

menTOR Voices #1 — Lab Showcase: Prof. Claudio De Virgilio



Welcome to the inaugural issue of menTOR Voices! Through this monthly series, we take you inside the laboratories, science, and people shaping the menTOR MSCA Doctoral Network.

For our first edition, we sit down with [Prof. Claudio De Virgilio](#) (Full Professor at the [Université de Fribourg - Universität Freiburg](#), Switzerland). A pioneer in TORC1/mTORC1 pathway regulation and nutrient sensing, his research provides fundamental insights into cell growth, cancer, and mTOR-associated diseases. In this interview, we explore two decades of TORC1 discoveries, the collaborative power of European doctoral networks, and his philosophy on mentoring the next generation of scientists.

Part 1: Deciphering the nutrient-sensing blueprint

[Jean M. GRANGEON](#) - Over the past two decades, your lab established foundational insights into cellular growth by discovering how amino acids signal through the EGO complex and Rag GTPases to activate TORC1 on the vacuolar membrane. Looking back at this 20-year scientific journey, how do your fundamental discoveries in yeast continue to provide a "reference manual" for understanding human mTOR signaling, metabolic control, and diseases like cancer or Ragopathies?

Claudio De Virgilio - *I think of yeast less as a simplified version of a human cell than as a system in which the fundamental logic of a pathway becomes unusually visible. Twenty*

years ago, when we discovered the EGO complex, we were trying to understand how a starving yeast cell decides when it is safe to grow again. We soon realized that the Gtr1-Gtr2 module might represent a conserved nutrient-sensing mechanism upstream of TORC1. What we could hardly have anticipated was how broadly that concept would later be validated and extended, all the way to human disease.

In a recent [Molecular Cell review](#) marking 20 years of the EGO complex, I tried to put this journey into perspective: what began as a yeast-genetics problem has become a conserved framework for understanding how nutrient signals are coupled to TORC1 across eukaryotes. The remarkable thing is not that every molecular detail is identical, but that the underlying principles are conserved: nutrients are translated into Rag GTPase nucleotide states, signaling is organized at specific membranes, and this spatial organization helps determine the outputs of TORC1.

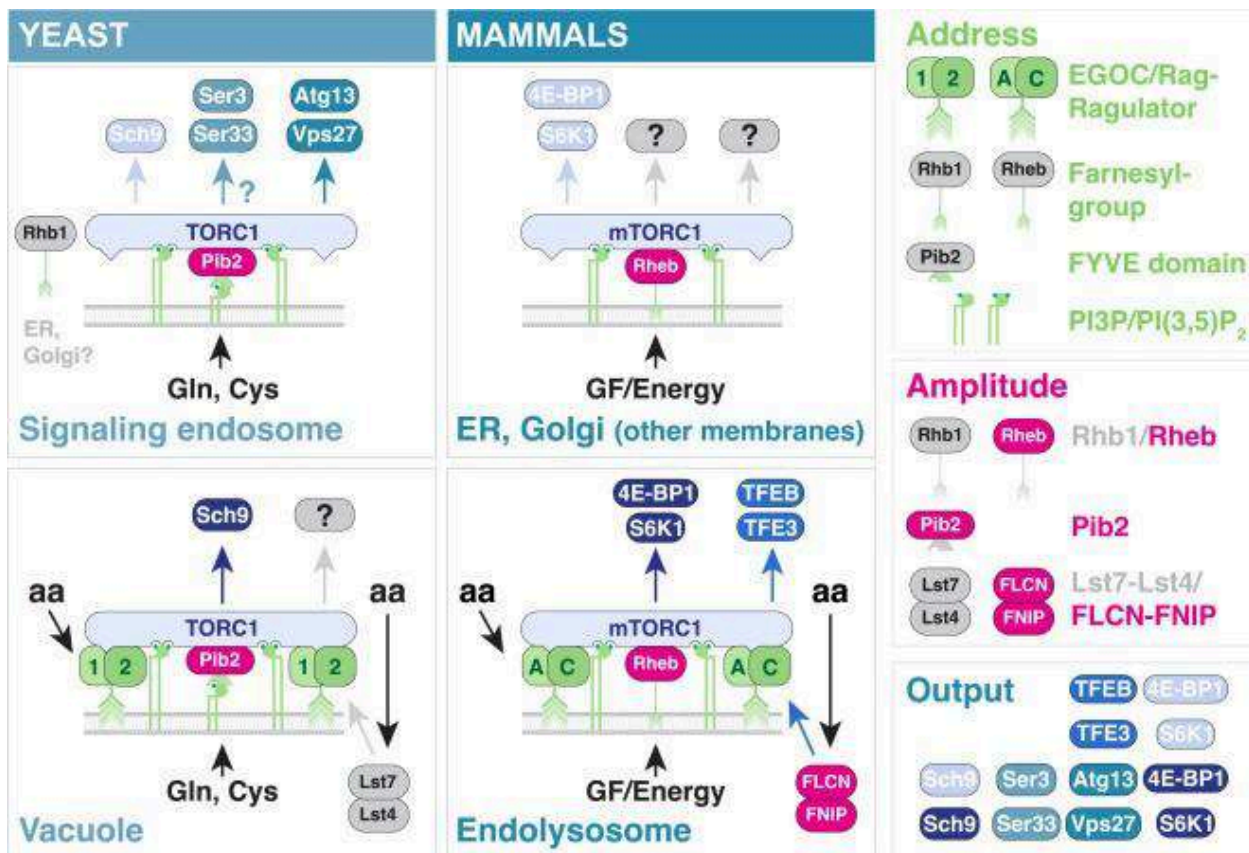


Figure (Adapted from De Virgilio, Molecular Cell): Conserved logic of (m)TORC1 nutrient sensing across yeast and mammals.

