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New leads in the struggle against a formidable leukemia

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A coordinated push to decrypt a complex form of leukemia is delivering a trove of new drug candidates and treatment ideas, a dozen of which will be presented at the American Society of Hematology Annual Meeting in Orlando, Florida (Dec. 5-8).

The research initiative generating these leads, Beat AML, is led by the Knight Cancer Institute at Oregon Health & Science University and The Leukemia & Lymphoma Society (LLS). Beat AML brings together academic health centers and biopharmaceutical companies to accelerate discoveries that will improve outcomes for patients with acute myeloid leukemia (AML), a blood cancer lacking effective treatments. Less than 25 percent of newly diagnosed patients survive beyond five years.

A total of nine pharmaceutical and biotech companies have joined the collaboration, providing 27 potential treatments for analysis on the research platform. Recent additions are: argenx; AstraZeneca; Genentech; Janssen Research & Development, LLC; Seattle Genetics; and Takeda Pharmaceuticals International Co. Among the participants that joined early on are Aptose Biosciences and Constellation Pharmaceuticals.

"Acute myeloid leukemia is now the most frequently diagnosed leukemia in adults, while the current standard of care is based on 40-year-old chemotherapy agents with a very poor cure rate," said Louis J. DeGennaro, Ph.D., LLS's president and CEO. "LLS, together with its partners in the Beat AML collaboration, has gone on the offense against

this deadly disease to lead the way to new treatment options desperately needed by patients."

Beat AML is amassing data on potential drivers of the disease by sequencing cancer cell DNA from hundreds of patients who volunteer samples. In the two years since the Beat AML initiative was launched, more than 450 samples have been collected by investigators at the Knight Cancer Institute as well as the other academic health centers that are part of the collaboration. Those institutions are: Huntsman Cancer Institute at the University of Utah, Stanford University, Sylvester Comprehensive Cancer Center at the University of Miami, UT Southwestern Medical Center and the University of Colorado Cancer Center.

To speed progress, work proceeds on two parallel fronts. A bioinformatics team pores over data sets to identify potentially significant mutations and other genomic alterations. Other researchers simultaneously test the response of leukemia cells to different drugs and combinations of drugs. This dual process better equips scientists to confirm that they have correctly identified a genetic driver of the disease, and more efficiently narrows the search for new drug leads.

Among the Beat AML findings to be presented at the ASH meeting are:

Using a unique method to test drugs used together, Knight Cancer Institute researcher Stephen Kurtz, Ph.D., and his colleagues, identified drug combinations that are active against leukemia cells in a patient-specific manner. The next step is to link these findings with the gene alterations that make cancer cells sensitive to the drug combinations, and use those results to design clinical trials. (Abstract 865)

Disrupting the cancer cell microenvironment shows promise as a new path to target AML. A particular type of immune cell supports the growth of AML cells, and two studies to be presented by Knight Cancer Institute researchers show that depleting these immune cells with a targeted agent eliminates the supportive environment, causing leukemia cells to die. (Abstracts 3824 and 4439)

Targeting a key inflammatory pathway offers a new therapeutic approach that could benefit AML patients. A Knight Cancer Institute team led by Anupriya Agarwal, Ph.D., found that increased secretion of pro-inflammatory cytokines in the microenvironment of leukemia cells drives disease progression in AML, and showed that blocking this signaling inhibits cancer cell growth. (Abstracts 570, 866 and 2603)

As the number of collaborators increases, so too will the variety of approaches treatment exploration can take moving forward including testing how pairs of drugs might work better in stopping some versions of the disease. The compounds already being tested deploy different means of halting disease progression, including using the immune system and targeting proteins.

By correlating the mutational profile of patient samples with the response of those samples to drugs, Beat AML researchers hope to discover biomarkers that can help determine the best treatment course for a patient.

"With the wide range of collaborators now involved in Beat AML, we are able to better explore innovative ideas for targeting the many drivers of this disease," said Jeffrey Tyner, Ph.D., a Knight Cancer Institute researcher who leads the industry collaborations that are part of Beat AML. "Integration of our strong drug-screening pipeline with the large amounts of genomic data being generated is allowing us to make great strides in understanding the connections between tumor genotype and

drug response."

Of the 27 potential treatments under analysis, 20 are already in clinical trials for other diseases; if these drug compounds show promise in treating AML, they have the potential for a faster approval process. Overall, more than 10 cell signaling pathways and mutations have been identified by Beat AML researchers as potentially playing a role in disease progression. These insights into the biology of AML will help identify biomarkers that can predict individual patients' responses to treatments, uncover the mechanisms by which experimental cancer drugs work, and potentially suggest new therapeutic targets for future drug development.

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