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Pushing the envelope in the mTOR pathway. The second generation of inhibitors

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Abstract

The phosphatydilinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway has been a major focus of attention for cancer researchers in the past decade. A preliminary and not complete understanding of the molecular biology of this complex network has not only importantly conditioned the development of the first generation of mTOR inhibitors, but also the biomarker studies designed to identify the best responders to these agents. Most recently, research in this pathway has focused in the fact of the dual nature of mTOR that is integrated by the mTOR complex 1 (mTORC1) and complex 2 (mTORC2). These two complexes are formed and regulated by different proteins, and also driven by multiple different compensatory feedback loops. This deeper understanding has allowed the development of a promising second generation of inhibitors which are able to block simultaneously both complexes due to their catalytic activity over mTOR. Moreover, some of them also exert an inhibitory effect over PI3K that is a key player in the feedback loops. This article reviews the newest insights in the signaling of the mTOR pathway and then focuses in the development of the new wave of mTOR inhibitors.

Keywords

Dual inhibitors; mTOR; mTORC1; mTORC2; PI3K; Rapamycin; Rapalogs

Introduction

Since the discovery of mammalian target of rapamycin (mTOR) in the early 1990s the volume of research performed in this pathway has been substantial. These data have provided us with an increasingly detailed knowledge about the proteins and regulators involved in it, their different functions, and the genetic abnormalities that are present across different tumor types. Moreover, the interest among the scientific community for this pathway has been fostered by the development of a natural product derived from the bacterium Streptomyces hygroscopicus. This compound called Rapamycin (Sirolimus, Rapamune; Wyeth) has shown inhibitory activity against mTOR protein after coupling its intracellular receptor. Subsequently, several compounds have been synthesized with similar characteristics to Rapamycin integrating the family of Rapalogs.

However, the clinical results obtained by targeting this pathway have not been as straight forward as it was presumed at the beginning. Moreover, drug development against mTOR

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was started when the knowledge about its functions was very preliminary. Several key findings have changed the course of clinical research in this field. First, the fact that mTOR is constituted by two complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2); those have a very intricate network of feedback loops, protein partners, substrates, and regulators that are specific to each. Second, the discovery that Rapamycin and Rapalogs exert an incomplete inhibition of mTORC1 and also are inactive against mTORC2. Finally, mTORC2 was shown to be one of the major regulators of the feedback loops associated with this pathway, thus explaining the limited activity of Rapalogs observed in clinical studies. Therefore, a closer analysis of the recent advances in the molecular biology of this pathway will help to correctly understand the results from previous *in vitro* studies and clinical trials.

In the present article we will review the data on the characterization of mTORC1 and mTORC2, their protein components, functions, and regulators emphasizing the role of the feedback loops recently described within this complex network. Then, the approved indications for the Rapalogs will be summarized. Finally, the last section will be devoted to a new class of compounds that are able to inhibit both mTOR complexes, and the new dual inhibitors that are also adding activity against the phosphatydilinositol-3-kinase (PI3K), a key component of the main feedback loop involved in this pathway.

Molecular biology of the mTOR pathway. A story of two complexes

The PI3K-AKT-mTOR pathway (Figure 1) is commonly altered in human cancers. Deregulation can be secondary to amplification or mutations in *PIK3CA*, which encodes the p110α catalytic subunit of the kinase complex and have been extensively described in several tumors (1); mutations and amplification in *AKT*; inactivation or mutations in phosphatase and tensin homolog (*PTEN*); and other less frequent events such as mutations in the insulin receptor-substrates (*IRS*) and the Ras homolog enriched in brain (*RHEB*) (2–4).

mTOR is a serine/threonine kinase formed by two signaling complexes called mTORC1 and mTORC2 that contain common and specific partners proteins. Both complexes share the following proteins: mTOR, mLST8/GβL, and the negative regulator Deptor. On the other hand, they are integrated by distinct partner proteins and regulatory mechanisms acting on different substrates, and having specific effects on distinct cellular functions (5). mTORC1 is specifically composed by a regulatory-associated protein of mTOR (Raptor) and a proline-rich AKT substrate of 40 kDa (PRAS40). mTORC2 couples with the Rapamycin-insentive companion of mTOR (Rictor), mSin1, and PRR5/Protor (Figure 1).

mTORC1 enhances cell growth and proliferation by inducing protein and lipid synthesis, ribosome biogenesis, and reduction of autophagy (6–9). Growth factors and nutrients, such as energy and amino acids, promote mTORC1 signaling through the phosphorylation of eukaryotic initiation factor 4E binding protein 1 (4E-BP1) and ribosomal S6 kinase 1 (S6K1) which are the best-known downstream effectors of mTOR (10).

