Acceptance speech
September 21, 2021

David M. Sabatini, awardee in the Biology and Biomedicine category (12th edition)

I am deeply honored to receive the BBVA Foundation's Frontiers in Knowledge Award in Biomedicine and in particular to share it with my colleague and friend Dr. Michael Hall, who I have known since the earliest days of my career. I was shocked and ecstatic when I received the news in what now seems like a lifetime ago as I received the call before the pandemic, when the world seemed like a happier place.

I never imagined that when in 1991 I walked into Dr. Solomon Snyder's lab at Johns Hopkins Medical School seeking to be a neuroscientist, I would one day find myself here. Sol gave us freedom to do what we wanted, and, while I never ended up working on the brain, in his lab I was introduced to a wonderous small molecule drug called rapamycin that changed my life. I sometimes jokingly challenge anyone to find a more important and interesting drug than rapamycin—there are few that have had as many clinical as well as basic science impacts!

My work in Sol's lab led to the discovery of a protein that we now call mTOR, which is the mammalian homologue of the TOR proteins that Mike Hall had found earlier in budding yeast. Mike's lab was the first to discover a TOR protein in any organism and he coined the TOR name as Target of Rapamycin. mTOR and the TORs are protein kinases and regulate the function of other proteins by adding phosphates onto them in a rapamycin-sensitive fashion. We now know that mTOR has hundreds of substrates and regulates dozens of central cellular processes.

So, what does mTOR do? mTOR and the signaling system it nucleates is the central regulator of growth in animals, that is the process whereby cells and organisms accumulate biomass and increase in size. The mTOR pathway is implicated in many diseases, such as cancer and neurological disorders, and also plays a major role in the aging process, explaining why there is tremendous interest in inhibiting mTOR to try to extend life and health span. I actually know many people who take rapamycin with the hope of living longer!

mTOR does not act alone and participates in two distinct large protein complexes that we and

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Mike's lab discovered: mTOR Complex 1 (mTORC1) and 2 (mTORC2). For almost 20 years my lab has largely dedicated itself to understanding mTORC1 function and defining the components of the pathway in which it participates.

We are particularly fascinated with mTORC1 because it is the true growth regulator: it controls the balance between anabolism and catabolism, that is, the making and breaking down of biomass, respectively. Most interestingly, mTORC1 is regulated by many different signals, including diverse types of nutrients; growth factors, like insulin; as well as stresses like hypoxia. Thus, understanding how mTORC1 functions is an interesting puzzle. How does it sense so many diverse signals—what are the sensors for each?-- and how are they integrated to set mTORC1 activity and thus the growth rate of the cell? Answering this big question is one of our long term goals.

Since I was a medical student I have been fascinated with the capacity of organisms to sense their environment. I remember my gastrointestinal physiology lectures in medical school on how an animal can sense it has eaten a meal with all the correct nutrients so that it can grow and survive. I never thought I would work in this area, but the connection of nutrients to mTORC1 put us squarely in the hunt for the nutrient-sensing mechanisms that control mTORC1.

This work has probably been our most interesting and impactful as we uncovered an entirely new signaling system upstream of mTORC1 that revealed an intimate connection between mTORC1 and a fascinating membrane-bound organelle called the lysosome. Lysosomes can degrade most cellular components and are sometimes, pejoratively, called the garbage can of the cell. More charitably, they are recycling centers that allow cells to re-use their cellular components upon nutrient starvation.

We found that nutrients, like amino acids, promote the movement mTORC1 to the surface of the lysosome, where it becomes activated. The lysosomal surface is an interesting place in the cell because via the cytosol it is exposed to amino acids that come from the extracellular world but also to those produced intracellularly in lysosomes by the degradation of proteins. We went on to define the machinery that does the translocation, particularly a set of odd GTP-binding proteins called the Rag GTPases and many of their regulators. For us a central goal was always to identify the sensors—the proteins that directly bind amino acids and transmit their levels to the Rag GTPases and thus mTORC1.

We have defined sensors for amino acids both in the cytosol as well as in lysosomes, including for leucine, methionine and arginine. In some cases, we have also solved their structures and know exactly how nature allows the mTORC1 pathway to sense an amino acid like leucine but not a similar one like isoleucine. Most importantly, the discovery of the nutrient sensors is opening a whole new chapter for us in understanding how specific cell types in vivo use a sensor to control

a particular physiology. A general theme that is emerging is that the nutrient sensors are expressed in specific cells and regulate specific physiology, like the capacity of flies to detect the protein content of their food by sensing its leucine content.

I want to close by thanking the members of my awesome lab for their contributions to the mTOR pathway and the field of metabolism in general. This award should of course be for them and not for me. These last few weeks have been very challenging for me. I am so grateful to the BBVA Foundation for having me here and for the love and support I have received from my friends, colleagues, and family. Only because of them can I contemplate a future and I will never forget the Foundation for welcoming me here. Thank you y muchisimas gracias.