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Disruption of NOTCH signaling by a small molecule inhibitor of the transcription factor RBPJ

Small molecule potently inhibited proliferation of hematologic cancer cell lines and promoted skeletal muscle differentiation from C2C12 myoblasts, featured in *Scientific Reports (Nature.com).*

San Diego, Calif., July 25, 2019 – Researchers at the Stanford Cardiovascular Institute and the Department of Medicine, Stanford University, Sanford-Burnham-Prebys Medical Discovery Institute, Icagen, Human BioMolecular Research Institute, University Medical Center Ulm, Germany, Regencor, Sanofi, France and ChemRegen, Inc., have reported on a small molecule that potently inhibited hematologic cancer and promoted skeletal muscle differentiation. Writing July 25, 2019 in the journal *Scientific Reports*, the team described how they found and tested a RBPJ Inhibitor-1 (**RIN1**), a small molecule, drug-like compound that can be used to decrease cancer.

“In the United States, hematologic cancer is a leading cause of cancer-related fatalities. Currently, 10% of new cancer diagnosis and 10% of cancer deaths are due to hematologic cancer“ said Jiongjia Cheng, Ph.D., a leading cancer researcher not involved with the study. “Using a non-toxic small molecule to decrease hematologic cancer is very attractive.”

Study leads to safe anti-cancer drug

NOTCH proteins are trans-membrane receptors that transduce signals from cell-bound families of ligands to mediate cell-cell interactions in processes as diverse as fetal development, heart disease and cancer. NOTCH plays a pivotal role during normal development and in congenital disorders and cancer. Inhibition of RBPJ was deemed a desirable point to modulate NOTCH signaling, potentially affording a useful probe and potential clinical candidate. RBPJ is the main transcriptional effector of NOTCH signaling. To identify selective inhibitors of RBPJ, a primary screen was developed to detect inhibitors of a functional interaction between RBPJ and the scaffold protein

SHARP that was followed by secondary assays to establish efficacy against NOTCH.

In early studies, a primary assay was screened against 1,780,000 compounds from Sanofi, Tucson. Primary positive “hits” were retested through a dose-range to confirm potency. Ultimately, 130 compounds showed dose-responsive inhibition comprising 14 distinct chemical families plus 17 singletons. Counter screens were run to show selectivity. The small molecule inhibitor **RIN1** disrupted the interaction between NOTCH and RBPJ. **RIN1** also blocked the functional interaction of RBPJ with SHARP, a scaffold protein that forms a transcriptional repressor complex with RBPJ in the absence of NOTCH signaling.

When added to hematologic cancer cells, **RIN1** potently suppressed the proliferation of three hematologic tumor cell lines (i.e., Jurkat and KOPT-K1 T-ALL, and REC-1 MCL). It is notable that the potencies and efficacies of **RIN1** relative to other agents was robust across cancer cell lines. **RIN1** effectively blocked proliferation of all cancer cells tested but it appeared RBPJ played a relatively more important role in controlling Jurkat cell proliferation than did NOTCH cleavage.

How RIN1 works

Developing new medications for cancer is important. Despite its prevalence, therapeutic options for hematologic cancer are limited. Drug resistance and drug-induced side effects also limit treatment.

For hematologic cancer, like other cancers, the challenging part is figuring out the cellular pathways that direct cancer growth and how these pathways can be interrupted and halted. A non-toxic chemical that inhibits key cancer-promoting pathways is a very promising strategy.

RIN1 is the first small molecule inhibitor of RBPJ signaling. RBPJ can either activate genes by forming a complex with the NOTCH ICD when NOTCH is active, or silence an overlapping but non-identical set of genes by recruiting co-repressors in the absence of NOTCH signaling. **RIN1** chokes hematologic cancer cell proliferation, ultimately altering cellular behavior and in this case decreasing cancer cell growth.

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Media contacts: To arrange on-site, phone, or Skype interviews with the researchers involved in this study, please contact John Cashman at (858) 458-9305 / JCashman@hbri.org.

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