The tuberous sclerosis complex 2 (TSC2) is an essential link between growth-factor signaling and the mTORC1 activation triggered via PI3K-dependent or -independent pathways (11–13). Growth-factor signaling phosphorylates and inhibits TSC2 (Tuberin), avoiding its association with TSC1 (Hamartin), thus activating the mTORC1 by releasing the inhibition of RHEB, a small guanosine triphosphatase (GTPase) necessary for the activation of mTORC1 (14). Likewise, inactivating mutations in the TSC1 or TSC2 genes cause hamartoma syndromes associated with elevated mTORC1 activity (15,16). However, TSC2 is not required for the regulation of mTORC1 by amino acids; the Ras-related GTPase (RAG) proteins, a family of small GTPases, are the key regulators for mTORC1 amino acid activation (17). Other regulators of mTORC1 are Raptor, that positively regulates mTORC1 and functions as a scaffold for recruiting mTORC1 substrates (18), and PRAS40 and Deptor that act as negative regulators (19,20). The function of mLST8/GβL remains yet unknown (21).

Much less is known about mTORC2 functions, substrates, and regulators. Unlike mTORC1, which is a direct-target of Rapamycin, mTORC2 was initially described as Rapamycin-insensitive (22), although it has been recently reported that continued exposure to Rapamycin also leads to its inhibition (23). mTORC2 promotes cell survival, actin cytoskeleton organization and is exclusively growth-factor responsive, being AKT its first recognized substrate protein. Full activation of AKT requires the phosphorylation of two residues: Ser473 by mTORC2 and Thr308 by phosphoinositide-dependent kinase-1 (PDK1) (24). Other mTORC2 substrates are serum- and glucocorticoid-induced protein kinase-1 (SGK1) and protein kinase C-alpha (PKCα) (25,26).

The regulatory mechanisms of mTORC2 also remain partially unknown, although it has been shown that Rictor and mSin1 enhance mTORC2 signaling while Deptor appears to negatively regulate it. TSC1 and TSC2 have also been involved in promoting mTORC2 activation. However, the function of PRR5/Protor is still not well defined (21,27).

Finally, the mTOR complex has also been suggested to play a crucial role integrating extracellular and intracellular signals that regulates cellular metabolism. This also includes the control of inflammatory and tolerance responses via regulation of TCRζ (28) and TGF-β-induced Foxp3, respectively (29). Although these physiologic functions need further mechanistic elucidation, they also open new avenues for development of biomarkers of mTOR inhibition through other alternative effects.

The mTOR pathway. An intrincated network with feedback loops

Development of resistance to mTORC1 inhibitors has been related with the presence of different feedback loops described within this complex network. Moreover, a better understanding of these mechanisms may help to identify novel therapeutic strategies to overcome the relative lack of efficacy of these compounds (5).

It is postulated that mTORC1 activation causes a negative feedback through S6K1 that reduce the activity of PI3K. The phosphorylation of S6K1 inactivates IRS-1 which is required for insulin signaling through PI3K (30). Therefore, mTOR inhibition will induce IRS-1 activation releasing the inhibition mediated by S6K1 and provoking the activation of AKT via an insulin growth factor receptor 1 (IGF-1R) dependent signaling process (31). O’Reilly et al published supporting evidence for this negative feedback loop. They have observed in a panel of cancer cell lines from different tumor types that Rapamycin was able to upregulate IRS-1 levels and promote AKT phosphorylation (32). Accordingly to these findings of a biomarker study developed in the context of the first phase I clinical trial with Everolimus (RAD001, Afinitor; Novartis) showed a dose- and schedule-dependent inhibition of mTOR and a subsequent upregulation of AKT. These effects were observed in 50% of the patients and were assessed in both tumor and skin biopsies, thus validating the *in vitro* observation (33). Moreover, Wan et al showed in human rhabdomyosarcoma cell lines and xenografts that blockade of IGF-1R led to an inhibition of the Rapamycin-induced AKT activation (31), providing evidence for a synergistic effect of mTOR and IGF-1R inhibition. This combination is currently under clinical evaluation in a phase I multiple-dose escalating study using Dalotuzumab, (a monoclonal antibody against IGF-1R; MK-0646; Merck) and Ridaforolimus (an mTORC1 small-molecule inhibitor analog of the Rapamycin; MK-8669, Deforolimus; Merck and ARIAD). Preliminary results have revealed important antitumor activity in estrogen receptor-positive and highly proliferative breast tumors, which frequently harbor *PIK3CA* mutations and IGF-1R overexpression (34). Other two studies of the combination of Cixutumumab (IGF-1R monoclonal antibody inhibitor; IMC-A12; Imclone) plus the Rapalog Temsirolimus (CCI-779, Torisel; Wyeth), and Figitumumab (IGF-1R monoclonal antibody inhibitor; CP-751871; Pfizer) plus Everolimus are underway (35,36).

