Getting more out of mTOR

By Tim Fulmer, Senior Writer

Researchers at the **University of California, San Francisco** have developed mTOR inhibitors for cancer that may have better activity than rapamycin and other first-generation molecules.[1] The compounds have been licensed and optimized by **Intellikine Inc.**, which hopes to submit an IND for its lead candidate in an undisclosed cancer by year end.

Mammalian target of rapamycin (mTOR; FRAP; RAFT1) exists in two multiprotein complexes—mTORC1 and mTORC2. Both complexes mediate cell growth and proliferation in a variety of cell types[2] (*see* **Figure 1, "mTOR in cancer"**).

The central role of mTOR in the proliferation of T cells has made it an ideal target to induce immunosuppression. Similarly, in a variety of cell types, hyperactivation of mTOR signaling has been associated with oncogenic proliferation, making it a good cancer target.

Marketed mTOR inhibitors to prevent transplant rejection include Rapamune sirolimus (rapamycin) from **Wyeth** and Certican everolimus from **Novartis AG**. An NDA for everolimus to treat advanced renal cell carcinoma (RCC) is under FDA review, with a decision expected this quarter.

However, rapamycin and its analogs (rapalogs) inhibit only the mTORC1 complex and cannot block growth signals through mTORC2.

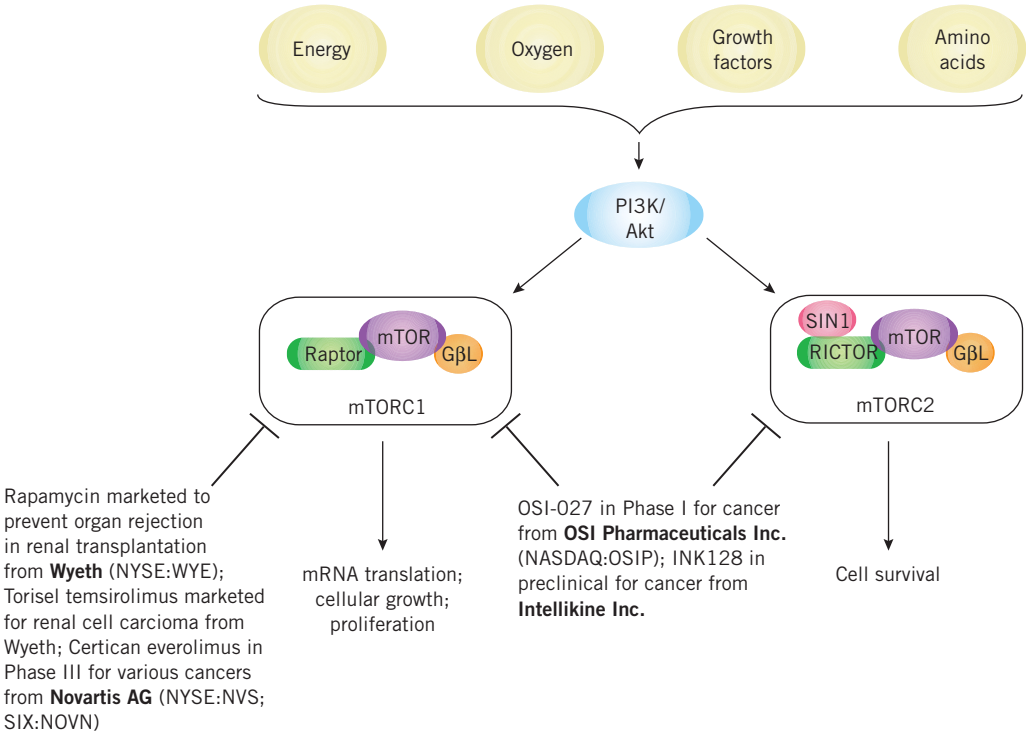

Figure 1. mTOR in cancer. A **University of California, San Francisco** group led by Kevan Shokat has characterized small molecule inhibitors of mammalian target of rapamycin (mTOR; FRAP; RAFT1). Unlike other compounds that target mTOR, these inhibitors are able to bind to two multiprotein complexes—mTORC1 and mTORC2—that form the target. These complexes play a central role in mediating cell growth, proliferation and survival in response to extracellular growth factors and other biochemical cues. mTORC1 is made up of Raptor (KIAA1303), mTOR and GBL G protein–β subunit-like (GBL; GβL), whereas mTORC2 is made up of mitogen-activated protein kinase associated protein 1 (MAPKAP1; SIN1), rapamycin-insensitive companion of mTOR (RICTOR), mTOR and GβL.

In cancer, certain growth factors and biochemical changes lead to the upregulation of the phosphoinositide 3-kinase (PI3K)/Protein kinase B (PKB; Akt) pathway, which in turn leads to the hyperactivation of mTOR-mediated signaling.

Intellikine Inc. has in-licensed and optimized the compounds from Shokat *et al.* to generate a lead dual mTORC1 and 2 inhibitor, INK128, which the company hopes to move into the clinic within a year or two. At least one dual mTORC1 and 2 inhibitor has already entered the clinic. OSI-027, from **OSI Pharmaceuticals Inc.**, is in Phase I testing to treat advanced solid tumors and lymphoma.

Other mTOR inhibitors include Rapamune sirolimus (rapamycin) and its analogs, which only bind mTOR in mTORC1.

In a paper in *PLoS Biology*, the UCSF group set out to characterize two previously described pyrazolopyrimidines that block mTOR signaling through both complexes by targeting the kinase's ATP binding site. In cell culture and mouse studies, the team characterized these small molecule mTOR inhibitors, dubbed TORKinibs, which inhibited the mTOR kinase activity common to both complexes.

One of the dual mTORC1 and 2 inhibitors, PP242, blocked proliferation of mouse embryonic fibroblasts in a dose-dependent manner. At high doses the compound had greater antiproliferative activity than rapamycin.

In wild-type mice, PP242 inhibited mTORC2 and rapamycin-resistant mTORC1 in fat, liver and skeletal muscle tissue.

The UCSF team was led by Kevan Shokat, professor of cellular and molecular pharmacology at UCSF, professor of chemistry at the **University of California, Berkeley** and cofounder of Intellikine.

Intellikine has since optimized PP242. The next-generation version, INK128, is the biotech's lead mTORC1 and 2 inhibitor.

The company initially plans to look for efficacy in a variety of cancer patient populations, according to Troy Wilson, cofounder, president and CEO. "We plan to enrich our patient population with renal cell carcinoma, which has shown responsiveness to rapamycin and related analogs (mTORC1 inhibitors), sex hormone–associated cancers and hematological cancers," he said.

"mTORC1/2 inhibitors offer a compelling rationale for combination therapies, and we are completely committed to the approach," added CSO Christian Rommel. "We are profiling a wide variety of genetic backgrounds and integrating this information with information on the mechanisms driving the observed efficacy."

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>
> ***—Christian Rommel, Intellikine Inc.***

Rommel said possible strategies could include combining INK128 with standard chemotherapy or with molecular-targeted anticancer drugs.

At least one other biotech has already moved a dual mTOR inhibitor into the clinic. OSI-027, a small molecule mTORC1 and 2 inhibitor from **OSI Pharmaceuticals Inc.**, is in a Phase I trial (NCT00698243) to treat advanced solid tumors and lymphoma.

OSI declined to comment on the *PLoS Biology* paper.

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COMPANIES AND INSTITUTIONS MENTIONED

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