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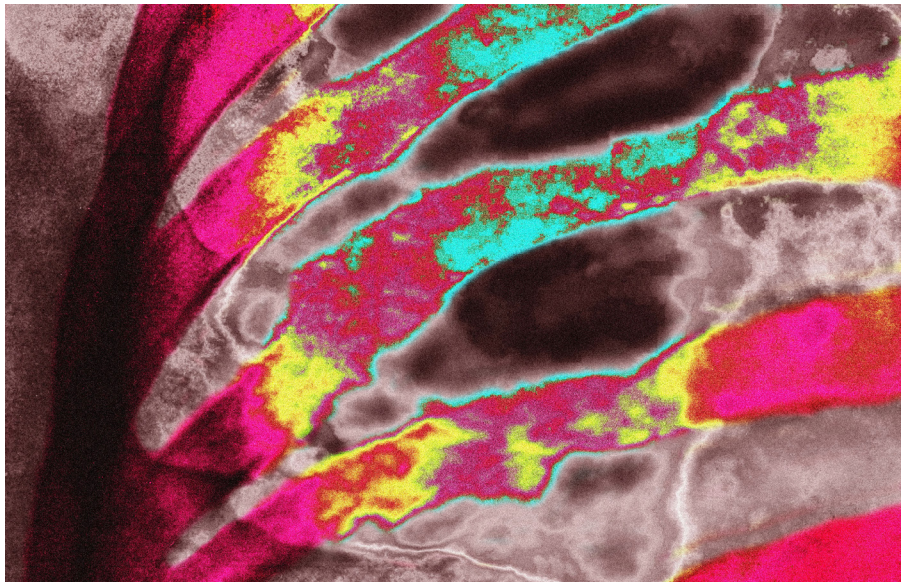
CRISPR therapeutics push into human testing

The first clinical trial in the US of a therapy based on the CRISPR–Cas9 gene editing system is more likely to be conducted by an academic group than by one of the biotech firms most closely associated with the commercial development of the technology. As *Nature Biotechnology* went to press, new entrant The University of Pennsylvania (UPenn), in Philadelphia, and its partners, the University of California, San Francisco, and the MD Anderson Cancer Center at the University of Texas, in Houston, planned to start a phase 1 trial of a T-cell-based cancer immunotherapy in the first quarter of this year, subject to US Food and Drug Administration (FDA) approval of its investigational new drug (IND) filing. The emergence of the UPenn-led academic consortium—to say nothing of a group led by Lu You, of Sichuan University, in Chengdu, China, which achieved a world-first last year in administering CRISPR–Cas9-modified T-cells to lung cancer patients (*Nature* **539**, 479, 2016)—shows that the competitive landscape for therapies based on CRISPR–Cas9 is already starting to gain complexity.

Cambridge, Massachusetts–based Editas Medicine is the only one of the companies established by the main inventors of the CRISPR–Cas9 technology with concrete plans to move into the clinic this year. The others, Intellia Therapeutics and CRISPR Therapeutics—as well as Casebia Therapeutics, the latter firm's joint venture with Leverkusen, Germany–based Bayer—are all in earlier stages of development (**Table 1**). Between them, these ventures have accrued a formidable $1 billion in aggregate funding—and with access to the key, albeit disputed, patents to the technology—they remain in the driver's seat in terms of commercial exploitation of CRISPR–Cas9.

Although these young biotech firms already have extensive capabilities in CRISPR–Cas9 gene modification, their therapeutic development efforts are necessarily early stage. Basel, Switzerland–based CRISPR and Editas were both established in the second half of 2013 (*Nat. Biotechnol.* **32**, 127, 2014), and Cambridge, Massachusetts–based Intellia was only formed in May 2014 (*Nat. Biotechnol.* **33**, 247–255, 2015). Meanwhile, several academic centers are attempting to apply to CRISPR their experience in introducing several other novel therapeutic modalities. Carl June, professor of immunotherapy at UPenn's Perelman School of Medicine and director of the UPenn arm of the newly established Parker Institute for Cancer Immunotherapy, is scientific advisor on the forthcoming trial.