Furthermore, preclinical data have shown that mTORC1 inhibition results in a hyperactivation of the PI3K pathway and simultaneous increase of the signaling through the mitogen–activated protein kinase kinase (MAPK) pathway (37), thus proving the existence of another feedback loop that connect the PI3K-AKT-mTOR with the MAPK pathway. This observation has provided rationale for combining several ongoing phase I clinical trials combining mTOR, PI3K, or AKT inhibitors with MAP/ERK kinase (MEK) inhibitors. However, the most optimal combination of inhibitors deserves careful consideration due to dense cross-talk interactions among protein components of these complex pathways. Sophisticated systems biology analyses have recently predicted adverse effects in terms of reduction of citotoxicity with the combination of a MEK and a first generation mTOR inhibitor. Specifically, *in vitro* validation of this *in silico* data showed that Rapamycin, which led to significant activation of AKT, upon combination with a MEK inhibitor (U0126) rendered an increase in cell viability. In contrast, simultaneous inhibition of PI3K-AKT and MAPK pathways decreased cell viability and pointed towards as this combination as the most optimal way to effectively inhibit both pathways (38). On the other side, clinical studies have reported significant toxicities in a phase I trial which is testing the combination of an AKT inhibitor and a MEK inhibitor. Considering these preclinical and clinical results in conjunction, the combination of PI3K or second generation mTOR inhibitors with MEK inhibitors warrants further clinical validation.

First generation of mTOR inhibitors

The first generation inhibitors of mTOR are derivatives of Rapamycin that specifically inhibit mTORC1. This group of drugs is integrated by Rapamycin and its analogs also known as Rapalogs: Everolimus, Temsirolimus, and Ridaforolimus (previously known as Deforolimus). Rapamycin has been clinically approved several years ago for prophylaxis of organ rejection for renal transplant patients (Table 1 and Figure 2) (39).

The mechanism of action of Rapamycin has been very well described. This drug along with the FK506-binding protein (FKBP12) targets the FKBP12-Rapamycin binding (FRB) domain adjacent to the catalytic site of the mTOR protein (40). Several studies have shown that mTORC2 is Rapamycin-insensitive (22,41), although long-term exposure to Rapamycin can also inhibit mTORC2 and then disrupt AKT signaling. Strikingly, this response has been shown to be tissue specific (23).

mTORC1-mediated 4E-BP1 phosphorylation induces the dissociation of 4E-BP1 from the eukaryotic initiation factor 4E (eIF4E), thus allowing the assembly of the eIF4F complex to initiate cap-dependent mRNA translation. 4E-BP1 is phosphorylated at multiple sites such as Thr36, Thr45, Ser64, Thr69, and Ser82 and needs to occur in a pre-specified order (42). The activation of Thr36 and Thr45 are the leading events necessary for phosphorylation of Thr69 that will be followed by Ser82 (43). Except for Ser82, all phosphorylation sites are sensitive to Rapamycin demonstrated by the complete inhibition of the initiation of cap-dependent mRNA translation by the treatment with Rapamycin in specific cellular and histological contexts (44). However, it has been recently observed in that Rapalogs may not fully block 4E-BP1 despite of a complete inhibition of S6K1 (45). This fact could be due to different reasons such as a relative lack of effect on the phosphorylation of Thr36 and Thr45 (46,47), the existence of unknown feedback loops, and the inability to inhibit mTORC2; and it explains the unpredictable antitumor effect of Rapalogs across different cancer subtypes (48–52). Mechanistic details are discussed in the section devoted to second generation inhibitors.

