscopy images

"Squassh" workflow for automatic segmentation and colocalization quantification



Dynamic distribution of 5HT2c receptor through 4 subcellular localizations

5HT2c receptor trafficking model (ODEs)

Publication Record

Publications

- Accepted (Nature Protocols): methodological paper on fluorescence images analysis workflow
- Planned (end of this year): extension of the analysis to three channels images
- Planned (next year): biological results paper on a model of serotonin signaling and trafficking

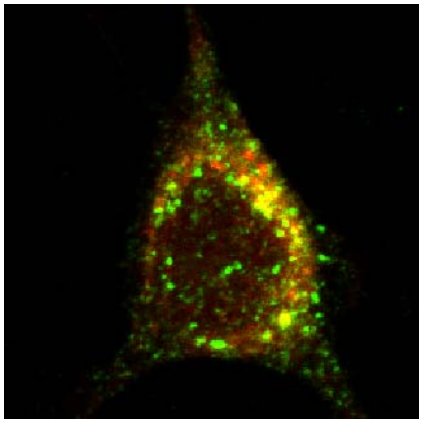
Conferences

- Poster at the Swiss Image Based Screening conference (SIBS Lausanne, June 2013)
- Invited talk at the Life Science in Switzerland meeting (LS2 Zürich, January 2013)

Collaborations

- Prof. Ivo Sbalzarini group, MPI Dresden (image analysis)
- Prof. Marcus Thelen group (CXCR7 trafficking)
- Prof. Luca Scorrano group, Université de Genève (mitochondria shape analysis)

Future work



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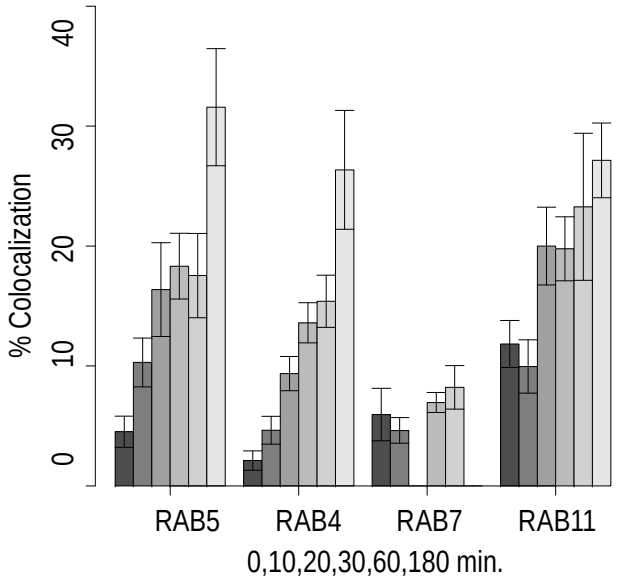
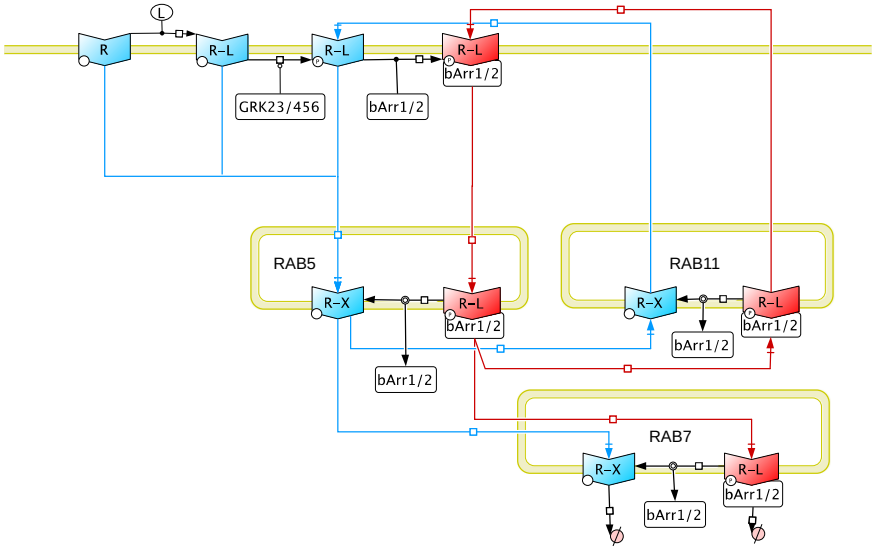


- screen other relevant trafficking compartments
- acquire data in other conditions (receptor mutants, trafficking regulators overexpression)
- acquire signaling data



- extend model to signaling pathways
- validate against 5HT2c signaling data from literature
- test hypothesis on mechanisms regulating signaling pathways

Contingency Plan

- Methodology for data acquisition and analysis is now established and tested.

Other possible applications from developed methodology:

- Relate signaling pathways to physiological outcome of drugs, find markers of undesired side effects
- Study other G protein coupled receptors
- Model variability amongst single cells
- Study cell trafficking machinery independently of receptors

Resources & Future Career

Resources

- Equipment for data acquisition and analysis is available at PSI (cloning, cell culture, SP5 Leica confocal microscope, Merlin cluster). Extension of systems biology group would allow to compare signaling across several G protein coupled receptors.

Future career

- Research position in academia in an interdisciplinary group working on systems biology
- My work at PSI in the BIO department complements my previous expertise in computational biology.
- I plan to use the mobility allowance to attend international systems biology conferences (ECCB, ISMB)

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