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CRISPR-Cas9 gene editing will be tested in patients with multiple myeloma, a type of bone marrow cancer (pictured).

Best known as a pioneer of CAR-T cell therapy, June has previous clinical experience with another gene-editing technology to develop an HIV therapy. His team used zinc-finger nucleases, to modify autologous CD4 T cells from individuals infected with HIV (*N. Engl. J. Med.* **370**, 901–910, 2014).

The T cells were engineered *ex vivo* to disrupt the gene encoding C-C chemokine receptor type 5 (CCR5), which most HIV strains exploit when entering T helper cells. The strategy—designed to mimic the CCR5Δ32 homozygous carriers from HIV infection—has already been emulated in the small-molecule drug Selzentry (maraviroc; ViiV Healthcare, Brentford, UK). The UPenn-sponsored phase 1 study was primarily designed to test safety. It also demonstrated that, although the gene-edited T cells persisted, the dose was insufficient to prevent viral rebound occurring when patients interrupted their drug regimens. "What we know for sure is zinc finger nucleases are safe," June says. The therapy, SB-728-T, is now in a phase 2 trial at Richmond, California–based Sangamo BioSciences.

CAR-T cell therapies, have achieved highly promising responses in cancer patients, but the approach is largely limited to hematological malignancies at present, however, and safety continues to represent a challenge (see page 6). The forthcoming trial using CRISPR–Cas9 gene editing, in patients with multiple myeloma, melanoma or sarcoma, involves an autologous T-cell therapy designed to attack cancer cells that express NY-ESO-1, a highly immunogenic cancer antigen. It builds on an earlier clinical study in myeloma patients, which involved the administration of T cells expressing an affinity-enhanced T-cell receptor (TCR) that

Box 1 Edited cells in manufacturing revamp

As UPenn gears up to launch its trial, manufacturing issues loom large. "It's not trivial to do the cell manufacturing," says June. As the protocol involves the modification of four different genes, the manufacturing process will actually generate 16 different T-cell genotypes. Rather than separate out the single genotype of interest, the clinical investigators will administer all 16 genotypes to the patients. "It's a competitive repopulation experiment," he adds. Although it is possible to isolate the T-cell population with the desired profile, doing so would add more time to the process, and the delay can impair engraftment. "The longer the cells remain in the lab the less well they do in patients," June says.

Paris-based Cellectis, in contrast, employs a purification column to fish out unedited cells during its production process. Cellectis and its partners Servier, of Suresnes, France, and Pfizer, of New York, are already in a clinical trial in B-cell leukemia with a CD19-targeting allogeneic CAR-T cell therapy (UCART19). "It is really important for us to have a defined product at the end of the process," says Julianne Smith, vice president for CAR-T development at Cellectis. The company employs a different gene editing technique, transcription activator-like effector nucleases (TALENs), to disrupt target genes. In the case of UCART19, the endogenous TCR-α chain is disrupted at several sites, to enable the chimeric antigen receptor to function and to allow the use of Campath (alemtuzumab), an anti-CD52 antibody, to inhibit host-versus-graft responses. *CS*

programs all target liver cells—LNPs exploit the apolipoprotein E4 transporter to deliver their CRISPR–Cas9 payload, but the particles can be formulated for preferential uptake to other tissues, such as muscle, the eye and the central nervous system, Bermingham says. Editas is following a dual strategy. It is employing an adeno-associated virus (AAV) vector for therapies aimed at eye diseases, but it remains open, for now, to either AAV or LNP delivery for genetic diseases, such as Duchenne muscular dystrophy and cystic fibrosis. CRISPR Therapeutics has not disclosed its delivery strategy for *in vivo* applications. Its first *in vivo* programs, according to a recent quarterly filing with the Securities and Exchange Commission "will leverage well-established delivery technologies for gene-based therapeutics." It has also entered several research collaborations to explore new delivery methods.

The UPenn-led trial will operate under safe harbor provisions, which obviate the need for a patent license, but if it is successful, Tmunity Therapeutics, a Philadelphia-based spin-off from the university, would seek to commercialize the program. The company would then require a commercial license from at least one of the patent holders, although at this point it is not clear which one. "I wouldn't know who to get a license from anyway, given the [uncertain] state of the technology," June says. A decision in the ongoing patent dispute would clarify that issue—and set the terms for the evolution of CRISPR–Cas9 from being a wildly popular research tool to an commercial-grade therapeutic modality.