Despite of their limited cytotoxic activity, Rapalogs have demonstrated antiproliferative properties. Temsirolimus and Everolimus have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for treatment advanced renal cell carcinoma; Temsirolimus has been authorized for treatment of relapsed or refractory mantle-cell lymphoma by the EMEA only (Table 1 and Figure 2). The approval of Temsirolimus for treatment of previously untreated metastatic renal cell carcinoma was based on the results from a phase III clinical trial in which 626 patients randomly received Temsirolimus, Interferon-alfa, or combination therapy with Temsirolimus and Interferon-alfa. Temsirolimus alone rendered longer overall survival (10.9 vs 7.3 months; HR=0.73; P-value = 0.008) and progression-free survival than Interferon-alfa alone (5.5 vs 3.8 months; P-value < 0.001). In addition, no differences between the combination-therapy and the Interferon group were observed in terms of overall survival (53). After that, Everolimus was approved for the treatment of patients with advanced renal cell carcinoma who had progressed on Sorafenib, Sunitinib, or both. The authorization was supported by the data coming from a phase III clinical trial that randomized 410 patients to receive Everolimus or placebo in a 2:1 radtio. Everolimus showed a significant improvement in progression-free survival with mild adverse effects (4 vs 1.9 months; HR=0.30; P-value <0.001) (54). Finally, Temsirolimus showed improvement in progression-free survival and higher objective response rates compared with investigator’s choice treatment in patients with relapsed or refractory mantle-cell lymphoma leading to the approval by the EMEA (55).

Therefore, the next step in the development of Rapalogs will be the discovery of new biomarkers to predict what tumor subtypes and specific molecular features are more likely to respond to mTOR inhibitors. In this regard, responses to PI3K-AKT-mTOR pathway inhibitors may be higher among those tumors harboring *PIK3CA* mutations (56) and also those with loss of *PTEN* (57). Another example of response to Rapalogs in specific tumor subtypes is the case of Microsatellite Instable (MSI) colorectal cancers. PI3K-AKT-mTOR pathway has been involved in the pathogenesis of colorectal cancer. In fact, PIK3CA mutations have been identified in approximately 20–30% of colorectal tumors, and have been associated with shorter cancer-specific survival, poorer outcomes and resistance to Cetuximab (1,58,59). Although single-agent Everolimus has not achieved objective responses in refractory metastatic colorectal cancer (48), *in vitro* studies have suggested that colorectal tumors displaying MSI could potentially respond better to therapies against the PI3K-AKT-mTOR pathway (60). According to these results, dual PI3K-mTOR inhibitors may represent an interesting option to be evaluated in this specific tumor subtype.

Second generation of mTOR inhibitors

Whereas Rapamycin exerts its action almost exclusively through mTORC1 inhibition, a second generation of inhibitors targeting the adenosine triphosphate site of the kinase domain of mTOR has been developed. These compounds are able to block both mTORC1 and mTORC2. Theoretically, their most important advantages would be a significant decrease of AKT phosphorylation upon mTORC2 blockade and a better mTORC1 inhibition. In addition, the preclinical data of these agents have contributed to a better understanding of the functions of mTORC2 and the limitations of Rapalogs.

Due to the fact that the catalytic domain of mTOR and the p110α subunit of PI3K are structurally related, some of these second generation compounds have dual activity against both PI3K and mTOR. These drugs compared to single specific-mTORC1 and -PI3K inhibitors have the potential benefit of inhibiting mTORC1, mTORC2, and all the catalytic isoforms of PI3K (61). Therefore, targeting both kinases simultaneously should reduce the upregulation of PI3K that typically produced upon inhibition of mTORC1 (30).