A particularly satisfying example came from our collaboration with [Andrea Ballabio and colleagues on disease-causing RagD variants](#). There, a very fundamental biochemical question - how mutations alter the Rag GTPase cycle - could be connected directly to selective mTORC1 regulation of TFEB and TFE3 and, ultimately, to human kidney and cardiac disease. For me, this illustrates why basic research remains so important. We usually cannot predict where a fundamental discovery will lead.

The field is now moving another step forward. I increasingly think that the most useful question is not simply whether mTORC1 is “on” or “off”. We need to ask where it is active, which substrates it can access, and which physiological output that particular pool controls.

That is where I believe yeast will continue to provide an exceptionally powerful reference system for understanding human biology and diseases ranging from rare genetic disorders to cancer.

Part 2: The power of European Doctoral Networks

J.M.G. - The menTOR program brings together academic institutions, clinical foundations, and industrial partners across Europe. Why are structured European Doctoral Networks like menTOR essential for advancing translational biomedical research, and how does combining fundamental bench science with interdisciplinary and public-private collaboration shape the future of European innovation?

C.D.V. - *What I particularly like about menTOR is that it brings us out of our usual scientific compartments. I come from a basic-science background; I do not see patients myself. That is precisely why a network like this is so valuable to me. A mechanism that looks*

elegant in yeast only becomes medically meaningful when colleagues can challenge it in mammalian cells, disease models or patient-derived systems - and eventually ask whether it might be therapeutically exploitable.

One of the strengths of menTOR is that it makes these connections part of the training itself. A question that begins as a mechanistic problem in one laboratory can be looked at from very different angles elsewhere in the network - through mammalian systems, disease models, structural approaches, proteomics or computational methods. That changes the questions we ask, not just the techniques we use. Industrial partners add another important perspective, because they force us to think not only about whether a mechanism is interesting, but also whether it is tractable, translatable or potentially useful. And importantly, I am learning from these interactions myself. I think that matters.

A successful consortium should not only educate its doctoral researchers; it should also make the supervisors reconsider their own models.

I have seen this very concretely through the menTOR activities themselves. At the mid-term meeting at [Telethon Institute of Genetics and Medicine \(TIGEM\)](#), the doctoral candidates presented and discussed their projects across the network. The associated menTOR School then brought the fellows into direct contact with leading scientists working across metabolism, mTOR signaling, cancer, disease genetics, proteomics and nutrient sensing. For a young scientist, having access to that breadth of expertise - and being able to discuss science informally with people they might otherwise know only from papers - is enormously valuable.



TOR de France meeting 2025 in Nice

The [TOR de France meeting](#) reinforced the same impression for me. Basic mechanisms of mTOR regulation, physiology and disease, and therapeutic approaches were being discussed in the same room, with established investigators and young researchers interacting very naturally. That kind of intellectual exchange across disciplines, institutions and borders is, in my view, one of the major strengths of European science and innovation.

Part 3: Bridging basic science and translational therapeutics

J.M.G. - Your PhD candidate, [Alisa Kirkin](#), is investigating non-canonical Rag-TORC1 pathways in yeast, with planned secondments at *TIGEM* in Italy and [BioSolveIT](#) in Germany. How does Alisa's project reflect the multidisciplinary spirit of menTOR, and

how will combining yeast genetics, mammalian validation at TIGEM, and drug modeling at BioSolveIT boost both her PhD training and potential medical discoveries?

C.D.V. - Alisa's project is almost a miniature version of the menTOR philosophy. It starts with a very fundamental biological puzzle: in yeast, how does the RagC/D orthologue Gtr2 control TORC1 signaling in ways that cannot be fully explained by the classical model?

The important point is that we are not forcing the experiments to confirm what we already think we know. Alisa has performed an unbiased mass-spectrometry-based interaction screen, and some of the most interesting candidate interactions are precisely those we would not have predicted from the canonical pathway. One emerging interaction in particular points toward a highly conserved signaling mechanism with potentially substantial relevance to human biology and disease. We are still validating that result, so I would rather not identify the candidate before the story is sufficiently mature. But this is exactly the kind of result I find exciting: an unexpected observation in yeast that forces us to reconsider how the pathway may be wired.

