IN brief

Benlysta makes history

The first new drug for lupus in almost 50 years has been approved by the US Food and Drug Administration (FDA). Human Genome Sciences (HGS) obtained the agency's go-ahead for its first-in-class drug Benlysta (belimumab) on March 9. The Rockville, Maryland, biotech and its partner, London-based GlaxoSmithKline (GSK), will sell Benlysta, a human monoclonal antibody, at an annual treatment cost of $35,000 to a target market of 200,000 US patients. The agency's approval, the first for lupus since 1956, was based principally on two clinical studies involving 1,684 lupus patients (*Nat. Biotechnol.* **27**, 779, 2009). Notably, African American individuals and people with African heritage did not appear to respond to treatment with Benlysta, raising concerns that labeling may be restricted. But FDA decided "the studies lacked sufficient numbers to establish a definite conclusion," and HGS will conduct an additional study in people with those backgrounds. Also, although the regulator recommended against treating patients with severe active lupus nephritis or central nervous system lupus—groups not included in the pivotal studies—there was no black box warning excluding them from treatment. Joseph Schwartz of Leerink Swann in Boston called the broad label for Benlysta the "best case scenario" for the company. HGS and GSK expect an approval decision on Benlysta in Europe in the second half of 2011. Schwartz estimates US Benlysta sales will exceed a billion dollars annually in the US by 2014. *Mark Ratner*

Open access consortium

The first public-private partnership aimed at tackling inefficiencies in drug validation to speed up drug discovery held its inaugural brain storming session on February 16. This open access consortium known as Arch2POCM was instigated by University of Toronto biologist Aled Edwards, head of the Structural Genomics Consortium, Stephen Friend of Sage Bionetworks and Chas Bountra, of the University of Oxford. This initiative was set up to move high-risk disease targets to the point of proof of clinical mechanism. That first meeting in Toronto included 43 representatives of industry, academia, regulatory agencies and patient groups (http://www.sagebase.org/partners/Arch2POCM.php). They discussed ways of getting around the privacy and intellectual property (IP) roadblocks that today cause pharma companies to waste time and money repeating experiments with novel compounds their competitors already know will fail. What sets Arch2POCM apart from similar endeavors (*Nat. Biotechnol.* **28**, 631–634, 2010) is their insistence on a practical agenda to implement open sourcing by both the public and private sectors. "Each of our groupings agreed to have one or two people work closely in the development of a business plan," said Edwards. *Stephen Strauss*

developing robust pharmacokinetics and pharmacodynamics (PK/PD) assays for small molecules and even biologics such as single mAb agents, Tibbitts says, the conventional assays aren't optimal for ADCs. In the case of conjugates, the DM1 doses are low and the exposure is low, he adds, but researchers are still trying to understand how the body processes ADCs, the risks they pose and how they are eliminated. "We're trying to figure out how to best study [ADCs]," Tibbitts says, "and what we need to balance risk and benefit."

Those issues are compounded by the need for models that better predict clinical outcomes from nonclinical data. Tibbitts and his colleagues have been building translational models in mice to understand the PK/PD of T-DM1. But several years of intensive research effort are now starting to reap rewards. For example, his research team now has dosing data from mice that predicts the optimal regimen of T-DM1 in the clinic (*J. Pharmacokinet. Pharmacodyn.* **37**, 221–42, 2010).

Optimism is tempered because the ADC field has already suffered clinical setbacks. Wyeth's Mylotarg (gentuzumab ozogamicin), which received accelerated approved in 2000 for acute myeloid leukemia, is currently the only ADC to have made it to market. But last July, New York–based Pfizer, which had acquired Wyeth, voluntarily pulled Mylotarg off the market after follow-up clinical trials revealed safety concerns and no clinical benefit in patients. The drug wasn't as stable in plasma as it needed to be, which led to problems with dosing, ImmunoGen's Junius says.

Genentech has also faced regulatory snags in its efforts to commercialize T-DM1. In late 2009, the company announced results from a study with the ADC in women with metastatic HER2-positive breast cancer, who had relapsed after receiving other treatments. The single-armed phase 2 study showed tumor shrinkage in 33% of the patients treated with T-DM1. Based on these data, Genentech applied for a BLA for accelerated approval of T-DM1 last July. But the following month, the US Food and Drug Administration (FDA) issued a refuse-to-file letter on the grounds that as other non-HER2-targeted therapies for breast cancer are available, T-DM1 does not fulfill an unmet need.

Genentech remains confident in their clinical data, however, and in the efficacy and safety of the drug, Pellegrino says. "We're in discussions with FDA about the ongoing development program for T-DM1 to best understand [the types of] data that will be needed to get a full approval of T-DM1." If results from the ongoing randomized, phase 3 trial of TDM-1 are positive, Genentech expects to submit that data for approval in mid-2012.

Another cancer-killing conjugate is ImmunoGen's IMGN901 (lorvotuzumab mertansine), a CD56-targeting humanized mAb conjugated to DM1 through the TAP linker (succinimidyl 4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate). IMGN0901 is indicated for use in a variety of tumors, including small-cell lung cancer and Merkel cell carcinoma, and is already in phase 2 studies for the former.

Elsewhere, Sanofi-aventis of Paris is developing SAR3419, a CD19-binding IgG1 mAb created and humanized by ImmunoGen with a *N*2′-deacetyl-*N*2′-(4-methyl-4-mercapto-1-oxopentyl)-maytansine (DM4) payload attached using the biotech's succinimidyl 4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate linker. The Paris-based pharma expects to initiate phase 2 trials in non-Hodgkin's lymphoma later this year.

For its part, Seattle Genetics is expecting accelerated approval for SGN-35, based on data reported at the American Society for Hematology Annual Meeting, which took place last December in Orlando, Florida. The drug is a chimeric IgG1 mAb against CD30—a protein selectively expressed in activated B and T cells and on hematologic cancers, such as Hodgkin's lymphoma and ALCL—attached to the cytotoxic drug MMAE by means of Seattle Genetics' valine-citrulline peptide linker. In separate single-armed phase 2 studies of SGN-35, researchers observed a 34% complete remission rate in patients with Hodgkin's lymphoma and a 53% remission rate in patients with ALCL. By comparison, phase 2 studies with the naked antibody at higher doses showed no effect. "When you show that data to people, it's hard to argue with the idea that the technology is what's making the difference here," says Seattle's Dobmaier. The company worked with the FDA to obtain a special protocol assessment that delineated trial endpoints for SGN-35, Dobmeier says. Seattle Genetics hopes to satisfy the priority review criteria, which could lead to a decision about their BLA later this year.

ADCs are just one of many complementary strategies for developing new mAb-based drugs, says Anthony Marucci of Celldex Therapeutics in Needham, Massachusetts. Celldex has developed CDX-011(glembatumumab vedotin) using Seattle Genetics' valine-citrulline peptide linker and MMAE cytotoxin attached to their in-house human IgG2 mAb against the melanoma antigen glycoprotein NMB, which is selectively expressed on the surface of melanoma, breast and other cancer cells. Celldex's CDX-011is currently in phase 2 studies. "Just like the antibodies, [ADCs] are going to have their own niche," Marucci says, "and I think they'll do well over the next 5 to 10 years."

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