The majority of dual PI3K-mTOR inhibitors have already entered into phase I–II clinical trials alone or in combination with other agents for different cancer subtypes (Table 2). NVP-BEZ235 (Novartis) is one of these dual kinase inhibitors and reversibly blocks the p110α catalytic subunit of PI3K and mTOR (62). Initial *in vitro* data analyzing pharmacodynamic endpoints in breast tumor xenografts treated with NVP-BEZ235 have shown a decrease in phosphorylation levels of AKT, 4E-BP1, and S6K1 following treatment with this drug and higher antiproliferative activity than Everolimus (63). A phase I of NVP-BEZ235 has been recently presented with promising efficacy. Among 51 evaluable and heavily pretreated patients, 14 achieved stable disease longer than 4 months and partial responses were observed in breast and lung tumors. However, pharmacokinetic studies showed that the area under the curve (AUC) increased non-proportionally with dose, so future studies will use a new formulation of the drug. No dose-limiting toxicities were reported and the maximum tolerated has not been reached (64). On the other hand, XL-765 (Exelixis) has exhibited potent pharmacodynamic effects on the inhibition of PI3K with a stable pharmacokinetic profile. In addition, durable disease stabilizations were observed in patients with different tumor types such as colorectal cancer, lung cancer, renal cell carcinoma, mesothelioma, and appendiceal cancer (65).

Regarding single specific mTOR catalytic inhibitors, several small molecules have also been identified (Table 2 and Figure 2), and three of them have entered into phase I clinical development [AZD-8055 (AstraZeneca), INK-128 (Intellikine), and OSI-027 (OSI Pharmaceuticals)]. Preclinical data with INK-128 have shown a potent inhibition of the phosphorylation of S6K1, 4E-BP1, and AKT at Ser473 *in vitro*, as well as important antiproliferative activity against multiple xenograft models and cells lines resistant to Rapamycin and pan-PI3K inhibitors (66). At the same time Feldman et al have reported the activity of two compounds PP-242 and PP-30 (University of California) with activity against both mTORC1 and mTORC2. These compounds are able to completely suppress 4E-BP1 and S6K1 along with a reduction of phosphorylation of AKT at Ser473, thus leading to a higher antiproliferative effect compared to Rapamycin. However, the inhibition of mTORC2 did not result in a total blockade of AKT, suggesting that additional mTORC1 inhibition by these compounds could be the basis for their superior antitumor activity (67). In this regard, Hsieh et al suggested that the therapeutic benefit of PP-242 is mediated through the inhibition of mTORC1-dependent 4E-BP1-eIF4E hyperactivation (68). Other preclinical studies with these ATP-competitive and -specific mTOR inhibitors have observed similar results and have confirmed its activity over those Rapamycin-resistant functions of mTORC1. In addition, these drugs induce a stronger G1 cell cycle arrest in several cancer lines and formidable autophagy activation (69–73). Finally, a first-in-human phase I study exploring three schedules of OSI-027 has been recently presented with preliminary evidence of pharmacological activity. The maximum tolerated dose has not yet been defined and dose escalation is ongoing. Left ventricular ejection fraction and fatigue have been reported as dose-limiting toxicities (74). In the following years, we will obtain more detailed data from phase I studies regarding the pharmacokinetic profile, optimal dose, toxicity and preliminary activity of all of these compounds.

Conclusions

mTOR is one of the signaling pathways that has attracted more interest among basic and clinical researchers. Two main factors are the responsible for this phenomenon: mTOR is a downstream central effector of multiple pathways thus making it a very attractive target, and the drug Rapamycin which renders an incomplete inhibition of this protein complex became available in 1975. These facts have fostered the efforts of the pharmaceutical industry in order to synthesize newer and better compounds against it. In a relatively short period of time several companies have launched development programs of different drugs blocking the same target, including clinical trials to examine the activity of these compounds in solid and hematologic malignancies. In parallel, basic scientists continued exploring and trying to fill the gaps in the knowledge of the molecular biology of this pathway. At some point, biomarkers studies and clinical trials were developed without having a final clear portrait of the biology behind mTOR. Therefore, several unexpected and initially unexplainable results came back as a consequence of these studies.

Initial disappointment about preliminary clinical results decreased the excitement for targeting mTOR. It was later known that the mTOR pathway is almost a duality constituted by two complexes with different functions and many feedback loops, thus changing the original simplistic view of it. Now, a second generation of smarter compounds developed taking into account the latest biologic data is currently being developed. For one side, these compounds are able to inhibit both mTORC1 and mTORC2, and in the other side also incorporate activity against PI3K. Initial data from phase I clinical trials with these drugs have recently shown significant clinical activity, particularly in patients with deregulation of the PI3K-AKT-mTOR pathway.