The secondments then allow us to ask how far that mechanism travels. At TIGEM, candidates emerging from yeast can be examined in the mammalian Rag-mTORC1 system and, importantly, in the context of non-canonical outputs such as the MiT/TFE pathway. The secondment at BioSolveIT adds another way of thinking: once an interaction or interface is understood mechanistically and structurally, computational approaches can help us ask whether it is conserved, how it might be manipulated and, in the longer term, whether it could become pharmacologically tractable.



👉 Watch Alisa Kirkin's video interview on her research experience and key takeaways from the menTOR Mid-Term Meeting at TIGEM (Naples, Italy).

For Alisa, this means learning much more than yeast genetics. She moves from genetics and quantitative proteomics to mammalian cell biology, structural and computational thinking, and disease-oriented questions. And for us, her project provides

a stringent test of a principle that has guided much of my own science: start with the biology, follow the unexpected result, and then ask how far the underlying mechanism is conserved.

Part 4: menTORing the next generation of scientists

J.M.G. - Doctoral training requires early-career researchers to master advanced laboratory techniques, cross-sectoral mobility, and science communication. As an experienced "*menTOR*", how do you approach guiding young researchers in menTOR, and what essential skills do you hope PhD candidates like Alisa will gain for their future careers in academia or industry?

C.D.V. - *My approach to mentoring is to provide a strong scientific and personal safety net, insist on rigor, but at the same time give young scientists enough freedom to surprise me. I recently wrote [a personal retrospective about my own rather non-linear route into science](#), and writing it reminded me how much a scientific career depends on people who give you confidence, freedom and room to follow an unexpected result at the right moment. My own path certainly did not follow a carefully designed career plan. Curiosity, chance encounters, good mentors, and collaborators were all enormously important*



Figure from FEMS Yeast Research - Tripping over my EGO: how a starving cell taught me to survive.

Some of the most interesting discoveries in my laboratory have similarly not come from following a grant proposal line by line. They came because somebody noticed something strange and had the confidence to pursue it. I have always encouraged what are sometimes called "Friday afternoon experiments" - high-risk, curiosity-driven ideas that may sit outside the main project but can open completely new directions. That kind of freedom only works in an environment of trust. I therefore care a great deal about creating a laboratory culture in which people help one another rather than seeing every colleague as a competitor.

For Alisa and the other menTOR fellows, I would like the outcome to go well beyond acquiring a catalogue of techniques. Of course they should become technically excellent. But they should also learn how to recognize an important question, how to follow the data even when it leads somewhere unexpected, how to combine curiosity with methodological

rigor, and how to communicate their science to people outside their immediate discipline. Most importantly, I would like them to become intellectually independent.

For me, the best outcome of mentorship is not that a student ends up thinking like the supervisor. It is that, by the end of the PhD, she is asking questions that the supervisor would not have thought of.

Part 5: Future horizons and societal impact

J.M.G. - As menTOR advances its research agenda under Horizon Europe funding, communicating societal return on investment is essential. What key breakthroughs do you anticipate in nutrient-sensing research over the next decade, and what ultimate legacy do you hope the menTOR network will deliver for medicine, biotechnology, and European citizens?

C.D.V. - *I think one of the major conceptual advances over the next decade will be to move beyond viewing mTORC1 as a single cellular switch. We are beginning to see it instead as a collection of spatially organized signaling machines. Different pools of TORC1 or mTORC1 can occupy different membranes, encounter different regulators and substrates, and therefore generate different biological outputs. That raises questions I find extremely exciting. What gives a TORC1 pool its molecular address? What determines the amplitude of its activity? How does location determine which substrates become accessible? And how are those parameters rewired when cells change their nutritional state?*

These are also questions driving our current work in Fribourg. Our present research asks how lipid-protein interactions establish TORC1 membrane localization, how nutrient-sensitive regulators control its catalytic activity, and how spatially distinct TORC1 pools generate substrate-selective outputs. The potential medical consequence is important. If some diseases arise not simply because there is “too much mTORC1” or “too little mTORC1”, but because the wrong pool is active in the wrong place or toward the

wrong substrate, then therapy could eventually become considerably more selective. Instead of globally inhibiting an essential growth pathway, one could imagine interfering with a specific docking interaction, spatial pool or disease-relevant output.

For menTOR, however, I would define the legacy even more broadly. Of course I hope the consortium produces important mechanisms, potential targets, enabling technologies and perhaps new therapeutic opportunities. But perhaps its most enduring legacy will be the scientific community it helps build. I hope we train scientists who are equally comfortable talking to a yeast geneticist, a mammalian cell biologist, a clinician, a computational scientist and an industrial drug developer - and who understand that none of these disciplines alone has the complete answer.

If menTOR succeeds in creating that generation of scientists, that would be a very meaningful return on Europe's investment in fundamental and translational research.



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The menTOR Doctoral Network investigates the mTOR signaling hub – a central regulator of cellular growth and metabolism. Aberrant mTOR activity drives major age-related diseases (cancer, obesity, diabetes) as well as rare genetic mTORopathies. Bringing together leading European partners, menTOR trains 18 Doctoral Candidates to decode these mechanisms, advance personalized medicine, and open new therapeutic avenues.

 Explore our network and research: mentor-program.eu

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