INTERNSHIP OPPORTUNITY
Massachusetts Institute of Technology / Whitehead Institute, MA, USA (2019, 2020)

Laboratory of **Professor David M. Sabatini**
Supervisor: **Izabella A Pena PhD,** Postdoctoral Fellow, Sabatini Lab, Whitehead Institute and Clinical Fellow, Department of Pathology, Massachusetts General Hospital
http://sabatinilab.wi.mit.edu

Prospective students, please contact Dr. Pena directly via email: ipena@wi.mit.edu
Attach your CV, and write a few lines (under a page long) explaining:
1) why this internship opportunity is interesting to you
2) why you think you will be the right candidate to carry out this project.
The most promising candidates who demonstrate a great interest in this project will be invited for an online interview.

The biochemical basis of lysosome dysfunction in neurodegenerative diseases

Background:

Numerous human genetic studies have implicated lysosome dysfunction in a plethora of age-associated neurodegenerative diseases including; Alzheimer's disease (AD), Parkinson's disease (PD), and frontotemporal dementia (FTD). However, the molecular and biochemical basis of this dysfunction has been difficult to establish because of the lack of tools to directly probe the protein, small molecule, and RNA content of lysosomes. To overcome this hurdle, our lab has recently developed a method for the rapid isolation of lysosomes (LysoIP) from cultured cells or mouse tissues that enables us to probe lysosomal contents under various metabolic and disease states. I propose to use our innovative technologies to, for the first time, accurately characterize metabolomic and proteomic alterations of lysosomes in cells and mice expressing inherited variants of neurodegenerative disease. We expect that our novel approach will enable the determination of the exact molecular events that lead to deterioration of cellular function during neurotoxicity and disease progression in Parkinson's disease and other NDs. We believe that our multi-faceted approach combining *in vivo* and *in vitro* systems, organellar isolations, profiling experiments and mechanistic dissections will bring about novel findings into the pathogenesis of disease.

My approach:

I developed neuronal and non-neuronal cell models expressing genes mutated in neurodegenerative diseases (see figure 1). I selected 10 different genes and their dominantly-inherited neurodegenerative disease variants for this goal. I am currently developing multi-omics approaches to understand the health of the lysosomes in each of these models (polar metabolomics, lipidomics and proteomics) and have exciting preliminary results. I am also in the process of establishing some mouse lines to further study the aspects of the most promising disease genes on an *in vivo* setting using pre-symptomatic versus diseased animals.

What you will learn:

This is an exciting opportunity to work in one of the best American biology labs, and in one of the top research institutes in the world – MIT /Whitehead Institute. You will have a chance to be a part of a team of very driven and dedicated scientists and also engage in the activities of the scientific community at the MIT. This project has different approaches and spans over a wide set of skills and methodologies. You will

work side-by-side with Dr. Pena, and will be trained in organellar biology, protein biochemistry, mass spectrometry-based targeted and untargeted metabolomics, and mouse biology, including many specialized approaches aimed at understanding lysosomal structure and function.

Who are we looking for?

This project will be most suitable to a passionate and dedicated Master's student with good communication skills and preferentially some prior wet lab experience and/or background in either of the following areas: LC-MS/metabolomics, cell biology, molecular biology, protein biochemistry or mouse biology. The way I usually train my students is to expose them to all techniques I use in the lab in the first few weeks/months and to get hands on in all the models we have. My expectation is that naturally you will find your own niche in my project (e.g. a topic, a favorite gene or research line you will be more focused to and will be the basis of your thesis work). In addition, I expect you will be able to provide some general assistance to the big project.

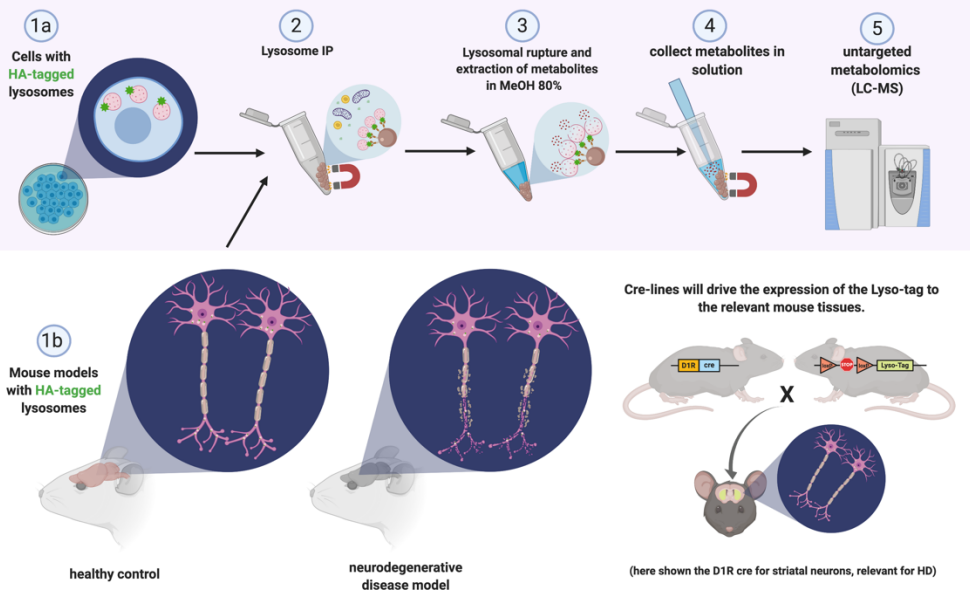

Figure 1. Stable cell lines with inducible expression of WT and dominant variants inherited in neurodegeneration (1A) or mouse models of disease (1B) were engineered to express a lysosome tag enabling quick purification of this organelle (2-3), extraction of analytes (4) and profiling using mass spectrometry techniques.

When can you start and how long can you stay?

We are quite flexible in terms of your start date and can take you in as early as late 2019. We will be happy for you to start in the spring or summer if that's better aligned with your university courses. More importantly, we expect from you a minimum of a 6-months commitment towards this project.

What about funding?

We will provide you with bench space, lab consumables, supervision, and your visa documentation. We cannot, however, cover living expenses or your visa fee, and therefore you should aim to obtain funding for this from your home university or your home country. We are ready to work with you to craft a compelling research proposal that you can submit for competitive scholarships. There are usually a number of funding schemes that one can apply for. Please get in touch, and together we will devise the best strategy that works for all of us.

We can only accept students who will receive credit through their Master's program for their internship in the Sabatini lab. Please note that you will need to provide official documentation from your Master's program as proof of credit.

Relevant articles:

For further reading, see below some papers that may be relevant to my research.

1. About neurodegeneration in general, lysosomes, autophagy and protein aggregates:
   https://www.nature.com/articles/nm1066.pdf
   https://www.nature.com/articles/nm.3232
   https://www.sciencedirect.com/science/article/pii/S0962892417300016?via%3Dihub

2. On the technique we have in the lab for isolation of pure intact lysosomes and mitochondria:
   http://sabatinilab.wi.mit.edu/pubs/2017/MAR%20science.aan6298.full.pdf
   http://sabatinilab.wi.mit.edu/Sabatini%20papers/PIIS0092867416309904.pdf and http://sabatinilab.wi.mit.edu/pubs/2017/WChen_nprot.2017.104.pdf

3. On the orbitrap technology for untargeted metabolomics we use in the lab
   https://planetorbitrap.com/untargeted-metabolomics