Therefore, it is important to learn the lessons from the development of Rapamycin and Rapalogs. A complete understanding of the molecular biology of the pathway and its actors is needed in order to appropriately develop its targeted drugs and to correctly interpret the results from clinical studies. Finally, identification of biomarkers based on genetic, genomic, and systems biology approaches will allow defining what tumor subtypes may derive in a higher benefit with the use of mTOR inhibitors. These studies should be run in parallel to early clinical development trials, thus accelerating its implementation into phase III trials. In this way, biomarkers will be validated and ready to be approved simultaneously with drug indication.

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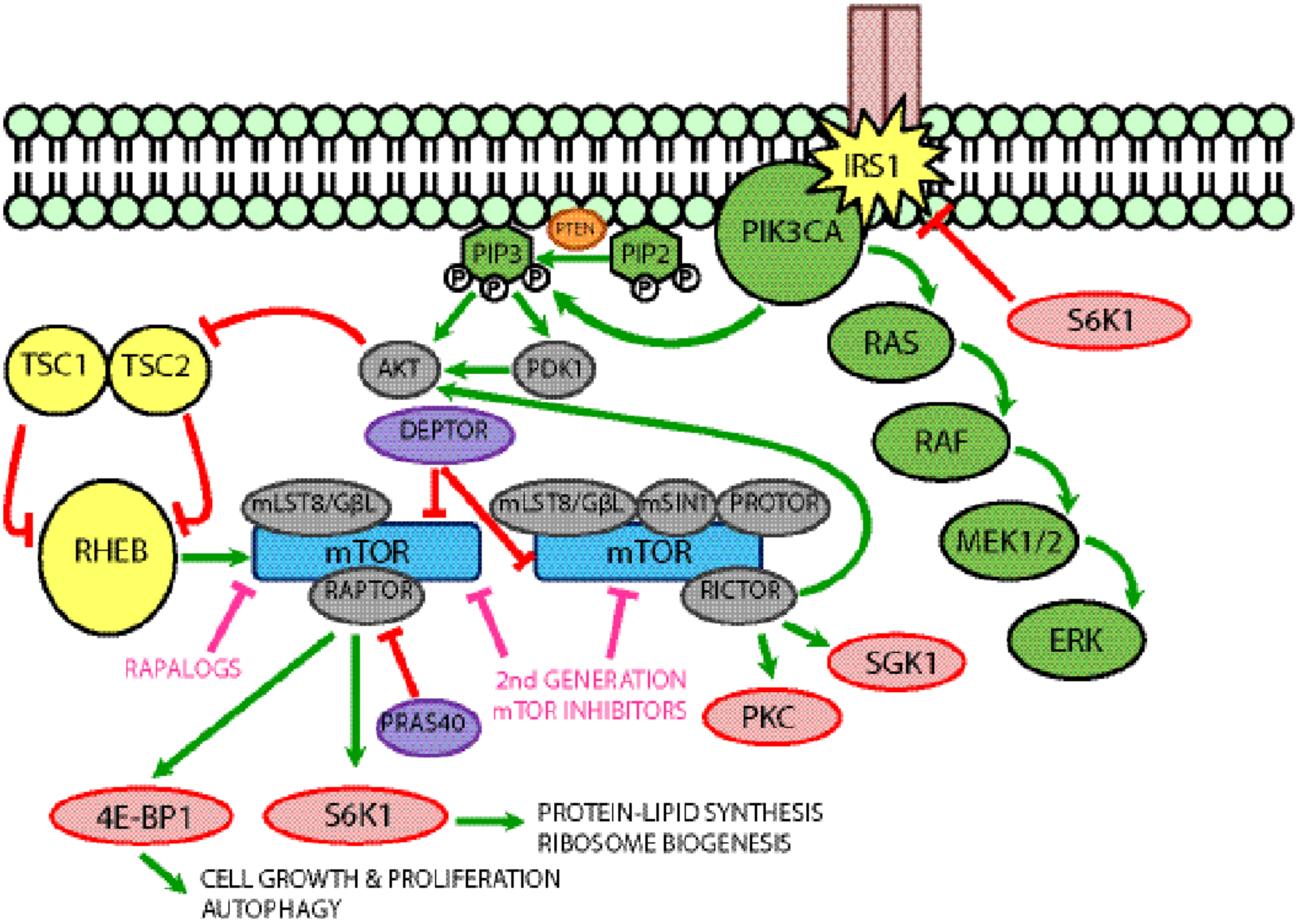

Figure 1.

