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REDUCING R(I)SK IN TNBC

BY STEPHEN HANSEN, ASSOCIATE EDITOR

Phoenix Molecular Designs could provide triple-negative breast cancer its first molecular marker to turn the intractable indication from a group of have-nots to a group of haves. With early evidence that RSK2 is activated in 80% of TNBC tumors, Phoenix aims to develop a targeted therapeutic, and has partnered with Roche on a companion diagnostic.

Phoenix announced the deal with Roche on Jan. 16 in which the partners will develop a tissue-based assay to detect RSK2 activation in cancer patients. Terms of the deal were not disclosed, though it is the first major deal for Phoenix, which raised $7 million in seed funding last year. The company also has $1.4 million in non-dilutive funding.

The marker would break open an indication that has suffered a lack of druggable targets, in large part because it is defined by the absence of the three most common receptors in breast cancer: estrogen receptor (ER), progesterone receptor (PR) and HER2. There have been no positive indicators in TNBC.

TNBC represents about 20% of breast cancer cases, but lacks any approved targeted therapies. First-line patients are typically treated with a combination of taxanes and anthracyclines in the neoadjuvant setting, and about one third of patients progress in the first three years. There is no established standard of care for metastatic disease.

Inhibitors of PARP and PD-L1 have shown activity in TNBC, and there are more than 20 therapeutics against other targets in clinical development. The most advanced is the antibody-drug conjugate sacituzumab govitecan from Immunomedics Inc. Last month, FDA issued a complete response letter for the ADC against EGP-1 due to CMC issues.

Phoenix CEO Sandra Dunn believes that the company's RSK2 inhibitor, PMD-026, could act as a monotherapy or in combination with a PARP or PD-L1 blocker.

The goal is to demonstrate that RSK2 can be the fourth major biomarker for stratifying breast cancer patients.

She said the program is based on unpublished data from Phoenix's analysis of 65 TNBC tumors that showed 52 (80%) with activated RSK2.

The goal is to demonstrate that RSK2 can be the fourth major biomarker for stratifying breast cancer patients. "It is the first biomarker that could identify patient populations that could respond to a targeted therapy in TNBC," Dunn said.

Dunn said part of the rationale for why RSK2 inhibition may work is that the enzyme sits at a major convergence point of two signaling pathways: the MAPK-MEK pathway, and the PDK pathway. In TNBC, activation of RSK2 causes the kinase to translocate to the nucleus, where it phosphorylates the transcription factor YBX1, which in turn stimulates tumor growth and cell invasion (see Figure "Convergence of RSK").

"You need to basically unplug TNBC at that central point in order for the cells to undergo apoptosis," Dunn said. "When we did our screens, if you individually inhibited PDK1 or if you inhibited MEK, it wasn't enough."

While other companies' RSK2 programs in cancer have run aground, Phoenix believes it has solved the pharmaceutical hurdles they faced. After TNBC, it plans to expand to other cancers where the logic of targeting the kinase should hold.

PMD-026 is slated to enter a Phase I/Ib trial in TNBC mid-year; the company has not disclosed a timeline for reporting data.

