# *The Story of TOR*

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**Introduction**

Cell growth is highly regulated. Cells grow in response to nutrients and other appropriate stimuli by up-regulating macromolecular synthesis. Conversely, cells respond to nutrient limitation or other types of stress by down-regulating macromolecular synthesis and enhancing turnover of excess mass. In addition to temporal control of cell growth, cell growth can be subject to spatial constraints. For example, budding yeast and neurons grow in a polarized manner as a result of new mass being laid down only at one end of the cell. Finally, in multi-cellular organisms, growth of individual cells is controlled relative to overall body growth such that the organs and tissues constituting the organism are properly proportioned. What are the mechanisms that mediate and integrate the many parameters of cell growth? In other words, what determines that a cell grows only at the right time and at the right place? Remarkably, the study of these mechanisms was taken up only relatively recently, despite cell growth being, along with cell division and cell death, one of the most fundamental (and obvious!) aspects of cell biology. Also remarkable is the finding that cell growth control, regardless of the eukaryotic organism or the physiological context,

appears always to involve the TOR protein and its eponymous signaling network. TOR is now known as a central controller of cell growth (SCHMELZLE – HALL 2000; LOEWITH – HALL 2004; WULLSCHLEGER et al. 2006; SAXTON – SABATINI 2017; SHIMOBAYASHI – HALL 2014; BATTAGLIONI et al. 2022).

TOR is a highly conserved protein kinase that controls cell growth in response to nutrients, growth factors (e.g., insulin), and cellular energy. TOR was originally discovered in budding yeast but is conserved in all eukaryotes including plants, worms, flies, and mammals. The discovery of TOR led to a fundamental change in how one thinks of cell growth. It is not a spontaneous process that just happens when building blocks (nutrients) are available, but rather a highly regulated, plastic process controlled by TOR-dependent signaling pathways. TOR mediates cell growth by activating and inhibiting several anabolic and catabolic processes, respectively. The anabolic processes include ribosome biogenesis, and protein, lipid and nucleotide synthesis. The catabolic processes include, most notably, autophagy – the breakdown of cellular components. Furthermore, TOR is found in two structurally and functionally distinct multi-protein complexes, TORC1 and TORC2, each phosphorylating its own substrates to signal via its own pathway. The two TORCs, like TOR itself, are highly conserved. Thus, the two TOR complexes constitute a primordial signaling network conserved throughout eukaryotic evolution to control the fundamental process of cell growth. As a central controller of cell growth and metabolism, TOR plays a key role in development and aging, and is implicated in a wide variety of age-related disorders such as cancer, cardiovascular disease, muscle atrophy, obesity, and diabetes. Indeed, the discovery of TOR and its cellular role has led to pharmacological extension of lifespan, at least in model organisms, and to new strategies for treatment of major disease.

Here, in a manner accessible to non-specialists, I describe our discovery of the TOR protein and subsequent elucidation of its function.

**Rapamycin**

TOR is an acronym for Target of Rapamycin. Thus, the TOR story begins with rapamycin (BENJAMIN et al. 2011). Rapamycin is a natural metabolite (a small molecule) produced by *Streptomyces hygroscopicus*, a bacterium isolated from a soil sample collected on Rapa Nui (Easter Island), hence the name rapamycin. Rapamycin was originally purified in the early 1970s as a novel antifungal agent, but was quickly discarded and largely forgotten due to an undesirable immunosuppressive side effect. Years later, once immunosuppressive therapy came into existence, it was "rediscovered" but now for the very reason that it was originally rejected – to suppress the immune system. In 1999, it received approval for use in the prevention of organ rejection in transplant patients. In 2002, rapamycin-eluting stents were developed for the treatment of restenosis after angioplasty. Finally, in 2007, having been shown to inhibit proliferation of tumor cells, rapamycin received approval for treatment of cancer. Thus, remarkably, rapamycin has applications in three major therapeutic areas: allograft rejection, coronary artery disease, and cancer. However, in the late 1980s, although rapamycin's therapeutic potential was known, its molecular mode of action was unknown. This was the state of knowledge when we initiated our studies to elucidate rapamycin action – studies that led to the discovery of the target of rapamycin.

