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Propellered to Success

Structural Study of PI3 Kinase Suggests Targeting Strategies

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Science Editor

When subtypes of PI3 kinases – a type of kinase that is frequently mutated in cancers, and hotly pursued by drug developers in both biotech and pharma – were discovered, their specific targeting at first looked like something of a fool's errand.

"By primary linear sequence, these isoforms are so similar that it was once thought that they could not be selectively targeted," Christian Rommel told *BioWorld Today*.

But biological studies rapidly showed that despite their sequence similarity, the functions of PI3 kinase isoforms are "rather different," implying that selectively targeting subtypes was both possible and desirable. Particularly for the treatment of chronic diseases, Rommel said, the reduced risk of side effects that goes along with better isoform specificity – especially when used as part of combination therapy – "will be a huge advantage."

The PI3K family includes alpha, beta, delta and gamma isoforms. Alpha and beta subtypes, Rommel said, are near-ubiquitously expressed, while the gamma and delta subtypes are "more restricted to the hematopoietic immune system." Deregulation of the delta and gamma subtypes have been linked with both hematological cancers and disorders with an immune system component, such as rheumatoid arthritis and asthma.

Several isoform-specific compounds have since entered the clinic, in trials for both cancer and thrombosis. But given their amino acid sequence similarity, specifically targeting one isoform is still anything but trivial. In the Jan. 10, 2010, advance online edition of *Nature Chemical Biology*, Rommel, who is chief scientific officer at La Jolla, Calif.-based start-up Intellikine Inc., and his colleagues from the Medical Research Council's Laboratory of Cambridge, Merck-Serono, and the University of California, San Francisco, reported crystal structure data for the delta subtype of PI3K, bound to different inhibitors, that sheds light on how to target the subtype more specifically.

In their paper, the team examined the crystal structure of the catalytic subunit of the delta subtype of PI3 kinase, when bound to nine different inhibitors – some which were

selective for that particular subtype and some which were nonselective or pan-inhibitors of PI3 kinase.

They found that with one exception, the inhibitors they studied fell into two different groups: One group, which the scientists described as "propeller-shaped" in their paper, is specific for the delta subtype because they change the shape of the ATP binding pocket when they bind; a second group of flatter inhibitors do not induce this shape change when they bind, and are not selective for the delta subtype.

In one sense, the work is similar to recent studies showing that G-protein coupled receptors with very similar amino acid sequences in their binding sequence can be specifically targeted. (See *BioWorld Today*, Jan. 11, 2010.)

But the nature of the targeting is different in each case: While the work on GPCR's suggested that allosteric modulation – inducing changes in the ligand-binding pocket through additional drugs that target other parts of the receptor – the data now published in *Nature Chemical Biology* suggested ways to design compounds that interact with the ATP-binding pocket – the classic target – but nevertheless bind specifically to one subtype.

In a press release announcing the publication of the paper, Intellikine said that "over the past several years, Intellikine scientists have exploited the insights from these co-crystal structures to design multiple series of isoform-selective inhibitors. As a result, we recently designated INK1197, an exquisitely selective delta/gamma isoform inhibitor, as a preclinical development candidate therapy for inflammatory and respiratory disease."

Rommel declined to give specifics on the shape or binding of INK1197, which was not itself used for the work published in *Nature Chemical Biology*. Two years after its founding, the company announced the start of its first trial with INK128, a small-molecule inhibitor of both the TORC1 and TORC2 complexes, which are key components of the PI3K/mTOR pathway, just last week. Rommel said that Intellikine hopes to be in the clinic with INK1197 "with a similar rate of urgency." ■

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