Researchers have identified a small molecule that stimulates the production of hematopoietic stem cells (HSC) in umbilical cord blood, improving the likelihood of successful transplants for many adults with blood-related cancers.

In the recently published study, researchers identified a prototype molecule, dubbed UM171, that when introduced into an automated fed-batch culture system promotes robust expansion of human cord blood stem cells (Science 2014;345:1509–12). Cord blood is the preferred source of stem cells when a transplant candidate cannot be matched with a family donor, because its naïve T cells are less likely to induce graft-versus-host disease. However, such transplants have been limited mostly to children because a single umbilical cord typically contains too few stem cells to treat an adult.

Guy Sauvageau, PhD, a hematologist at Maisonneuve-Rosemont Hospital’s Hematopoietic Stem Cell Transplantation Program, which is affiliated with the University of Montreal in Canada, and his team screened a library of more than 5,000 low-molecular weight compounds for their ability to expand peripheral blood cells enriched with long-term HSCs (LT-HSC) and zeroed in on UM729. They then examined more than 300 newly synthesized analogues of UM729 and found that one—UM171—was 10 to 20 times more potent in stimulating the expansion of HSC-enriched cells.

The researchers hypothesize that UM171 works by enhancing the action of LT-HSCs, which show a delayed engraftment pattern and the capability to repopulate and produce mature blood cells indefinitely, thus lowering the risk of graft failure. UM171 promotes LT-HSC self-renewal independently of aryl hydrocarbon receptor suppression, which has also been shown to promote cord blood cell expansion but appears to produce mainly non-renewing, short-lived progenitor cells.

“If the new process works, an expanded cord blood transplant could become the best option when a patient doesn’t have a family-matched donor,” says Jean Roy, MD, a hematologist working with Sauvageau who will lead the upcoming clinical trials for UM171. Such a development would particularly affect nonwhite transplant candidates, who often have no therapeutic options due to a lack of compatible donors.

Roy aims to begin a phase I clinical trial this month that will include patients with hematologic malignancies who require an urgent transplant or cannot be matched with an unrelated registry donor. Researchers plan to enroll 15 patients at Canadian transplant facilities in Montreal, Quebec City, and Vancouver.

The trial is expected to conclude by December 2015, says Roy. If the results are positive, researchers will launch a larger, 50-patient phase II study.

“At the present time, only about 5% of all adult allogeneic transplants are using cord blood because of low stem-cell count,” says Roy. “This study represents a scientific breakthrough that could lead to a clinical breakthrough with wide applicability to patients.”

Researchers have found a way to stimulate the production of hematopoietic stem cells in cord blood (left). When introduced to the prototype molecule UM171, the cells proliferate and remain in their undifferentiated state (right).

Drug Combos Validated in BRAF-Mutant Melanoma

Combination therapy is likely to become the standard of care for patients with advanced or metastatic melanoma with BRAF mutations, according to three phase III studies presented or published during the European Society for Medical Oncology (ESMO) 2014 Congress in Madrid, Spain, in September.

The studies show that combining BRAF and MEK inhibitors improves progression-free survival (PFS) and overall survival (OS), compared with BRAF inhibition alone, in patients with metastatic melanoma with BRAF V600E or V600K mutations. Simultaneous inhibition of BRAF and MEK also can mitigate the emergence of resistance and reduce toxicities associated with BRAF inhibitors.

“Whereas the earlier studies demonstrated that response rates were higher and more durable with the combination, now we have conclusive evidence that patients who take the combination therapy live longer,” says Antoni Ribas, MD, PhD, a hematologist/oncologist and professor of medicine at Jonsson Comprehensive Cancer Center at the University of California, Los Angeles. “At the same time, when you put these two classes of drugs together, it decreases the main toxicity of BRAF inhibitors alone, which is the development of secondary squamous cell carcinomas.”

Up to a quarter of patients treated with BRAF inhibitors develop new skin cancers due to “paradoxical” activation of the MAPK pathway with upstream activation of signaling by preexisting RAS mutations. MEK inhibitors can block RAS signaling along the MAPK pathway.