**The Discovery of TOR and Rapamycin Mode of Action**

The discovery of TOR, as I describe it below, is actually three discoveries in one. The first is the discovery of TOR itself. The second is the discovery of the function of TOR – in other words, the finding

that TOR controls cell growth, rather than cell division as we originally thought. The third sub-discovery is that TOR forms two structurally and functionally distinct complexes that control growth through two separate signaling pathways.

We became interested in rapamycin in the late 1980s when Joe Heitman, an outstanding American postdoc, joined our laboratory. He was an MD-PhD and, given his medical background, was interested in how drugs worked. Another fortuitous circumstance was an ongoing collaboration with Rao Movva, a group leader at a local Basel pharmaceutical company then known as Sandoz, now called Novartis. Rao was interested in rapamycin, among other immunosuppressants, because immunosuppression was a major focus of Sandoz. Joe and Rao had the bright idea of using yeast to elucidate the molecular mode of action of rapamycin. This was also an unusual idea because, at the time, rapamycin was being developed for use in humans, and to give it to yeast cells was viewed as physiologically irrelevant if not pure folly. However, it was a justifiable idea given that rapamycin was originally isolated as an antifungal agent (yeast is a fungus). The reason Joe and Rao chose to use yeast cells to study rapamycin action was that they wanted to take a genetic approach. In those days, before the discovery of CRISPR and gene knock-down technology, it was difficult if not impossible to do genetics with mammalian cells. Our genetic approach was to isolate yeast mutants that are resistant to the antifungal effect of rapamycin (HEITMAN et al. 1991). Joe simply selected spontaneous yeast mutants that grew on solid medium containing rapamycin. Most mutants were altered in the *FPR1* gene which encodes the FKBP protein. The few remaining mutants were altered in either one of two new genes we named *TOR1* and *TOR2*. *FPR1* has a different name because Joe had already characterized this gene while studying another

immunosuppressive drug called FK506. *TOR1* and *TOR2* were previously unknown genes.

Why did we obtain rapamycin resistance-conferring mutations in these three genes, and why were *FPR1* mutations common and *TOR* mutations rare? Also, what did the *TOR* genes encode? To answer these questions, two very talented students joined the project, Jeannette Kunz and Stephen Helliwell (Swiss and British, respectively). They cloned and sequenced the *TOR* genes. This revealed the identity of the proteins encoded by the *TOR* genes and why we obtained mutations in three genes (Kunz et al. 1993; Helliwell et al. 1994). FKBP, the product of the *FPR1* gene, is a cofactor or receptor required for drug action. Its normal function is to mediate protein folding, but rapamycin binds FKBP and thereby corrupts it to perform a new, nefarious function. The FKBP-rapamycin complex binds and inhibits TOR. Rapamycin requires FKBP to inhibit TOR, explaining why we obtained mutations in the *FPR1* gene. These mutations were common because FKBP is not essential for cell viability (although essential for rapamycin action) and thus any simple loss-of-function mutation anywhere in the *FPR1* gene confers rapamycin resistance. Unlike FKBP, TOR is essential for cell viability. Thus, the mutations we obtained in *TOR* were confined to a single codon specifying a key residue in the rapamycin binding site, explaining why the mutations were rare. The mutations prevented FKBP-rapamycin binding to TOR without otherwise affecting TOR function or cell viability. So, our early mutations in yeast turned out to be very informative. They not only identified TOR, but also identified the rapamycin binding site in TOR and the mechanism of rapamycin action, i.e., rapamycin forms a complex with FKBP to inhibit TOR. Why rapamycin needs FKBP to inhibit TOR, although rapamycin can bind TOR in the absence of FKBP, was revealed later when we determined the atomic structure of TOR (see below).

But what is TOR? The sequence of the *TOR* genes revealed that the two TORs are similar proteins, 70% identical, and displayed homology to only two other proteins known at the time, mammalian PI3 kinase p110a and yeast VPS34, both of which are lipid kinases. Thus, we originally thought TOR was a lipid kinase, but it is in fact a protein kinase. It turned out to be the founding member of the so-called PIKK family, a family of atypical protein kinases all of which resemble lipid kinases but are protein kinases. In 1994 and 1995, four competing groups subsequently succeeded in identifying the target of rapamycin in mammalian cells (BROWN et al. 1994; CHIU et al. 1994; Sabatini et al. 1994; SABERS et al. 1995). Mammalian TOR was first named FRAP (BROWN et al. 1994), RAFT (SABATINI et al. 1994) and RAPT (CHIU et al. 1994) but is now known as mTOR (Sabers et al. 1995) based on the precedent of yeast TOR. In subsequent years, TOR was characterized in other eukaryotes including Drosophila (dTOR), C. elegans (CeTOR) and Arabidopsis (AtTOR). These studies showed that TOR is indeed conserved from yeast to human, as we originally assumed when we decided to exploit yeast genetics to search for the target of rapamycin (CRESPO – HALL 2002).

