Rexinoids May Be Ready for Prime Time in Prevention, But Challenges Remain

Don’t call rexinoids retinoids. Like a younger brother always standing in his big brother’s shadow, rexinoids are frequently confused with their retinoid kin, the vitamin A derivatives that have been used in chemotherapy and to quell severe acne, among other things. Those who study rexinoids say few scientists are familiar with this class of compounds that deserves serious attention in chemotherapy and chemoprevention.

“Most people think of rexinoids as just another form of retinoids, but they most emphatically are not so,” said Michael Sporn, M.D., of Dartmouth Medical School in Hanover, N.H., at a session he organized on rexinoids and their chemoprevention potential at the third annual American Association for Cancer Research Frontiers in Cancer Prevention Research conference held in October in Seattle.

Preclinical studies have shown that rexinoids, compounds that selectively bind the multifunctional nuclear retinoid X receptors (RXRs), appear to maintain the cancer prevention potential that made retinoids exciting chemoprevention candidates a decade ago, but without their disappointing toxic side effects. And new studies are showing that rexinoids, when combined with a selective estrogen receptor modulator (SERM), have emergent properties that effectively kill breast cancer cells.

“RXR is a unique partner,” said Ronald Evans, Ph.D., of the Salk Institute for Biological Studies in San Diego. “It is the master heterodimerizing receptor in the superfamily of nuclear non-steroidal receptors.”

Molecular studies in Evans’ laboratory and others have demonstrated that RXR pairs with at least 20 different receptor partners, including the retinoid receptor family RAR, and in turn modulates the transcription of dozens of genes involved in the control of cell growth and differentiation, energy metabolism, and inflammation. But while some retinoids, such as 9-cis-retinoic acid, bind both RXR and RAR, a new generation of RXR-specific ligands appears to avoid toxic side effects such as skin changes and liver toxicity that plagued efforts to put the rexinoids to clinical use.

It is the multifunctional effects of RXR-specific ligands that excite Sporn. “If one thinks about cancer as a disease that involves multiple gene dysfunction, from my position I think it’s very, very unlikely that we are going to be able to deal with the vast majority of human cancers with a single drug,” said Sporn. “In that sense, I think rexinoids, because of their polyfunctionality, are extremely interesting.”

Indeed, preclinical studies in the laboratories of Sporn and Powel Brown, M.D., Ph.D., from the Baylor College of Medicine in Houston, have shown evidence that at least two rexinoid compounds have potent antitumor effects.

Brown has studied a selective rexinoid compound called Targretin (bexarotene), which is approved by the U.S. Food and Drug Administration for cutaneous T-cell lymphoma.

In an article published Nov. 15, 2002, in Cancer Research, Brown and his colleagues studied the ability of Targretin to suppress development of breast tumors in the mouse mammary tumor virus–erbB2 transgenic model, a well-documented estrogen receptor (ER)–negative model of breast cancer. The mice were treated for 14 months with high-dose (100mg/kg), low-dose (10mg/kg), or no Targretin. At the end of the study period, all of the control mice had developed tumors, whereas 74% of the low-dose animals and 24% of the high-dose animals developed tumors.

Similar studies looking at the effect of Targretin on ER-positive breast cancer mouse models have shown enough promise that a clinical study is now under way at the Baylor College of Medicine to test its efficacy in inhibiting breast cell growth in women at high risk of breast cancer. Women will receive a month of treatment with Targretin, followed by a breast biopsy that will look for markers of breast cell growth, including growth factors, Cox-2 enzyme, and other biomarkers, said Brown.

About half of the target 100 women have been recruited for the trial, but no preliminary data are available yet. Side effects seen so far include an elevation of blood triglyceride levels in a few patients, Brown said.

“Bringing these novel agents to clinical trials is difficult, and the reason we were able to do this is this particular agent [Targretin] was already being tested in treatment protocols,” said Brown. “Not everyone should take RXR ligands, but I think they are ready for prime time in high-risk individuals.”

Sporn is already looking ahead to what seems to be the most promising future for rexinoids: in combination therapy with other drugs.

In a study published May 15 in Cancer Research, Sporn and his colleagues reported that the SERM arzoxifene and the selective rexinoid LG100268, made by Ligand Pharmaceuticals Inc., work cooperatively to induce apoptosis of cancerous breast cells and to dramatically shrink tumors in an ER-positive rat model.

“We see the emergence of a new activity by this combination [of arzoxifene and LG100268],” he said. “Neither induce apoptosis alone, but the combination of the two is strongly...
apoptotic. The combination makes tumors disappear.”

To try to understand the mechanism behind this synergistic effect, Sporn and his colleagues studied levels of caspase 3, a marker of apoptosis. The level of caspase 3 increased substantially in tumor samples after 1 week of treatment with both agents, but not after treatment with either agent by itself.

Sporn reported that arzoxifene stimulated transforming growth factor β3, a known inducer of apoptosis, but this induction alone was not sufficient to induce apoptosis in the rat cell model. But work in Sporn’s laboratory showed that the synergistic effect of LG100268 with arzoxifene could be explained by data showing that LG100268 inhibits the cell survival pathways involving PI3K and nuclear factor κB, which, when active, can be a “back door to turn off apoptosis,” he said. “Our studies show [LG100268] can reverse that.”

In a separate prevention protocol published in the same paper and presented at the meeting, Sporn found that there was a dramatic reduction in tumor volume in tumor-bearing rats after three courses of treatment with arzoxifene and LG100268. One or two courses of the treatment had an intermediate effect.

“It’s already clear that the rexinoids, when used in combination, at least in experimental animals, offer not just a possibility but a demonstration of prevention of ER-negative breast cancer,” said Sporn. “Whether that can be extrapolated into a human clinical trial remains to be seen.

“Maybe we don’t need to give people preventative drugs forever if we can cause enough premalignant cells to undergo apoptosis,” continued Sporn. “Intersmittent administration of drugs is standard protocol in almost all chemotherapy, and why we haven’t adopted that yet in our chemoprevention studies I really don’t know.” He suggested his methodology may be the first wave in a whole new way to think about cancer prevention.

“Giving these two agents together you have the exciting possibility that you could actually induce apoptosis of precancerous cells and consequently only have to give these two agents together for a relatively short period of time,” said Carol Fabian, M.D., director of the Breast Cancer Prevention Center at the University of Kansas Medical Center in Kansas City.

Sporn and Fabian have discussed the possibility of doing a phase II clinical trial with a SERM and a rexinoid, but they have run into a stumbling block in getting the makers of the drugs to work together to design such a trial, said Sporn.

“I don’t think there’s a real problem with two companies working together to bring a combination therapy forward,” said Bill Lamph, associate director of molecular oncology at Ligand Pharmaceuticals and lead investigator for the company’s rexinoid program. “It’s just a matter of timing. Everybody is running into this wall of asking, ‘will this take 10 years or 20 years,’ and companies just don’t have the ability to make those kinds of investments.”

Fabian, who is the lead investigator in an ongoing phase II chemoprevention study of the Cox-2 inhibitor celecoxib for the prevention of ER-negative breast cancer, agreed that often compounds that look promising for prevention never get tested.

“It sounds so simple until you try to start doing these kinds of trials,” she said. “I just think we need to get to a point in this country where the [National Cancer Institute] takes over [testing] the drugs that have been developed by individuals or drug companies that are very interesting for prevention in combination because the drug companies themselves are not going to make the investment.”

—Karyn Hede