IN brief

Indiana's game-changing venture

An industry-driven biosciences research institute, in partnership with the state's research universities, opened on May 30 in Indiana, focused on commercializing home-grown healthcare innovations. The Indiana Biosciences Research Institute (IBRI) supported by the region's BioCrossroads—an initiative to strengthen life sciences businesses across the state—will collaborate with Indiana University, Purdue University and the University of Notre Dame. On its board of directors sit industry players, including Indianapolis-based Eli Lilly, Dow AgroSciences and Roche Diagnostics, Warsaw-based Biomet Biologics, and Cook of Bloomington. As for funding, the state of Indiana has appropriated \$25 million of the \$50 million biennium startup costs, and Lilly Endowment, an Indianapolis-based private philanthropic foundation, donated \$10 million in June. The remainder is being sought from corporate and philanthropic sources, to reach an estimated \$360 million. Industry is anticipated to provide up to a third of the annual operating budget through sponsored research, a level unprecedented anywhere else in the country, according to David Johnson, BioCrossroads' CEO. Additional operating cash flow will come from IBRI endowment proceeds and federally funded research. In Indiana, the diverse life sciences cluster and university assets are unlike those in any other state, creating opportunities for collaboration towards common scientific discoveries, according to Darren Carroll, vice president for Eli Lilly's corporate business development, and also on IBRI's board. IBRI will focus on cardiovascular disease, diabetes, obesity and nutrition. Details about how discoveries will be taken forward remain sketchy, although Carroll says each will be handled on a case-by-case basis, and intellectual property policies have yet to be finalized. *Emma Dorey*

IN their words

"This is more of Myriad's arrogant monopolist behavior that is so harmful to patients, science and health-care costs." Dan Ravicher, president of the New York-based Public Patent Foundation, comments

on the filing by Myriad of two suits for patent infringement against companies offering BRCA1/2 testing. (*liveMint*, 10 July 2013)

the ignition switch, if you will, rather than... putting the brakes on," says immunologist James Allison of the MD Anderson Cancer Center in Houston. So combining the two inhibiting antibodies is a rational approach, despite the theoretical risk of unleashing a massive autoimmune response. In preclinical models, "the combination of CTLA4 blockade and PD-1 appears to be synergistic in rescuing those exhausted cells," says Nils Lonberg, senior vice president of biologics discovery at Bristol-Myers Squibb. Nivolumab activates the exhausted cells, Lonberg explains, but Yervoy plays a key role, too. "If you have a T cell that is exhausted and is expressing both CTLA4 and PD-1, you have to overcome both," he says. Yervoy not only removes the brake on T-cell activation, but also kills regulatory T cells in the tumor microenvironment, further boosting the antitumor response (*J. Exp. Med.*, in press).

Whatever the mechanism, combining Yervoy and nivolumab in the clinic was spectacular. Given concurrently in the phase 1 trial, the combination produced an objective response rate of 53% at the optimal dose level (*New Engl. J. Med.*, **369**, 122–133, 2013). All nine responders at the second dose level had more than 80% tumor shrinkage, including three complete responses, a rare occurrence for either drug given alone. "The rate of [antitumor] activity was incredible," says trial co-lead investigator Mario Sznol, of Yale University Medical School in New Haven, Connecticut.

Sznol cautions that patient numbers are small and that a phase 3 trial, already underway, is needed to confirm that the combination is superior to nivolumab alone. Fortunately, "synergy in therapeutic benefit... was not accompanied by a synergistic increase in toxicity," says Allison. The drug combination produced more toxicity than either drug alone, but the side effects were manageable and generally reversible.

With combination therapy making clear inroads on drug resistance to both immunotherapy and targeted therapy in melanoma, an obvious step is to combine both approaches. Bristol-Myers Squibb and Genentech in South San Francisco, California, jointly sponsored such a trial, combining

Yervoy with the targeted therapy Zelboraf (vemurafenib), an FDA-approved, small-molecule BRAF inhibitor from Daiichi Sankyo in Tokyo. BRAF inhibitors like Tafenlar and Zelboraf quickly shrink BRAF-mutant tumors, but responses are rarely complete or durable. Yervoy is the opposite—relatively few responses, which tend to be late, deep and lasting. The combination promised the best of both worlds. At the cellular level, rapid tumor cell killing by Zelboraf should release dozens of tumor "neoantigens" generated by genomic instability, and thus provoke a strong, multipronged immune response. "The targeted therapies make really good vaccines," says Allison.

But the phase 1/2 clinical trial of concurrent Zelboraf and Yervoy ended earlier this year when six out of the first ten patients developed grade 3 elevations in aminotransferase levels, indicating possible liver damage. (The symptoms were reversible.) A phase 2 trial of the drugs, given sequentially, continues to accrue patients. Although waiting between treatments may help minimize toxicity, Allison stresses that Yervoy must be given very soon after targeted therapy, before the vaccine effect disappears. "Timing has got to be really, really quick," he says. "Dendritic cells don't hang around for very long, after they get loaded with antigen. So you've got to give the immunotherapy while they're still there."

Sznol is confident that the issues can be solved. "As a field we'll work out dose and schedule issues, and be able to get those combinations forward," he says.

Given the impossibility of testing more than a fraction of the possible combinations in clinical trials, continued progress rides on individualized approaches like Novartis's pending LGX818 trial, and similar efforts in the immunotherapy realm. For example, researchers are testing patient tumor expression of PD-L1, the ligand for PD-1, to predict response to anti-PD-1 antibodies, but results so far have been inconclusive. At this stage, "there are more questions than answers," said Walter Urba, of Providence Portland Medical Center in Portland, Oregon, at the ASCO meeting. As the current clinical trials unfold, that may soon change.

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