**TOR Controls Cell Growth and Metabolism**

By the mid 1990s, it was clear that TOR is a highly conserved kinase and the in vivo target of rapamycin. However, the cellular role of TOR was not yet known. We still knew almost nothing about TOR other than it was bound by rapamycin. What is upstream and downstream of TOR? What biology does TOR mediate? Why does rapamycin binding to TOR inhibit cell proliferation? We originally thought, incorrectly, that TOR controlled the cell cycle, i.e, the process of cell division. This incorrect assumption was based on a defect in cell cycle progression we observed upon inhibition of TOR.

After a long and frustrating period during which we performed futile experiments to characterize TOR's role in cell division, experiments based on the misleading cell cycle defect, we finally determined that the cellular role of TOR is to control cell growth (HALL 2016; HALL 2017). Cell growth is an increase in cell size or mass whereas cell division is an increase in cell number. The realization that TOR controls cell growth was perhaps our most important and gratifying discovery. It was a major advance because conventional wisdom at the time was that cell growth is passively regulated simply by the availability of nutrients or building blocks, rather than actively regulated by a dedicated molecular system. The advance was made possible by a great deal of work by our group and a number of other laboratories showing that TOR controls a large and diverse set of processes all of which collectively determine mass accumulation and thereby cell size. These various processes can be grouped into two categories, the anabolic processes that TOR activates and the catabolic processes that TOR inhibits. The anabolic processes include ribosome biogenesis, translation, transcription, and lipid and nucleotide synthesis (BARBET et al. 1996; BECK et al. 1999, MARTIN et al. 2004; HAGIWARA et al. 2012; ROBITAILLE et al. 2013). The catabolic part includes processes, such as autophagy, that break down and recycle cellular components. Thus, TOR controls growth by balancing the opposing forces of synthesis (energy consuming) and degradation (energy producing) such that cell mass is properly adjusted relative to the available nutrients. Hence, we also learned that TOR responds to nutrients. Finally, we learned that the misleading cell division defect was an indirect effect of the primary defect in cell growth – a cell will not divide unless it has achieved an adequate size to yield two "daughter" cells.

It is now known that TOR controls cell growth very widely – widely in terms of both organism and physiological context. For example, TOR controls growth in yeast, worms, flies, plants and mammals. TOR also controls growth both in a developing embryo and in adult tissues, for example, in muscle in response to exercise. Indeed, TOR is a central controller of cell growth (SCHMELZLE – HALL 2000).

**Two TOR Signaling Pathways and Complexes**

After our discovery that TOR controls cell growth in response to nutrients (BARBET et al. 1996; BECK et al. 1999; HALL 2016), we had another conundrum. We knew from our earlier work that the two TORs in yeast, although 70% identical and functionally similar, were not functionally identical. Based on our genetic analysis, we knew TOR2 had two essential functions whereas TOR1 had only one function. We also knew that the single TOR1 function was redundant with one of the two TOR2 functions. In other words, if we knocked out the *TOR1* gene, nothing happened. If we knocked out the *TOR2* gene, the cells died based on loss of its essential function that TOR1 could not perform. If we knocked out both genes simultaneously, the cells died but not in the same way as they did when we knocked out only *TOR2*. Thus, we knew TOR2 had two functions, one of which overlapped with the one function of TOR1. But what were these two so-called functions and how could we explain the overlap at the molecular level? Further genetic experiments in our laboratory revealed that the two TOR functions are two distinct signaling branches or pathways. The general picture that emerged was that TOR1 and TOR2 control their various growth-related readouts via two major signaling branches (LOEWITH – HALL 2004). One branch contains TOR1 or TOR2 and we thus called this the "TOR-shared branch". This branch activates mass

accumulation, for example protein synthesis, and we thus considered this branch as mediating temporal control of cell growth (BARBET et al. 1996). The second major branch contains only TOR2 and we thus referred to this branch as the "TOR2-unique branch". This branch controls polarization of the actin cytoskeleton and we thus viewed it as mediating spatial control of cell growth (SCHMIDT et al. 1997). Hence, via the two different signaling branches, TOR integrates temporal and spatial control of cell growth.

