IN brief

T-DM1 impresses at ASCO

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A breast cancer cell

Genentech released the results from the first phase 3 trial of T-DM1 (trastuzumab emtansine) at the annual meeting of the American Society of Clinical Oncology (ASCO) in June. The data from the S. San Francisco, California–firm's trial in HER2-positive breast cancer impressed oncologists and provided a big boost for the burgeoning field of antibody-drug conjugates (ADCs) (*Nat. Biotechnol.* **29**, 297–298, 2011). "This was the most compelling example to date of an ADC in cancer therapy," says Louis Weiner of Georgetown University in Washington, DC. "Other investigators and companies will now go back to their freezers and see what they have in stock—they may have monoclonal antibodies and drugs that may be linked to go after many different targets in many different cancers." T-DM1 combines Genentech's blockbuster HER2-targeted monoclonal antibody Herceptin (trastuzumab) with antimitotic cytotoxin *N2′*-deacetyl-*N2′*-(3-mercapto-1-oxopropyl)-maytansine (termed DM1), using linker technology from ImmunoGen of Waltham, Massachusetts. The results show T-DM1 met its co-primary progression-free survival endpoint in women with HER2-positive metastatic breast cancer whose disease had progressed after treatment with Herceptin. The 991-patient EMILIA study compared T-DM1 to the small-molecule HER2-targeted drug Tykerb (lapatinib) plus Xeloda (capecitabine) chemotherapy. Median progression-free survival was 9.6 months and 6.4 months, respectively. Although the overall survival analysis did not yet reach statistical significance, two-year survival was 65.4% for T-DM1 and 47.5% for control. "If this trend continues, median overall survival with T-DM1 will be at least a year longer than with control," says Weiner. Severe adverse events were less frequent with the ADC than with control. Genentech and Roche plan to file this year for US and European approval for T-DM1 in HER2-positive metastatic breast cancer. An ongoing phase 3 trial in first-line metastatic breast cancer is comparing T-DM1 alone, T-DM1 plus Genentech's recently approved Perjeta (pertuzumab), and Herceptin combined with taxane chemotherapy. Seattle Genetics, which last year secured approval for its ADC Adcetris (brentuximab vedotin) to treat relapsed or refractory Hodgkin's lymphoma and anaplastic large cell lymphoma, is testing it in four ongoing and planned phase 3 trials in earlier-stage Hodgkin's lymphoma and T-cell lymphoma, and in relapsed cutaneous T-cell lymphoma. Pfizer is testing its ADC inotuzumab ozogamicin in a phase 3 trial in aggressive non-Hodgkin's lymphoma. In June, Merck of Whitehouse Station, New Jersey, entered a deal worth up to $288 million with Ambrx to develop ADCs. *Malini Guha*

Administration for permanent use in the body. The pouch vascularizes and forms a natural chamber for delivering human islets. After implantation, a tissue matrix forms around the pouch—mimicking the natural environment and allowing the islets to stay in place and expand, in effect forming the ultimate scaffold for an artificial organ.

Scaffolds are also becoming more important in the delivery of mesenchymal stem cells, which in the past have been injected or infused locally at the site of tissue repair. Chemical, mechanical (e.g., material stiffness) and structural aspects can regulate the fate of those cells in a fairly precise manner, says Mooney, with clinical implications for tissue regeneration. And there's already a lot of interest in their hematologic activity due to paracrine effects and their ability to manipulate local inflammation. This anti-inflammatory capacity is evidenced by Columbia, Maryland–based Osiris Therapeutics' use of injectable mesenchymal stem cells in graft-versus-host disease, for which it gained recent regulatory approvals in Canada and New Zealand (*Nat. Biotechnol.* **30**, 571, 2012). "I think the immunology and the mechanisms underlying [the signaling] component of how they are functioning is fairly open at this time," he says. "They have potent effects but how to regulate that I don't think is very clear yet."

"In an ideal world, we'd prefer to not have to transplant cells at all," says Mooney, instead tapping the power of cells that exist in the body that look like they have tremendous potential therapeutically. Instead of *ex vivo* manipulation and reintroduction of the cells, the idea is to do that all *in vivo*. The premise is to place biomaterials in the body with the right recruiting signals to recruit the cells of interest. "In that way, we create an environment distinct from the host environment, and now we potentially have a lot of control over those cells," he says.

In cancer therapy, for example, a biomaterial scaffold could be implanted in the body at a location remote from the malignant growth—thereby avoiding tumor-associated immunosuppressive cells, cytokines and other factors that confound immunogenicity—and be used to present a tumor antigen to progenitors of dendritic cells (recruited from elsewhere in the body) that would then be activated and induced to migrate to the lymph nodes where they would interact with T cells and generate a potent anticancer T-cell response. Mooney's laboratory is gearing up to do a clinical trial later this year or early next year to do just that.

Mark Ratner *Boston*

Box 1 Shire's cell therapy strategy

Shire began investing in regenerative medicine in 2007, inking a hefty deal with Manchester, UK–based Renovo for a phase 3 program using human TGF-beta 3 as a treatment for scarring, at a cost of $75 million upfront and a $50-million investment in Renovo. The TGF program wasn't successful, but it solidified Shire's view of regenerative medicine as being at much the same stage of development as was protein therapy for genetic diseases in 2005, when Shire bought Transkaryotic Therapies of Lexington, Massachusetts, challenging Cambridge, Massachusetts–based Genzyme in the market for expensive biologics to treat rare diseases.

Through Renovo, Shire saw the start of a critical mass of development activity in cell therapy. Shire followed that investment with the acquisition of Advanced BioHealing in 2011 for its approved product Dermagraft (fibroblasts from donated newborn foreskin tissue, used to treat diabetic foot ulcers). "It's clear that by investing around $750 million [in [Advanced BioHealing] that it's just the beginning of Shire's building a regenerative medicine franchise," says Kevin Rakin, who heads Shire's regenerative medicine division.

Like Transkaryotic Therapies' positioning seven years ago, regenerative medicine offers an opportunity to focus on specialist physicians with smaller sales forces and products that have biotech-style barriers to entry. Aside from Shire, pharma has not shown any recent interest in investing in the commercial cell therapy field. The only other notable cell therapy or biomaterials deal is Melbourne-based Mesoblast's distribution agreement with Israeli generic drugmaker Teva, in Petach Tikva, for its adult mesenchymal stem cells for bone and cartilage repair—a legacy venture initiated in December 2010 by Cephalon, which Teva later acquired.

In commercializing cell therapies, the main challenges are access to the capital needed to scale up manufacturing and knowing how to fight through reimbursement. "When you do the return on capital of these things, plus the risk of getting approval, it's hard to get the public markets or the [venture capital] markets to fund them," Rakin says. But Shire, owing to its protein manufacturing expertise and existing infrastructure, can take these opportunities forward, he says. *MR*