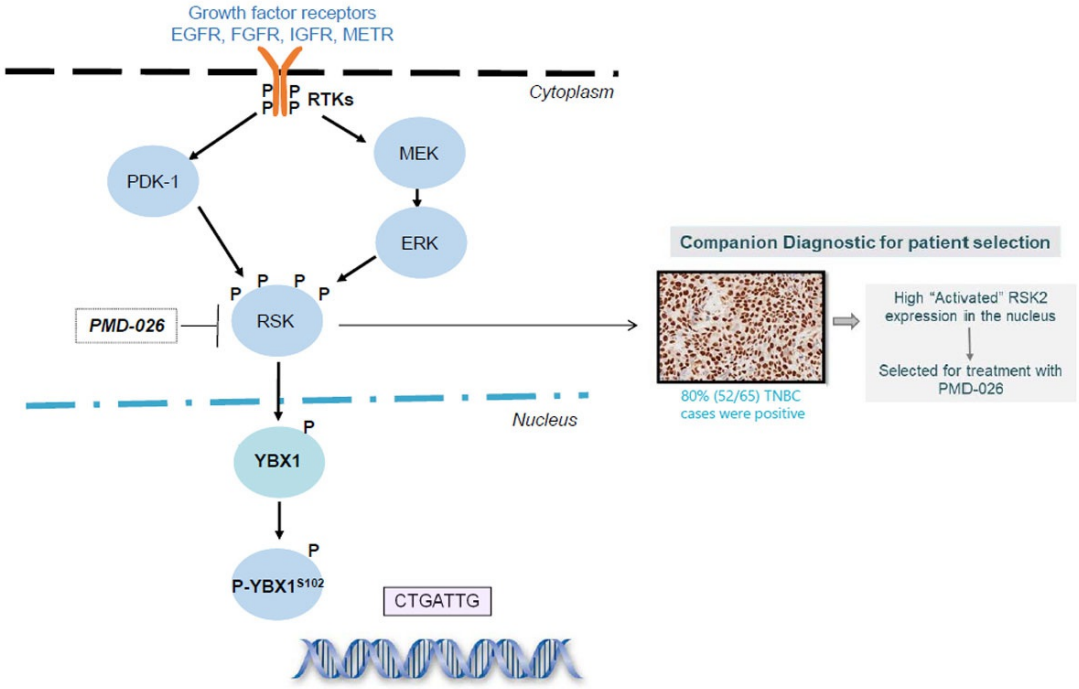
FIGURE: CONVERGENCE OF RSK

RSK2 sits at a major convergence point for two cancer signaling pathways: the MAPK-MEK pathway and the PDK pathway. In TNBC, signaling through either pathway activates RSK2, causing the kinase to translocate to the nucleus where it phosphorylates the transcription factor YBX1. This in turn stimulates tumor growth and cell

invasion.

Phoenix Molecular Designs and Roche (SIX:ROG; OTCQX:RHHBY) are developing a companion diagnostic to identify RSK2 in the nucleus as a signal of RSK2 activation. *Source: Phoenix Molecular Designs*

MAPK (ERK) - MAP kinase; PDK - pyruvate dehydrogenase kinase; RSK2 - Ribosomal protein S6 kinase 90kDa polypeptide 3; YBX1 (YB1) - Y box binding protein 1



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NEEDLE IN THE KINASE HAYSTACK

Phoenix's program began as an academic pursuit to identify human kinases that could serve as a positive risk factor or drug target for TNBC.

"What we were really interested in figuring out was, out of all the 519 human kinases, which were most important for TNBC?" said Dunn, who led the work as an associate professor in medicine at the University of British Columbia.

The group used an siRNA-based synthetic lethality screen to systematically silence each of the human kinases across multiple TNBC cell lines.

"When we inhibited RSK2, it did a great job of blocking the growth of TNBC", said Dunn, who noted that RSK2 inhibition stopped tumor growth independent of other mutations such as EGFR amplifications, BRCA1 mutations or p53 mutations.

"We needed a hot knife across butter, something that really cut across that heterogeneity," she said.

Phoenix has preclinical data demonstrating the efficacy of PMD-026 *in vitro* and *in vivo*. In an unpublished xenograft mouse model of RSK2-positive TNBC, PMD-026 led to a 73% regression in tumor volume vs. control ($p<0.001$).

According to Dunn, Phoenix is the first company to validate RSK2 for TNBC. The company is moving forward with development, despite the fact that at least three other companies have discontinued their RSK2 inhibitors for cancer.

"We needed a hot knife across butter, something that really cut across that heterogeneity."

Sandra Dunn, Phoenix Molecular Designs

Novartis AG, Boehringer Ingelheim GmbH and Vanderbilt University have all developed preclinical cancer

programs, but Dunn said each faced either bioavailability or pharmacokinetic issues and were discontinued. Boehringer and Vanderbilt did not respond to requests to comment. Novartis was not able to respond in time for publication.

Dunn said Phoenix was able to design an RSK2 inhibitor that is orally bioavailable and demonstrates good tissue penetration, though she declined to disclose details.

Principia Biopharma Inc. had also developed a series of RSK2 inhibitors for cancer and fibrosis, but spokesperson Alex Sharif told BioCentury that the biotech didn't uncover "sufficient activity to warrant a full-fledged development program." He said the company still has preclinical potent and selective RSK2 inhibitors it is exploring for other undisclosed indications.

TNBC LANDSCAPE

Dunn sees opportunities in the fact that PARP inhibitors and PD-L1 inhibitors have shown activity in TNBC patients. PMD-026 could either be used in patients with tumors resistant to PARP inhibitors or in combination with immunotherapy.