At this stage, there were many new questions. How is TOR signaling diversity determined, i.e., signaling through two separate branches? How is TOR signaling specificity determined, i.e., TOR2 signaling via both branches whereas TOR1 via only one? Also, puzzling was our observation that only the TOR-shared signaling branch was rapamycin sensitive. Why can rapamycin seemingly inhibit TOR2 (and TOR1) in the TOR-shared signaling branch but not in the TOR2-unique branch? To address these questions, Robbie Loewith, an outstanding Canadian postdoc, and my long-term technician Wolfgang Oppliger focused on biochemical characterization of the TOR proteins. We resorted to biochemistry at this stage because our ongoing genetic approach was not yielding the answers we sought. The new, biochemical strategy was to identify proteins that directly interacted with TOR. To identify TOR binding proteins, we developed a gentle purification scheme for TOR1 and TOR2 such that interacting proteins would co-purify with TOR. In essence, we used TOR as bait to fish for proteins that are physically (and functionally) linked to TOR.

We succeeded in identifying two multi-protein TOR complexes which we named TORC1 and TORC2 (LOEWITH et al. 2002). TORC1 consists of TOR1 or TOR2 and the two other proteins KOG1 and LST8. TORC2 consists of TOR2, AVO1, AVO2, AVO3 and LST8. After characterization of the cellular function of the two TOR complexes, we

found that they corresponded to the two previously identified TOR signaling branches. TORC1 mediated the TOR-shared branch whereas TORC2 corresponded to the TOR2-unique branch. In other words, TOR forms two structurally and functionally distinct kinases, each mediating its own signaling pathway. This was a major breakthrough because it provided a molecular basis for the diversity of TOR signaling. The characterization of the two TORCs also explained the specificity of the two TOR proteins, i.e., why TOR2 is functionally more versatile than TOR1 and able to signal via both signaling branches. TOR2 is able to assemble into both complexes whereas TOR1 is found only in TORC1. Finally, the two complexes revealed the reason for the differential rapamycin sensitivity of the two TOR signaling pathways. Rapamycin inhibits the TOR-shared signaling branch but not the TOR2-unique branch because rapamycin is able to bind only TORC1. Why TOR in TORC2, but not in TORC1, is inaccessible to rapamycin would be revealed years later (see below).

It was a very gratifying moment in our laboratory when we found that the two TOR complexes corresponded to our two previously identified TOR signaling pathways. This was a confluence of several years of genetic and biochemical research which in the end cross-validated each other. Thus, we had a high level of confidence in our unified "2 branches, 2 complexes" model of cell growth control. Confidence in this model was further strengthened by the finding that the TOR complexes are conserved from yeast to human.

In 2002, when we identified the two TOR complexes in yeast, a complete sequence of a mammalian genome was not yet available. However, based on the then available partial human genome sequence, it appeared that most, if not all, TOR binding proteins identified in yeast were conserved in mammalian cells. Furthermore, others showed that a mammalian ortholog of yeast KOG1 interacted with mTOR (HARA et

al. 2002; KIM et al. 2002). This suggested that the two complexes are conserved from yeast to human. Estela Jacinto, Robbie Loewith and many others in our laboratory (LOEWITH et al. 2002; JACINTO et al. 2004), and others in the groups of David Sabatini, Kun-Liang Guan, and the late Kazu Yonezawa, showed that TORC1 and TORC2 are structurally and functionally conserved in mammalian cells. These were our first experiments on TOR in mammalian cells. The two mammalian complexes are now known as mTORC1 and mTORC2 (WULLSCHLEGER et al. 2006). All the TORC components identified in yeast have a counterpart in mammals. For example, KOG1 is Raptor in mTORC1 and AVO3 is Rictor in mTORC2. We also found that both yeast TORC2 and mTORC2 are rapamycin insensitive (LOEWITH et al. 2002; JACINTO et al. 2004). Thus, the overall architecture of the TOR signaling network, like TOR itself, is conserved from yeast to mammals. Indeed, the picture that emerged was that TOR constitutes a primordial or ancestral signaling network conserved throughout eukaryotic evolution to regulate the fundamentally important process of cell growth.

