said Kathy Hudson, PhD, NIH deputy director for science, outreach, and policy, in testimony before the Committee on Energy and Commerce. Although the bill’s provisions to increase funding for research and drug development have met with widespread support, proposed changes to the drug approval process have sparked some controversy. A recent commentary in *The New England Journal of Medicine*, for example, takes issue with the bill’s directive that the FDA develop criteria for considering nontraditional data sources—including observational studies and patient registries—instead of large, randomized clinical trials when reviewing new uses for existing drugs (N Engl J Med 2015;372:2473–5).

“Although such data can provide important information about drug utilization and safety once a medication is in use, there is considerable evidence that these approaches are not as rigorous or valid as randomized trials in assessing efficacy,” wrote Jerry Avorn, MD, and Aaron Kesselheim, MD, JD, MPH, both of Harvard Medical School and Brigham and Women’s Hospital in Boston, MA.

The bill would also encourage the FDA to rely more on biomarkers rather than clinical endpoints in assessing drug efficacy, the researchers said, a strategy that can be faster and cheaper but not always accurate in predicting patient outcomes.

FDA officials have expressed concern over insufficient funding in the bill, which may force the agency to generate more revenue through user fees or shift funding away from other priorities.

“A total of $550 million was added to accomplish certain activities called for in the bill,” said Stephen Ostroff, MD, acting commissioner of the FDA, at a meeting of the Alliance for a Stronger FDA. “But it is not enough. The biggest concern I have is ending up with yet another unfunded, or partially funded, mandate.”

**Revving Up the Immune Therapy Business**

As checkpoint inhibitors and other cancer immune therapies continue to advance in the clinic, giant pharmaceutical companies and nascent biotechs are positioning themselves to make the most of these agents.

Merck and Bristol-Myers Squibb both have FDA-approved checkpoint inhibitors on the market to treat melanoma—pembrolizumab (Keytruda) and nivolumab (Opdivo), respectively—and are pushing to expand their approved uses. For example, nivolumab was approved in March to treat advanced squamous non–small cell lung cancer. Novartis has gained ground on competitors by buying GlaxoSmithKline’s cancer portfolio, investing in Aduro Biotech (Berkeley, CA), and hiring a leader in the field, Glenn Dranoff, MD, PhD, this past spring from Dana-Farber Cancer Institute in Boston, MA, to head their efforts.

These companies are also developing first-line therapies, as well as reexamining their portfolios to find other drugs—some already FDA-approved, others not—that might prove effective in combination with checkpoint inhibitors. Research presented at major conferences this year supported the idea that patients will see greater benefits if checkpoint inhibitors are given together or in combination with targeted therapies, chemotherapy, or cancer vaccines. Companies are testing many combinations to determine which are most effective against which types of cancer.

“The trend toward consolidation in cancer—where a single pharma company can offer a suite of agents covering a range of cancers and combinations—is definitely real,” says Bruce Booth, a partner in Atlas Venture, a Cambridge, MA–based venture capital firm specializing in life science research and technology.

Dranoff agrees, saying it makes sense to have a wide range of therapies in-house that can be tested in combination. He notes that Novartis now has programs in checkpoint inhibitors, cancer vaccines, and CAR T cells, in addition to treatments such as imatinib (Gleevec) that are directed at specific genetic defects.

“I think there’s enormous potential for coupling,” Dranoff says. “That’s going to be a theme of the work we’ll be doing.”

Large companies are also buying and partnering with start-ups to augment their pipelines, says Booth, referring to a flurry of recent sales, including AbbVie’s $21 billion purchase of Pharmacyclics (Sunnyvale, CA) to acquire the hematologic oncology drug ibrutinib (Imbruvica).

In June, Celgene and Juno Therapeutics of Seattle, WA, announced a 10-year collaboration to develop CAR T-cell therapies, a deal that will net Juno about $1 billion. In addition, Novartis has invested $280 million in Aduro Biotech, an immune therapy company developing small molecules to activate the STING pathway, which may detect tumor cells and trigger an aggressive antitumor response.

Meanwhile, young biotechs, such as Jounce Therapeutics of Cambridge, MA, are advancing the science on other immune modulators. However, these biotechs have to be more selective, says Jounce CEO Richard Murray, PhD. They cannot cast a wide net, testing many compounds, like large pharmaceutical companies can.

