mandatory funding over 5 years for the NIH. Representatives proposed funding the bill by selling some of the nation's petroleum reserves. The Senate is now considering its own version of this legislation.

Against that backdrop, "it's not surprising that mandatory funding appeared in the budget proposal," says Mary Woolley, president of Research!America. "It's still a high-risk strategy, albeit not the first time a tactic of this kind has played out between a president and Congress when they're of different parties, over something as inherently popular as medical research." She points out that during the Clinton administration, "budgets with very modest increases for the NIH were put forward. President Clinton knew full well that Congress would add considerably to what he proposed—which they did."

Representative Tom Cole (R–OK) and Senator Roy Blunt (R–MO), who lead the appropriations subcommittees overseeing the NIH and other health and education programs, have already announced their intention to boost the NIH's budget, even "at the expense of other agencies within [our] jurisdiction."

Plus, with public enthusiasm for medical research running high, those seeking reelection in November "will pay exquisite attention to what their constituents want," Woolley adds.

"We're of the view that where there's a will, there's a way," she continues. "Congress will find a way to put money behind its priorities. I do think they'll do much more for the NIH, specifically, than the president did in his budget proposal." *–Alissa Poh* ■

Metastatic Sites Predict Prostate Cancer Survival

According to a new meta-analysis of clinical trial data from patients with metastatic castration-resistant prostate cancer (mCRPC), overall survival (OS) is strongly influenced by where this disease spreads (J Clin Oncol 2016 March 7 [Epub ahead of print]). Previous reports had indicated as much but involved only small numbers of patients, warranting a more comprehensive investigation.

An international team of researchers—led by Susan Halabi, PhD, a professor of biostatistics at Duke University School of Medicine in Durham, NC—gathered information from nine phase III studies, encompassing 8,736 men with mCRPC. The patients in these trials had all received docetaxel as standard therapy. The researchers classified them into one of four groups corresponding to the site of metastases: bone, liver, lungs, and lymph nodes. Most (72.8%) had bone metastases; another 8.6% and 9.1% had metastatic lesions in the liver and lungs, respectively, while those with lymph node metastases made up the smallest group (6.4%).

The researchers confirmed earlier studies identifying visceral disease—liver and lung metastases—as a negative prognostic factor of survival. Patients with liver metastases fared worst, with a median OS of just 13.5 months; those with lung metastases had a slightly longer median OS of 19.4 months. In contrast, patients with disease involving bone or lymph nodes had median survival times of 21.3 and 31.6 months, respectively.

Anthony D'Amico, MD, PhD, chief of genitourinary radiation oncology at Dana-Farber/Harvard Cancer Center in Boston, MA, suggests that particular variants of mCRPC could explain the poorer survival of patients with visceral disease. "Classic prostate adenocarcinomas have a penchant for bone-only metastases," he explains. "Certain other prostate tumors, though, have a mixed histology that includes a neuroendocrine or small-cell component. These readily spread to internal organs like the liver and lungs and are associated with a worse prognosis." Recent research has shown that even classic prostate adenocarcinomas can acquire neuroendocrine expression over time, he adds.

Distinguishing neuroendocrine and small-cell prostate cancer from adenocarcinoma is important, D'Amico says, because approved hormone therapies like abiraterone acetate (Zytiga; Janssen) and enzalutamide (Xtandi; Astellas) are not effective against these variants. Rather, "you want to consider chemotherapy that's used in such histologies—platinum drugs, for instance, or etoposide."

The study researchers think the significantly different outcomes seen with these four subgroups highlight the importance of reporting end points, including OS, by metastatic site—although this has yet to be widely implemented in phase III studies of mCRPC. D'Amico agrees, adding that "future trials should be directed based on the biopsy of a patient's metastatic lesion, so we know exactly what we're dealing with and can figure out the best treatment." *–Alissa Poh* ■

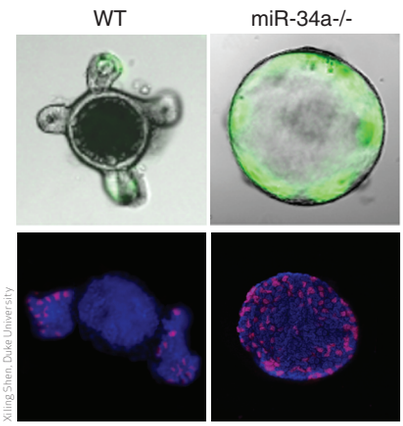
Inflammation May Activate Antitumor Mechanism

Inflammation promotes colorectal cancer, but it may also trip a molecular switch that hinders tumor growth by stimulating stem cells to divide asymmetrically, a recent study reported (Cell Stem Cell 2016;18:189–202).

Many types of normal stem cells divide asymmetrically, typically producing another stem cell and a cell that goes on to differentiate; normal intestinal and colon stem cells divide symmetrically. Cancer stem cells can divide symmetrically or asymmetrically, and "the consensus is that asymmetric division limits or suppresses cancer," says Xiling Shen, PhD, of Duke University in Durham, NC, because it caps the number of cancer stem cells.

Shen and his colleagues investigated what controls intestinal stem cells' mode of division, focusing on the developmental genes Numb and Notch and the tumor suppressor miR-34a. Notch stimulates cell division and promotes colon cancer, whereas Numb and miR-34a cause cells to differentiate and develop normally.