**TOR Signaling at the Whole-Body Level – Beyond the Cell**

At this stage in the story, we and others had developed a rather sophisticated mechanistic model of how TOR controls cell growth. The next challenge was to understand how TOR coordinates growth over a whole-body plan. This new direction was stimulated by the French developmental biologist Pierre Leopold who first showed the importance of understanding TOR signaling in individual tissues in multicellular organisms. He found that a TOR defect specifically in the so-called fat body (a tissue equivalent to the liver in vertebrates) of the fruit fly reduced the size of that tissue but, surprisingly, also the size of other tissues (COLOMBANI et al. 2003). This observation suggested

that there is TOR-dependent inter-tissue signaling to ensure organs are properly proportioned. In other words, TOR controls growth not only of the cell in which it resides, known as cell autonomous growth control, but also growth and metabolism of distant cells in the same organism. Thus, in a cell non-autonomous manner, TOR coordinates whole-body growth – a new level of growth control. To study this new level of TOR-dependent growth control, we made tissue-specific mTORC1 or mTORC2 knockouts in the mouse, focusing on adipose tissue and liver (POLAK et al. 2008; CYBULSKI et al. 2009, HAGIWARA et al. 2012). These ongoing studies, initiated in collaboration with my Biozentrum colleague Markus Rüegg, have yielded many interesting findings. For example, adipose-specific mTORC1 knockout mice are resistant to diet induced obesity (POLAK et al. 2008). Indeed, these mice are metabolically healthier than wild type mice, displaying lower insulin and cholesterol levels. Conversely, adipose-specific mTORC2 knockout mice displayed a pre-diabetic condition (CYBULSKI et al. 2009). Importantly, these studies showed that adipose mTOR controls not only cell growth and metabolism, but also systemic growth and metabolism in a cell non-autonomous manner, similar to Leopold's findings in the fruit fly (POLAK – HALL 2009; ALBERT – HALL 2015).

In the studies described directly above, we abolished mTORC1 or mTORC2 in specific tissues. In studies described further below, we did the inverse. We hyperactivated mTORC1 and mTORC2. In this case, the mice developed severe cancer, again underscoring mTOR's role as a controller of cell growth.

**mTORC1 and mTORC2 Structures**

While studying the physiological and pathophysiological roles of the mTORCs at the tissue level, we were also interested in determining the

structure of the mTORCs at the atomic level. Given the large size (~ 1megaDalton) and low abundance of the TORCs, determining their atomic structures was a difficult task made possibly only by a collaboration with two outstanding structural biologists, Timm Maier (Biozentrum) and Nenad Ban (ETHZ). We used cryo-EM in combination with crystallography to determine the structure of human mTORC1, including mTORC1 with FKBP-rapamycin bound (Aylett et al. 2016). The structure of mTORC1 revealed that mTOR has a conventional kinase structure consisting of two lobes separated by a cleft. The kinase catalytic site is at the bottom of the cleft. The structure of mTORC1 with FKBP-rapamycin bound confirmed earlier suggestions of FKBP-rapamycin action. Rapamycin inhibits mTORC1 by gluing FKBP to the lip of the catalytic cleft, thereby forming a lid that sterically hinders access of substrates to the catalytic site. Rapamycin alone can bind but does not inhibit mTOR because it alone does not have sufficient bulk to block access to the catalytic site. In other words, rapamycin acts as a molecular glue. More recently, we described a 3.2Å resolution cryo-EM structure of human mTORC2 (SCAIOLA et al. 2020), shortly after Karuppasamy et al. (2017) reported a 7.9Å resolution structure of yeast TORC2. Comparison of mTORC1 and mTORC2 revealed that mTOR itself is unchanged and that functional differences of the two complexes are due to the different subunits that "decorate" mTOR. For example, the mTORC1 subunit Raptor is an adaptor that presents specific substrates to the mTOR catalytic site in mTORC1 (BÖHM et al. 2021). Furthermore, the mTORC2 structure (and the yeast TORC2 structure) revealed the molecular basis of our earlier observations that yeast TORC2 and mTORC2 are rapamycin insensitive (LOEWITH et al. 2002; JACINTO et al. 2004). The mTORC2 subunit Rictor masks the FKBP-rapamycin

binding site in mTOR, thereby preventing rapamycin from inhibiting mTORC2.

