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