PI3K-AKT-mTOR signaling pathway. A more detailed description of the biology of the mTOR has revealed the presence of two complexes and has led to the development of new drugs targeting specifically these complexes. In addition, feedback loops have been better characterized.

Phosphatydilinositol-3-kinase, PI3K; mammalian target of rapamycin, mTOR; mTOR complex, mTORC; tuberous sclerosis complex, TSC; eukaryotic initiation factor 4E binding protein 1, 4E-BP1; ribosomal S6 kinase 1, S6K1; Ras homolog enriched in brain, Rheb; serum- and glucocorticoid-induced protein kinase-1, SGK1; protein kinase C, PKC; insulin receptor-substrate 1, IRS-1; mitogen–activated protein kinase kinase, MEK; receptor tyrosine-kinase, RTK; regulatory-associated protein of mTOR, Raptor; proline-rich AKT substrate of 40 kDa, PRAS40; phosphatase and tensin homolog, PTEN; Phosphatidylinositol (4,5)-bisphosphate, PIP2; Phosphatidylinositol (3,4,5)-trisphosphate, PIP3; phosphoinositide-dependent kinase-1, PDK1.

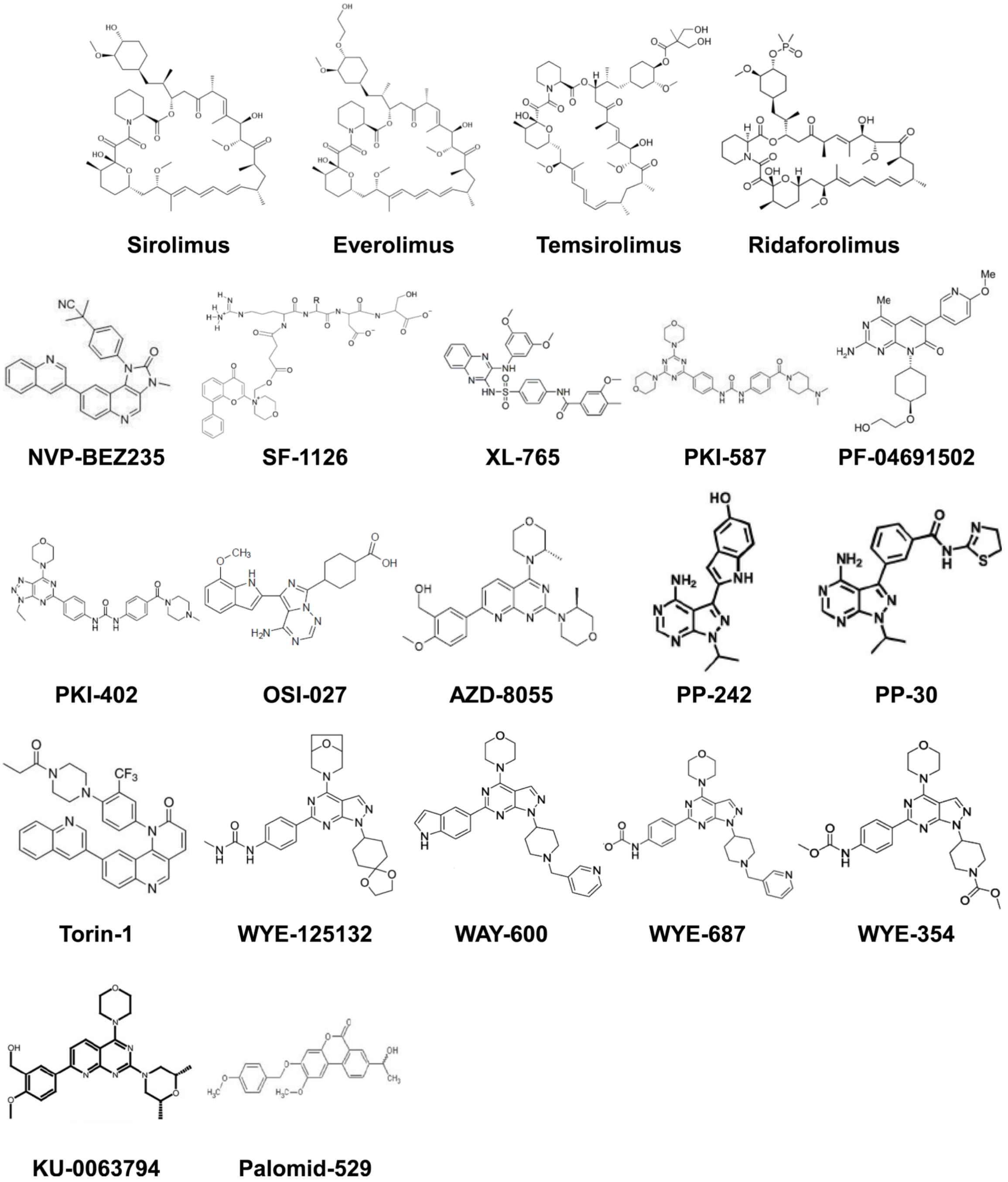

Figure 2.
Molecular structures of first and second generation of mTOR inhibitors. Rapalogs are displayed in the first row. Second generation inhibitors are displayed in the second and subsequent rows. Structures of NVP-BGT226, GDC-0980, SB-2312, INK-128, XL-388 have not been disclosed at the time of publication of this article.

Table 1

Rapalogs and approved indications from the FDA and EMEA. Food and Drug Administration, FDA; European Medicines Agency, EMEA.

Compound	**Approved indication**	**Agency**	**Ref**
Sirolimus	Prophylaxis of organ rejection in renal transplant patients	FDA/EMEA	(39)