**TOR in Disease and Aging**

Another remarkable aspect of TOR biology is the unusually large number of diseases due to defective mTOR signaling (DAZERT – HALL 2011; SAXTON – SABATINI 2017). Consistent with the fact that TOR is a central controller of cell growth, increased mTOR activity underlies several diseases characterized by cell overgrowth, such as cancer, hamartoma syndromes, and cardiac hypertrophy. Interestingly, some of these diseases were not known to be etiologically related until they were found to have dysregulated mTOR signaling in common. To determine how hyperactive mTOR signaling drives tumor development, we generated and characterized an mTOR-driven, liver cancer mouse model (GURI et al. 2017; PARK et al. 2022; MOSSMANN et al. 2023). These studies have provided important insight on how metabolic pathways are rewired to support the increased demands of proliferating tumor cells. They have also revealed new therapeutic strategies for the treatment of cancer.

mTOR dysregulation also results in metabolic diseases such as obesity and type 2 diabetes. Obesity stems from the fact that the mTOR pathway activates adipogenesis in response to excess nutrient intake. Obesity may, in turn, lead to type 2 diabetes. However, diabetes may also result from inhibition of mTOR signaling, particularly in adipose tissue. As mentioned above, we found that adipose-specific inhibition of mTORC2 confers a pre-diabetic condition (CYBULSKI et al. 2009). We spent over a decade investigating how adipose mTORC2 impacts whole-body metabolism to have this effect. We recently made the exciting breakthrough that adipose mTORC2 is required to maintain

sensory neurons in adipose tissue (FREI et al. 2022). Thus, adipose tissue, and in particular adipose mTORC2, may be affecting whole-body metabolism via the central nervous system. This discovery poses many new questions which we are pursuing. Our findings in this area could also be translated to the clinic, for example, for the treatment of diabetic neuropathy.

It is noteworthy that many mTOR-associated diseases, such as cancer and diabetes, are age-related. Possibly this correlation and our finding that TOR controls cell growth (and metabolism) in response to nutrients led others to investigate whether TOR might also control lifespan in response to nutrients. Indeed, Vellai et al. (2003) found that a TOR (CeTOR) deficiency in C. elegans more than doubles the worm's natural lifespan – the first demonstration that TOR controls aging. Others subsequently showed that TOR controls lifespan in yeast, flies and mice. Thus, like its role in cell growth control, TOR's role in aging is evolutionarily conserved. Rapamycin is now the most robust and reproducible lifespan-extending intervention in eukaryotes. Importantly, the finding that TOR is a nutrient sensor provided a mechanism for lifespan extension by dietary restriction (less nutrients). The model is that dietary restriction reduces TOR activity which in turn leads to metabolic changes that, in sum, have a salubrious, lifespan-extending effect (CORNU et al. 2013).

**Conclusion**

Since its discovery over thirty years ago, TOR has attracted the interest of basic, clinical, and industrial researchers. As a result, there is now an immense body of knowledge on TOR signaling and cell growth control. Indeed, we now have a good understanding of TOR signaling in health and disease, and how it can be targeted for therapeutic benefit. Nevertheless, much remains to be done. We will continue to study

mTOR signaling mainly in the context of disease. We will pursue our recent finding that dysregulated mTOR promotes tumor growth by reprogramming metabolism. In particular, we will focus on arginine and polyamine metabolism in liver cancer. We will also pursue our exciting discovery that adipose mTORC2 is required to maintain sensory neurons in adipose tissue (FREI et al. 2022). We are particularly interested in determining whether loss of sensory neurons in adipose tissue, due to loss of adipose mTORC2, plays a role in the development of diabetes.

I would like to conclude with three general points. First, like many discoveries, the discovery of TOR was the work of an exceptional group of students, postdocs and collaborators – these are the heroes of the story. I have acknowledged some in the above text. Unfortunately, due to space limitations, there are many from our laboratory and beyond whom I could not acknowledge. The second point is that the story of TOR is an example of how an invertebrate model organism such as yeast can be used for biomedical research to develop treatments for patients. Whereas invertebrate model organisms are now commonly used in biomedical research, in the late 1980s, this was a case of "thinking outside the box". The third and final point is that the discovery of TOR was curiosity-driven research. When we started to select yeast mutants resistant to a small molecule produced by a soil microbe from Rapa Nui, we could not predict what we would find. We thought we would find something interesting, but we did not dream it would lead to fundamentally and clinically important discoveries worthy of the prestigious Balzan Prize.

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