In the COMBI-v study, presented at ESMO, 704 patients were randomly assigned to receive first-line therapy with the BRAF inhibitor dabrafenib [Tafinlar; GlaxoSmithKline (GSK)] plus the MEK inhibitor trametinib (Mekinist; GSK), or the BRAF inhibitor vemurafenib (Zelboraf; Genentech) alone. The study was stopped early after patients receiving the combination experienced significantly longer OS than patients given the single agent (median OS not reached vs. 17.2 months), as well as higher PFS (11.4 vs. 7.3 months) and duration of response (13.8 vs. 7.5 months).

The COMBI-d study, published in The New England Journal of Medicine (NEJM), demonstrated that dabrafenib plus trametinib given as first-line therapy resulted in a 25% relative reduction in the risk of disease progression compared with dabrafenib alone, as well as a higher response rate (67% vs. 51%; N Engl J Med 2014 September 29 [Epub ahead of print]).
In the third study, cobRIM, also presented at ESMO and published in NEJM, 495 previously untreated patients were randomly assigned to receive vemurafenib either with the MEK inhibitor cobimetinib (GDC-0973; Roche) or with placebo. Combination therapy resulted in improved PFS compared with the control group (9.9 months vs. 6.2 months) and a higher 9-month OS rate (81.1% vs. 72.5%; N Engl J Med 2014 September 29 [Epub ahead of print]).

Earlier this year, the FDA granted accelerated approval of GSK’s dabrafenib–trametinib combination for melanoma patients with the BRAF V600 mutation, based on results from phase II studies. COMBI-v and COMBI-d validated that approval, says Ribas, and, along with cobRIM, paved the way for developing other BRAF–MEK combinations.

“BRAF–MEK inhibition is a very elegant combination that slows tumor activity while decreasing the main side effect of the single agent,” says Ribas. “With these new data, there is no reason to consider starting a patient with BRAF mutation–positive melanoma on single-agent therapy.”

PROMPT to Detail Breast Cancer Risk

When women undergo genetic testing to see if they have an increased risk for breast cancer, many learn that they have changes in genes other than BRCA1 and BRCA2. Although mutations in p53, PALB2, RAD51C, CDH1, and other genes have been associated with an increased risk of breast cancer, doctors don’t know much about them—they don’t know to what degree the mutations heighten risk, how those mutations might interact with others, or at what age the risk starts to climb.

Four major cancer institutions—Dana-Farber Cancer Institute (Boston, MA), Mayo Clinic (Rochester, MN), Memorial Sloan Kettering Cancer Center (MSKCC; New York, NY), and Penn Medicine (Philadelphia, PA)—are now teaming up to address these types of questions. By combining their expertise and partnering with commercial laboratories—Ambry Genetics, Gene Dx, Myriad Genetics, Pathway Genomics, and Quest Diagnostics have all agreed to participate—they hope to enroll enough patients in an online registry to better understand the effects of these genetic mutations. Although they are starting with breast cancer, the registry, called Prospective Registry Of Multi-Plex Testing, or PROMPT, will also gather information on other cancer-associated genes.

“We have had 20 years to get really great evidence for what to recommend for individuals with BRCA1 and BRCA2 mutations, and we want to quickly obtain such evidence for these other high, moderate, and unknown penetrant genes,” says PROMPT co-founder Susan Domchek, MD, director of the Basser Research Center for BRCA in the University of Pennsylvania’s Abramson Cancer Center in Philadelphia.

When doctors order multigene panel tests, several of the labs that conduct those tests will send information about the registry to patients and providers and invite them to participate, says Domchek. If patients choose to join, they can contribute their gene test results and family history to the registry. Over time, they will be informed of any relevant findings the consortium might make.

Findings will be made publicly available, and participants may volunteer for other studies as well. “We want to build a resource that many different investigators will use to try to [answer] questions as quickly as possible,” says Mark Robson, MD, PROMPT co-founder and clinic director of the Clinical Genetics Service at MSKCC.

Each of these gene mutations is likely to be uncommon, which is why the group needs to enroll a large number of patients. However, that can take a long time. In a recent paper, for instance, researchers reported that it took them several years to enroll the 150 families needed to analyze, with sufficient statistical power, links between PALB2 and breast cancer (N Engl J Med 2014; 371:497–506).

“To try to get the answers in a meaningful timeframe, we have to throw a much, much wider net and make [studies] available to a much, much broader group of people,” Robson says.

For more news on cancer research, visit Cancer Discovery online at http://CDnews.aacrjournals.org.