Everolimus	Refractory advanced renal cell carcinoma	FDA/EMEA	(54)
Temsirolimus	Poor-prognosis untreated advanced renal cell carcinoma	FDA/EMEA	(53)
	Refractory mantle-cell lymphoma	EMEA	(55)
Ridaforolimus	No approved indication. Phase I-II-III trials ongoing	ClinicalTrials.gov	

Table 2

Dual PI3K-mTOR, mTORC1 and mTORC2 inhibitors and status of drug development

Phosphatydilinositol-3-kinase (PI3K); mammalian target of rapamycin (mTOR); mTOR complex (mTORC). Clinical Development, CD.

Compound	Drug Company	Targets	Status
NVP-BGT226	Novartis	PI3K/mTORC1/mTORC2	CD terminated
NVP-BEZ235	Novartis	PI3K/mTORC1/mTORC2	Phase I/II
SF-1126	Semaphore Pharmaceuticals	PI3K/mTORC1/mTORC2	Phase I
XL-765	Exelisis	PI3K/mTORC1/mTORC2	Phase I/II
PKI-587/PF-05212384	Pfizer	PI3K/mTOR	Phase I
PF-04691502	Pfizer	PI3K/mTOR	Phase I
GDC-0980	Genentech	PI3K/mTOR	Phase I
SB-2312	S*Bio	PI3K/mTOR	Preclinical
PKI-402	Pfizer	PI3K/mTOR	Preclinical
OSI-027	Osi Pharmaceuticals	mTORC1/mTORC2	Phase I
AZD-8055	Astra Zeneca	mTORC1/mTORC2	Phase I
INK-128	Intellikine	mTORC1/mTORC2	Phase I
XL-388	Exelixis	mTORC1/mTORC2	Preclinical
PP-242	University of California	mTORC1/mTORC2	Preclinical
PP-30	University of California	mTORC1/mTORC2	Preclinical
Torin-1	Gray Laboratory Harvard	mTORC1/mTORC2	Preclinical
KU-0063794	Kudos Pharmaceuticals	mTORC1/mTORC2	Preclinical
WYE-125132	Wyeth	mTORC1/mTORC2	Preclinical
Palomid-529	Paloma Pharmaceuticals	mTORC1/mTORC2	Preclinical
WAY-600	Wyeth	mTORC1/mTORC2	Preclinical
WYE-687	Wyeth	mTORC1/mTORC2	Preclinical
WYE-354	Wyeth	mTORC1/mTORC2	Preclinical