Cormac Sheridan *Dublin*

"Merck has not wavered in our sustained commitment to investing in R&D." Ken Frazier, Merck's CEO, emphasizes despite the company spending $4 billion less in 2015 than in 2010. (@biotechreader, 15 November 2016)

"The world is full of pretty stodgy foundations that generally do pretty safe things. I'd rather see what happens when you do something totally different that's never been tried." Sean Parker, whose institute, The Parker Institute for Cancer Immunotherapy, asks its academic members to collaborate, not compete, and to emphasize getting drugs approved over getting publications. (*Bloomberg,* 2 December 2016)

"The real reason we're not liked, in my opinion, is because we as an industry have used price increases to cover up the gaps in innovation. That's just a fact." Leonard Schleifer CEO of Tarrytown, New York–based Regeneron, with a view that was not universally shared by other CEOs at the Forbes Healthcare Summit in New York in December. (*Bloomberg,* 1 December 2016)

"It would be folly to deprive US citizens of access to potential life-saving drugs simply to satisfy a declining gaggle of aging [Cuban] exiles in Miami." Richard Feinberg of the Brookings Institution refers to worries that Cuban-made biotech therapies will be kept out of the US, following Trump's campaign rhetoric about reversing Obama policies. (*STAT News,* 2 December 2016)

BMS in microbiome immuno-oncology deal

Global pharma Bristol-Myers Squibb (BMS) entered a pact with French biotech Enterome Bioscience in November to exploit gut microbiome knowledge and its role in modulating cancer therapeutics. The New York–based BMS agreed in November to pay the Paris-based biotech $15 million upfront to access Enterome's technology platforms for fecal bacterial genetic screening. The focus is on identifying microbiome-derived biomarkers that enhance clinical responses for patients treated with BMS's immunotherapeutic drugs. Enterome has two platforms, one is a quantitative metagenomics platform to characterize a person's metagenome and its associations with a disease phenotype. The other is a functional metagenomics platform to identify new targets and for drug discovery. Enterome is eligible to receive milestone payments for each licensed product discovered and developed during the collaboration. Also in November, BMS entered a five-year research alliance with Johns Hopkins University in Baltimore to study how patients' tumors, microbiome and anti-tumor immunity are modulated by checkpoint inhibitor immunotherapies, including BMS's Opdivo (nivolumab) and Yervoy (ipilimumab). BMS is not the first big pharma to take an interest in the hot area of microbiome research. Takeda and Janssen Biotech have also partnered with Enterome. And in November 2015, Enterome partnered with Institut Gustave Roussy of Villejuif, France, to investigate the microbiome's role in treating cancer.

Ganymed's Claudin win

Astellas will pay $1.4 billion for Ganymed and its oncology pipeline of monoclonal antibodies targeting the tight-junction protein Claudin-18.2. The Tokyo-based Astellas announced in October it will pay €422 ($461) million upfront and up to €860 ($940) million in milestones to acquire the biotech located in Mainz, Germany, and its new class of therapeutic drugs called Ideal Monoclonal Antibodies. Ganymed, founded in 2001 as a spin-off from the Universities of Mainz and Zurich, owns a portfolio focused on a unique cancer target, the tight-junction protein Claudin-18.2, which regulates cellular permeability by sealing the space between the epithelial and endothelial cellular sheet. Claudin18.2 is expressed on differentiated stomach cells only and is absent in healthy tissues. It is expressed, however, in up to 80% of gastrointestinal adenocarcinomas, 60% of pancreatic tumors and in other solid tumors. Some 24 Claudins have been described in humans. Ganymed's IMAB362 is a first-in-class anti-Claudin-18.2 mAb currently in phase 2 trials for gastroesophageal cancer. The IMAB027, in phase 1 trials, targets Claudin-6, an embryonic antigen present in a wide range of cancers but absent from healthy adult tissue.