PARP inhibitors Lynparza olparib and Talzenna talazoparib are approved for HER2-negative breast cancer patients with BRCA mutations; the product labels for both drugs include data from TNBC patients enrolled in the Phase III studies (see **"Triple's Shot"**).

Lynparza is marketed by AstraZeneca plc, and Merck & Co. Inc., and Talzenna is marketed by Pfizer Inc.

Last year, the Genentech Inc. unit of Roche reported data showing PD-L1 inhibitor Tecentriq atezolizumab met the co-primary endpoint of improving progression-free survival (PFS) in the Phase III IMpassion130 trial as first-line treatment for TNBC. Tecentriq is under Priority Review with FDA for the indication with a PDUFA date of March 12.

Dunn said Phoenix has unpublished data demonstrating RSK2 inhibition leads to 80% suppression of PD-L1 in TNBC tumors, although she acknowledged that the mechanism isn't well understood yet.

"We are doing these experiments now," she said. "We wondered if we gave the system a two-hit punch between blocking the PD-1 receptor and internally downregulating the PD-L1 ligand, would that two-hit punch be just what TNBC needs to take it out completely?"

DIAGNOSING RSK2

The development of a companion diagnostic for RSK2 activation should enable Phoenix's long-term goal of developing PMD-026 for tissue-agnostic RSK2-positive cancers.

Dunn said the biology of RSK2 makes the assay straightforward -- since RSK2 is translocated to the cell's nucleus following activation, the presence of nuclear RSK2 is a clear indicator of RSK2 activation.

According to Dunn, Phoenix and Roche had been collaborating for about a year prior to the announcment of the deal, and Roche has already completed validation and tested the stability of the RSK2 antibody.

"Would that two-hit punch be just what TNBC needs to take it out completely?"

Sandra Dunn, Phoenix Molecular Designs

The goal is to use the diagnostic in the Phase Ib cohort of the trial that will enroll 45 TNBC patients, measure the level of RSK2 activation, and correlate the data with response to PMD-026.

She said the advantage of this diagnostic approach is that it seamlessly fits into the current treatment paradigm for patients. Breast cancer patients already have a biopsy taken for immunostaining, commonly on a Roche Ventana system, to determine ER, PR or HER2 status.

"It would be great if we could just add on the RSK2 antibody and see if she's triple-negative and RSK2 positive," Dunn said.

Eventually, Phoenix hopes to follow the tissue-agnostic development path blazed by Loxo Oncology Inc., which is in the process of being acquired for $8 billion by Eli Lilly and Co.

"We'd like to take our first approach in TNBC because that's where the discovery was made. But then going further, we think it could be tissue agonistic," Dunn said.

She noted that at least 13 other cancer types have been shown to express activated RSK2, across both solid tumors and hematological malignancies.

The first glimpse could come from the first part of the Phase I/Ib trial, where Phoenix expects to enroll patients with a variety of tumors to establish any dose-limiting toxicity.

Phoenix hopes to raise $10 million in a series A round this half to fund the clinical trial and another $20 million in a B round by 2023 to fund Phase II testing of PMD-026.

COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Boehringer Ingelheim GmbH, Ingelheim, Germany
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Genentech Inc., South San Francisco, Calif.
Immunomedics Inc. (NASDAQ:IMMU), Morris Plains, N.J.
Loxo Oncology Inc. (NASDAQ:LOXO), Stamford, Conn.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Phoenix Molecular Designs, Vancouver, B.C.
Principia Biopharma Inc. (NASDAQ:PRNB), South San Francisco, Calif.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Vanderbilt University, Nashville, Tenn.
University of British Columbia, Vancouver, B.C.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

TARGETS

BRCA1 - Breast cancer 1 early onset
EGFR (ErbB1; HER1) - Epidermal growth factor receptor
EGP-1 - Epithelial glycoprotein-1
HER2 (EGFR2; ErbB2; neu) - Epidermal growth factor receptor 2
MAPK (ERK) - MAP kinase
p53 (TP53)
PARP - Poly(ADP-ribose) polymerase
PD-L1 (B7-H1; CD274) - Programmed cell death 1 ligand 1
PDK - Pyruvate dehydrogenase kinase
RSK2 (RPS6KA3) - Ribosomal protein S6 kinase 90kDa polypeptide 3
YBX1 (YB1) - Y box binding protein 1

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