To the team's surprise, they found that in addition to directly inhibiting Notch, miR-34a inhibits Numb—which is also an inhibitor of Notch. This counterintuitive result made sense, however, because the researchers determined that Numb, Notch, and miR-34a interact to form an incoherent feed-forward loop, a control circuit that behaves like a switch, directing cells to one of two fates. Flipping the switch in one direction produces high levels of Notch and causes symmetric



Xiling Shen, Duke University

Scientists grew two sets of cellular "miniguts" on culture dishes and stimulated them with inflammatory factors; those on the left are normal. However, the deletion of miR-34a causes stem cells (top right in green and bottom right in red) to divide out of control, causing the minigut to bloat into a cancerous sphere.

division and retention of stemness. Flipping the switch in the opposite direction results in low Notch levels, leading to asymmetric division and spurring differentiation.

When the scientists examined intestinal samples from genetically modified mice that lack miR-34a, they found no differences in the number of intestinal stem cells, suggesting that the switch is not necessary under normal conditions.

However, they found that the switch does play a role during inflammation. Adding the inflammation-promoting molecule TNFα to cultured intestinal stem cells increased the rate of asymmetric division from 4.6% to 19%. To determine whether that increase also occurs *in vivo*, the team stimulated intestinal inflammation in mice that do or do not express miR-34a. The frequency of asymmetric divisions among intestinal stem cells rose from 2% to 13% in normal mice, but this increase didn't occur in miR-34a–deficient mice.

Given that inflammation may be a cause of colorectal cancer, the authors suggest that the shift to asymmetric division may be a safeguard against too much stem-cell self-renewal after inflammation-induced damage—and possibly under oncogenic stress—and thus may serve as a tumor-suppressive mechanism. Indeed, when Shen and colleagues compared healthy and cancerous intestinal tissue from patients with colorectal tumors, they found that asymmetric division was more common in the tumor samples.

Although the switch can curb division, it may not be successful in preventing tumors. If they form, they eventually eliminate miR-34a, restoring symmetric division and accelerating cellular proliferation, says Shen. "That unleashes the badness."

The symmetric division of normal intestinal stem cells has been "a paradox," says Sharon Pine, PhD, of Rutgers University in New Brunswick, NJ, who wasn't connected to the study. "This work adds a new element to the equation—inflammation" and suggests that asymmetric division "is a mechanism to curb expansion of the stem cells during injury and repair."

The work also offers an explanation for how miR-34a controls tumor growth, adds Tannishtha Reya, PhD, of the University of California, San Diego. "This study suggests that miR-34a could act as a tumor suppressor in part by regulating asymmetric division." *–Mitch Leslie* ■

Analysis of ALL Subtypes May Improve Treatment

A new study identifies the underpinnings of a genomic alteration that occurs in children and young adults with a particularly aggressive form of acute lymphoblastic leukemia (ALL), potentially leading to targeted treatment options for those whose tumors progress on standard therapy. The findings will aid in designing clinical trials in which patients with Philadelphia chromosome–like (Ph-like) ALL will receive a combination of chemotherapy and approved drugs.

In previous studies, researchers from St. Jude Children's Research Hospital in Memphis, TN, identified chromosomal rearrangements of the erythropoietin receptor (*EPOR*) gene in Ph-like ALL, but they did not understand how the rearrangements occurred or how they activated the JAK–STAT signaling pathway in ALL.

In this study, the researchers analyzed 3,115 cases of childhood, adolescent, and young adult B-cell precursor ALL, 212 of which had a gene expression profile of Ph-like ALL (Cancer Cell 2016;29:186–200). Of the latter, 19 had *EPOR* rearrangements, including those identified in previous research, representing about 9% of their Ph-like ALL cases.

Each *EPOR* rearrangement results in overexpression of a truncated form of the receptor, which is hypersensitive to erythropoietin, says the study's senior investigator, Charles Mullighan, MD, co-leader of the Hematological Malignancies Program at St. Jude. Erythropoietin then binds to the overexpressed receptors, leading to heightened activation of the JAK–STAT pathway.

The researchers demonstrated that combining the JAK–STAT inhibitor ruxolitinib (Jakafi; Incyte)—currently approved to treat myelofibrosis—with conventional chemotherapy slowed tumor growth in engineered mouse cells and human leukemic cells.

"We found that JAK–STAT inhibitors were active and that they synergized with the chemotherapy drugs that we routinely use now," including dexamethasone, vincristine, and daunorubicin, Mullighan says. "We saw remarkable and dramatic improvements in tumor cells that were often refractory or partially resistant to active chemotherapy."

St. Jude is now working with the Children's Oncology Group (COG) to design trials using whole-genome sequencing to detect targetable alterations and guide patients with leukemia into appropriate clinical trials. As part of their research, Mullighan's team developed a diagnostic test using gene expression assays that could be used to screen for *EPOR* rearrangements.

The findings will help inform research on many Ph-like ALL alterations, which tend to increase with age and are present in about 27% of all patients with ALL between ages 21 and 39, says Lee Greenberger, PhD, chief scientific officer of the Leukemia and Lymphoma Society, based in White Plains, NY. The *EPOR* rearrangements, which are found in 3% to 4% of Ph-like ALL tumors, are among many chromosomal rearrangements that are targetable by inhibiting the JAK–STAT or other signaling pathways.

"There could be other kinase inhibitors that might work for these patients," he says. "This paper shows that diagnostic tools for specific rearrangements can be developed and