

# BIO WORLD<sup>®</sup> TODAY

THURSDAY  
JANUARY 14, 2010

THE DAILY BIOTECHNOLOGY NEWSPAPER

VOLUME 21, No. 9  
SPECIAL REPRINT

## Combination Tricks

### Two Studies Show New Frontlines Against Cancer

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Science Editor

In the Jan 14, 2010, online edition of *Nature Medicine*, researchers reported the discovery of a new inhibitor that targets the mTOR kinase via a different mechanism than rapamycin, and is synergistic with approved anticancer agents imatinib (Gleevec, Novartis Inc.) and dasatinib (Sprycel, Bristol-Myers Squibb Co.) in killing cells that have the BCR-ABL kinase.

Surprisingly, the compound also had fewer effects on normal B cells than rapamycin.

The mTOR kinase is part of a pathway – the kinase- and acronym-riddled PI3K/TSC/Akt pathway – that is “perhaps the most frequently dysregulated pathway in human cancers,” co-author Christian Rommel told *BioWorld Today*. Rommel is chief scientific officer at La Jolla start-up Intellikine, which recently started Phase I trials with a related compound, and also is working on targeting PI3 kinase directly (See *BioWorld Today*, Jan 13, 2010.)

mTOR is inhibited by the immunosuppressive drug rapamycin – indeed, mTOR stands for “mammalian target of rapamycin.”

But though rapamycin is decades old, it has only recently become clear that the mTOR kinase is part of two distinct protein complexes, TOR complex 1 and TOR complex 2, with distinct functions.

Rapamycin, which acts at a site that is distant from the ATP-binding pocket, partially blocks the first complex but has “little to no effect” on the second one, leading to hopes that directly targeting the ATP-binding site would lead to more effective blockage.

In their paper, the authors studied acute lymphoblastic leukemia or ALL. ALL – like the more famous chronic myelogenous leukemia – results from a genetic rearrangement that brings two distant gene regions into contact, resulting in the hyperactive bcr-abl kinase.

Senior author David Fruman, an associate professor of molecular biology and biochemistry at UC Irvine, told *BioWorld Today* that there is a greater need for new approaches to ALL than there is to CML; while CML “is the success story for Gleevec and Sprycel,” ALL is less depend-

ent on bcr-abl and most ALL patients treated with bcr-abl inhibitors enjoy a brief remission at best. Because mTOR is hyperactive in most leukemias, Fruman sees the work on ALL as a proof of concept.

The authors first tested the effects of PP242 on Bcr-abl cells in cell culture, and found that the compound killed greater than 90 percent of them. When PP242 was given together with either imatinib or dasatinib, it was synergistic in killing cells.

In xenografted animals, PP242 delayed the onset of leukemia either alone or in combination with imatinib. In combination with dasatinib, PP242 was more effective in decreasing tumor burden than dasatinib alone – an encouraging finding, as combination therapy will be the likely path for novel cancer drugs in both clinical trials and, if they pan out, clinical practice.

Perhaps the most striking thing about PP242 was its effect – or lack thereof – on the immune system. Rapamycin is an immunosuppressant – the drug is, in fact, used in transplant therapy to avoid rejection. But PP242 was much less immunosuppressive than rapamycin, which could translate into a better ration of efficacy to toxicity in the clinic.

When asked for the reason that PP242 is less toxic than rapamycin, Fruman's answer was blunt: “We don't understand why,” he said, adding that his lab is looking for the answer.

That one reason may lie in the way that rapamycin acts, he said: It does not kill cells outright, but instead “causes a lot of rewiring on the way cells do their business” – and in the course of that rewiring, “sets off a number of compensatory mechanisms that we are just beginning to understand.”

Those compensatory mechanisms may damage normal B cells more than the inhibition by PP242, which is direct, but at the doses used in the study “may not fully inhibit the mTOR enzyme all the time.”

Fruman stressed that it is not possible to say, at this point, that there is no effect of PP242 on the immune sys-

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tem. "It may have effects on the immune system that we didn't study," he said, adding that after 30 years, the study of rapamycin is still yielding new insights into how it affects the immune system.

A separate paper in the Jan 14, 2010, issue of *Cell* reported that mutations in separate cells can cooperate to cause metastatic cancer: An oncogenic mutation in one cell and a loss-of-function mutation in another could cooperate to cause tumors – at least in fruit flies, the model in which the experiments were conducted.

The importance of tumor cells' interaction with the microenvironment has become increasingly clear in recent years.

However, the new paper described how changes in separate cells can work together to lead to cancer. The authors investigated the cooperation of adjacent epithelial cells, one of which had the oncogene Ras, and the other had a mutation in the tumor suppressor gene scribbled.

They found that adjacent cells with such mutations communicated with each other via cytokines produced in scribble-defective cells.

Those cytokines are released from scribbled-mutant

cells and activate the jun kinase or JNK in the RAS mutant cells. Jun kinase, in turn, up-regulates signaling of the JAK/STAT pathway in RAS-mutant cells, leading them to divide uncontrollably; tumors that form through such cell-to-cell communication consist mainly of Ras-mutant cells. Such tumors also tended to metastasize to the nervous system.

Jun kinase is activated in response to several stressors, and the authors found that injury, too, could lead to uncontrolled cell division and tumor formation, though such tumors did not metastasize.

Senior author Tian Xu, professor and vice chairman of genetics at Yale University, minced no words about the implications of the findings, calling both the fact that mutations in separate cells – which are statistically more likely to occur – and the added evidence that stress signaling can help cancer cells grow "bad news" in a press release announcing the findings.

But, he added, such findings also show scientists the next battleground: "Better understanding of the underlying mechanism causing cancer always offers new tools to battle the disease." ■