“Biotech probably has to really start pushing the boundaries of where some of these new pieces of biology and therapeutic paradigms might emerge,” says Murray, whose company is pursuing T cell–directed therapy, as well as therapies aimed at macrophages and other cell types that may initiate or improve the immune system’s antitumor response.

“A balancing approach between the more established space and the new frontier ... makes sense,” he says.

**Gene “Switch” Stops Colon Cancer in Mice**

Reactivating a tumor suppressor gene that is mutated in the majority of human colorectal cancers led to rapid tumor regression and restoration of normal cell function in mice, according to findings from a recent study that may help spur development of targeted treatments (Cell 2015;161:1539–52).

Researchers used RNAi to generate transgenic mice in which they could alternately silence and restore expression of the tumor suppressor gene adenomatous polyposis coli (APC) by administering or withdrawing doxycycline. As expected, they found that APC suppression produced tumors in the small intestine and colon triggered by deregulation of the Wnt signaling pathway, which controls cell proliferation and survival. Within 2 weeks of APC restoration, the tumors completely regressed, and there were no signs of relapse over a 6-month follow-up period, even in tumors containing p53 or KRAS mutations.

“We’ve known that the APC gene is important to drive the initial events of...
colorectal cancer, but not whether it is required to sustain tumor growth,” says the study’s senior author Scott Lowe, PhD, chair of the Cancer Biology and Genetics Program at Memorial Sloan Kettering Cancer Center in New York. “Instead of deleting the gene, which is the standard method, we used a genetic trick to silence it and turn it back on, which allowed us to see not only what initiates a cancer but also what maintains it once it’s already formed.”

The ability to alternately silence and reactivate APC expression solves a long-standing problem of how to suppress gene expression without completely blocking Wnt signaling and damaging normal intestinal cells, says Lowe. He noted that normal cell differentiation began to occur almost immediately following APC restoration, suggesting that only partial inhibition of Wnt signaling is required to induce tumor regression, thus sparing surrounding normal tissue.

Lowe’s team was surprised to observe that suppressing APC expression led to rapid regression in tumors with KRAS and p53 mutations, which are found in about half of all colorectal tumors. While it was known that these mutations promote tumor growth in APC-mutated colorectal cancer, it was not known whether they would continue to drive disease progression when APC is active.

“We thought that KRAS and p53 mutations would at least blunt the ability of APC to regress the tumor,” says Lowe. “Instead it appears that by restoring this one gene in tumors with multiple genetic alterations, the tumor cells go through a normal process of differentiation and some even seem capable of returning to normal stem cells.”

The findings may help inform efforts to develop drugs that target the Wnt pathway, says Lowe. Recently, small-molecule tankyrase inhibitors have shown promise in cell culture and animal studies for modulating Wnt signaling and potentially suppressing colorectal cancers driven by APC mutations.

“This study might be the best validation to date of the Wnt pathway as a mechanism to activate once it’s already formed,” says Lowe. “Noted San Diego developer and philanthropist Conrad Prebys will donate $100 million to the Sanford Burnham Prebys Medical Research Institute in nearby La Jolla, CA. In recognition of his contribution, the Institute has changed its name to the Sanford Burnham Prebys Medical Discovery Institute.

Hawaii’s governor signed a bill raising the legal smoking age to 21 statewide, making Hawaii the first state to do so. The law will also ban the sale, purchase, and use of electronic cigarettes by anyone under 21. The law will take effect on January 1, 2016.

A recent study found that older patients who received stem cells from younger, unrelated donors with higher numbers of CD38 cells had significantly reduced risk of disease relapse and improved survival compared with those who received stem cells from donors with low numbers of CD38 cells, including older matched siblings (J Clin Oncol 2015 June 8 [Epub ahead of print]).

Ventana Medical Systems announced that the FDA approved its ALK assay as a companion diagnostic to aid in the identification of patients with non–small cell lung cancer likely to benefit from crizotinib (Xalkori; Pfizer).

In a phase III trial involving 326 patients with relapsed acute lymphoblastic leukemia, the investigational antibody-drug conjugate inotuzumab-ozogamicin led to complete responses in 80% of patients compared with 33% of patients treated with standard care, usually chemotherapy. The findings were reported at the 20th Congress of the European Hematology Association in June.

The FDA is teaming up with the online network PatientsLikeMe to better understand the side effects of 1,000 different drugs, including anticancer drugs, as reported by the site’s 350,000 members. Because the data are generated by patients, the information provides insights into their experiences over time, including drug tolerance, adherence, and quality of life.

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

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