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ROCKing in hematology

By Lauren Martz, Staff Writer

A team at the **Indiana University School of Medicine** has published the first evidence that rho kinase inhibitors could help treat acute myelogenous leukemia and other hematological malignancies.[1] The researchers now hope to repurpose Eril fasudil, a rho kinase inhibitor marketed in Japan by **Asahi Kasei Pharma Corp.** to treat aneurysm.

Rho kinases are expressed in a variety of tissues and are involved in multiple cellular processes, including the organization of the cytoskeleton and cell motility, growth and survival.

Although Eril is the only rho kinase inhibitor on the market, multiple companies are pursuing the target for glaucoma, neurodegeneration, pain and solid tumors.

Indeed, previous studies have shown aberrant upregulation of rho kinases in solid cancers.[2] Thus, Reuben Kapur and colleagues hypothesized that rho kinases might also be upregulated in hematological cancers.

Kapur is professor of pediatrics, molecular biology and biochemistry, medical and molecular genetics, and microbiology and immunology, and director of the program in hematologic malignancies and stem cell biology at the Herman B. Wells Center for Pediatric Research at the Indiana University School of Medicine's Cancer Research Institute.

In cultured human acute myelogenous leukemia (AML) and mastocytosis cells, Eril and other small molecule rho kinase inhibitors decreased cell growth compared with no treatment.

In mice transplanted with myeloid cells expressing chemotherapy-resistant oncogenic mutations, the rho kinase inhibitors prolonged survival and reduced cellular signs of myeloproliferative disease compared with saline control.

The findings were published in *Cancer Cell*. The paper also included researchers from the **Cleveland Clinic**, the **Broad Institute of MIT and Harvard,** and **Northwestern University**.

Masha Poyurovsky, senior director of molecular oncology and head of the ROCK2 (rho-associated coiled-coil containing protein kinase 2) program at **Kadmon Corp. LLC**, told *SciBX* that "this work opens up blood cancers as a whole new area of cancers that can be treated by rho kinase inhibition."

"It has been considered that rho kinase inhibitors could be used to treat cancer, but it's usually been thought that they would be most useful to limit metastasis, and therefore would be used in an adjuvant setting. This paper is different because it suggests that rho kinase inhibitors could be useful frontline agents for these forms of hematological malignancies," said Michael Olson, professor of molecular cell biology at **The Beatson Institute for Cancer Research**.

Olson told *SciBX* that inhibiting rho kinase has a beneficial effect in limiting metastasis due to the kinase's role in cell-cell adhesion and motility.

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>
> *—Masha Poyurovsky, Kadmon Corp. LLC*

Selectivity for safety

Kapur said his group is now determining a path for testing Eril as a cancer therapy, including the types of preclinical studies that will be required.

Repurposing Eril in oncology will have to take into account the drug's action on rho kinases in cardiovascular smooth muscle cells. Although Eril prevents apoptosis and rupture of vessel walls by inducing smooth muscle relaxation in aneurysm patients, this effect could lead to unwanted hypotension in cancer patients.

"Fasudil has been used in Japan for the treatment of cerebral vasospasm for a number of years, so it would be relatively straightforward to set up clinical trials with an agent that has a track record of being safe to test its effectiveness in myeloproliferative disease," Olson said. "The effects on blood pressure would have to be built into any clinical trial design to ensure it isn't a real problem."

Poyurovsky told *SciBX* that the effects on smooth muscle relaxation are "holding back the rho kinase inhibitors for indications other than cardiovascular indications." She believes that inhibitors that target specific isoforms of rho kinase could be a way of avoiding those side effects.

The rho kinases come in two isoforms: ROCK1 and ROCK2. ROCK1 is more highly expressed in the lungs, liver and kidneys, and ROCK2 is more highly expressed in the brain and heart.

Eril targets both rho kinase isoforms.

Poyurovsky thinks the rho kinase isoforms have distinct functions and that inhibiting only the ROCK2 isoform could decrease effects on the cardiovascular system.

"It would have to be tested whether the selective ROCK2 inhibitors were effective on myeloproliferative disease the way the non–isoform-selective inhibitors in this paper were, but if so, that would be one way to deal with the potential hypotension problems," Olson said.

Kadmon's KD025 is the only disclosed inhibitor that is selective for ROCK2. KD025 is in Phase I testing to treat solid tumors.

"It would now be possible for us to pursue these indications with our own inhibitor," Poyurovsky said.

Kapur said Indiana University has filed for a patent covering the use of Eril to treat mastocytosis and AML. The IP is available for licensing.

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REFERENCES

1. Mali, R.S. *et al. Cancer Cell*; published online Sept. 12, 2011; doi:10.1016/j.ccr.2011.07.016

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2. Greenman, C. *et al. Nature* **446**, 153–158 (2007)

COMPANIES AND INSTITUTIONS MENTIONED

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