Dual Inhibitor Combats Triple Negative Breast Cancer

There are more than 40,000 women newly diagnosed with triple negative breast cancer every year in the United States, the only subset of breast cancers that doesn’t have an FDA-approved targeted therapy. Despite advances in non-targeted chemotherapies, the risk of recurrence within five years in patients with TNBC is around 40 percent.

The Solution

A University of Michigan team, led by Sofia Merajver, M.D., Ph.D., and Matthew Soellner, Ph.D., has developed a class of mechanistically novel dual c-Src/p38 kinase inhibitors that have shown significant activity in both in vitro and in vivo models of TNBC. The novel inhibitors are tested for their in vivo efficacy in TNBC animal models and in samples of human tumors obtained from the biopsies. Inhibiting activity of c-Src and p38 kinases has been shown to slow the progression of TNBC, lower recurrence, and provide non-toxic treatment with minimal side effects; the researchers have also shown significant tumor reduction in animal xenograft models.

Abnormal expression of the c-Src enzyme has been detected in various types of tumors, with it being highly overexpressed in TNBC. This overexpression of c-Src, as well as increased activity of p38 enzymes, has been shown to play important roles in the cancerous proliferation and invasion of TNBC cells. Based on these findings, c-Src and p38 kinases are attractive targets to develop new treatments.

GOAL

improving treatment for triple negative breast cancer patients

THERAPEUTIC IMPACT

The University of Michigan Translational Research and Commercialization (MTRAC) for Life Sciences Innovation Hub is supported by the U-M Medical School, U-M Tech Transfer Office, and the Michigan Economic Development Corporation and works to “fast forward” projects that have a high potential for commercial success, with the ultimate goal of positively impacting human health. The TNBC inhibitor project is just one of 11 projects in the 2017 cohort funded by MTRAC. In 2014, the program funded 11 teams for early commercialization development, while 11 teams were funded in 2015, and 12 projects were funded in 2016.
Molecule offers dual targeting of c-Src/p38 kinase in triple negative breast cancer patients

Significant Need
TNBC is the only subset of breast cancers that doesn’t have FDA-approved targeted therapies, and clinicians rely upon non-specific toxic agents for tumor control. Despite advances in non-targeted chemotherapies, the risk of recurrence within five years in these patients is nearly 40 percent, which is substantially higher than for hormone receptor tumors.

Compelling Science
Inhibiting c-Src enzymes in a specific conformation alters the cellular localization and decreases the accessibility of their regulatory domains, thus preventing interaction with other important signaling proteins.

Competitive Advantage
In addition to treating TNBC, the therapeutic has the potential to treat other tumor types, such as aggressive pancreatic cancers and some sarcomas, which are also c-Src and/or p38 dependent. Other FDA-approved Src inhibitors do not have this capability.

With the help of MTRAC funding, we will test the efficacy of novel c-Src/p38 dual inhibitors already efficacious against tumors resected from patients with triple negative breast cancer. This would allow us to address the therapeutic gaps of approximately 200,000-300,000 newly diagnosed women with this or potentially similarly aggressive breast or other cancers every year, worldwide.

MTRAC Project Key Milestones

UM-193, UM-232 and UM-310 will be tested for selectivity in human receptor and off-target panel and hERG assay

Determine pharmacokinetics and toxicity in an additional animal species (rats)

Mechanistic studies of metabolism and plasma protein binding

Overall Commercialization

Start a company; progress dual Src/p38 inhibitor to Phase I clinical trial in 2019 and demonstrate “first-in-man” efficacy

Get an IND to conduct clinical trials; upon completion, will apply for NDA

Commercialization Strategy

Regulatory Pathway

Intellectual Property

A provisional patent has been filed and is currently being converted to PCT