Another CRISPR win for Zhang and Broad

A court ruling issued in September brings the fight over who owns the use of CRISPR in eukaryotic cells one step closer to the finish line. The Court of Appeals for the Federal Circuit (CAFC) affirmed an earlier decision giving the Broad Institute ownership of the key patent at issue. In February 2017, a US Patent and Trademark Office appeal board said that the patent granted to the Broad's Feng Zhang, covering the gene editing technology's use in eukaryotic cells, does not interfere with CRISPR intellectual property from the University of California, Berkeley and co-inventors Jennifer Doudna and Emmanuelle Charpentier, which covers its use in cell-free systems, thus rendering both methods as patentable separately (*Nat. Biotechnol.* **35**, 184, 2017). The CAFC's ruling effectively ends Berkeley's challenge to the patent's validity. Berkeley had filed for intellectual property of the technology in May 2012, six months before Zhang, but in April 2014, under a fast-track program, Zhang was issued the first patent. After reviewing the evidence, the CAFC confirmed that it stood by its previous decision, stating that "the Board performed a thorough analysis of the factual evidence and considered a variety of statements by experts for both parties and the inventors, past failures and successes in the field, evidence of simultaneous invention, and the extent to which the art provided instructions for applying the CRISPR-Cas9 technology in a new environment." The University of California has not indicated whether it will appeal the ruling to the Supreme Court. "We are evaluating further litigation options," said UC general counsel Charles Robinson in a statement.

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"I think fetal genome editing may be where fetal surgery once was, and that one day we'll use it to treat diseases that cause significant morbidity and mortality," William Peranteau of the Children's Hospital of Pennsylvania, comments on a study (*Nat. Med.* **24**,1513–1518, 2018) he co-leads, in which the gene that causes hereditary tyrosinemia type 1 was corrected in mice fetuses using a CRISPR base editor. (*Scientific American*, 9 October 2018)

"Perhaps a better-tasting tomato could help to bring more policymakers on side." A delicious genetically engineered tomato highlights problems with Europe's outdated approach to gene editing, argues a *Nature* editorial. (*Nature,* 2 October 2018)

"The reason I'm really thrilled about this is I'm a basic scientist. I didn't get into these studies to cure cancer. I wanted to know how T cells work." Jim Allison on receiving the 2018 Nobel Prize in Physiology and Medicine. (*NPR Shots: Health News from NPR*, 1 October 2018)

Table 1 Selected afucosylated antibodies in clinical development

Company	Agent	Target	Indication	Stage
Kyowa Hakko Kirin Pharma	Poteligeo (mogamulizumab)	CCR4	Mycosis fungoides, Sézary syndrome	Approved Japan 2012, US 2018
Genentech (Roche)	Gazyva (obinutuzumab)	CD20	Chronic lymphocytic leukemia (2013), follicular lymphoma (2016, 2017)	Approved 2013
MedImmune (AstraZeneca),	Fasenra (benralizumab)	IL-5 receptor-α	Severe eosinophilic asthma	Approved 2017
Five Prime Therapeutics	Bemarituzumab (FPA144)	FGFR2	Gastric and gastroesophageal cancer	Phase 3
TG Therapeutics	Ublituximab (TG-1101)	CD20	Multiple sclerosis (MS), B cell cancers	Phase 3 (MS), phase 1/2 (blood cancers)
Viela Bio	Inebilizumab (MEDI-551)	CD19	Neuromyelitis optica	Phase 2b
GlaxoSmithKline	GSK2857916 (ADC)	BCMA	Multiple myeloma	Phase 2
Merus	MCLA-128	Her2, Her3 (bispecific)	Breast cancer	Phase 2
Argenx (Breda, the Netherlands)	ARGX-110	CD70	T cell lymphoma, acute myeloid leukemia	Phase 2
Bristol-Myers Squibb	BMS-986218	CTLA4	Advanced solid tumors	Phase 1/2
Cantargia (Lund, Sweden)	CAN04 (nidanilimab)	IL1RAP	Solid tumors	Phase 1/2
Argenx	ARGX-111	c-Met	Advanced cancer	Phase 1 complete
Janssen (Johnson & Johnson)	JNJ-61186372 (CNTO4424)	EGFR, cMet (bispecific)	Non-small cell lung cancer	Phase 1
Five Prime Therapeutics	FPA150	B7-H4	Solid tumors	Phase 1
Seattle Genetics	SEA-CD40	CD40	Solid tumors	Phase 1
Seattle Genetics	SEA-BCMA	BCMA	Multiple myeloma	Phase 1
Viela Bio	VIB7734	ILT7	Myositis	Phase 1
Merus	MCLA-158	EGFR, Lgr5 (bispecific)	Solid tumors	Phase 1

Source: company websites; Clinical trials.gov; Proceedings, American Association for Cancer Research 2018 annual meeting

says Roland Kolbeck, vice president for respiratory, inflammation and autoimmunity at MedImmune in Gaithersburg, Maryland. Medimmune omitted fucose molecules from its antibody Fasenra (benralizumab), for treating severe eosinophilic asthma. Last November, Fasenra became the second afucosylated drug to win FDA approval. It targets interleukin (IL)-5, a cytokine critical for the activity and survival of eosinophils, immune cells that contribute to the pathogenesis and severity of about half of all asthma cases. Fasenra entered phase 1 trials in 2007, and its remarkable effects became rapidly apparent. "After a single dose of benralizumab, 24 hours later, we hardly could find eosinophils in the blood anymore," recalls Kolbeck. "And the antibody was so powerful that indeed we de-escalated the dose during the study."

Fasenra quickly eliminates eosinophils by ADCC, unlike two recently approved IL-5 blocking antibodies that remove these cells by interfering with cytokine signaling. Although MedImmune has its own afucosylated antibody preclinical programs, in February 2018 it spun out a new company, Viela Bio, which has two more afucosylated antibodies in clinical trials.

Seattle Genetics initially focused on afucosylation almost by accident. The biotech's scientists were trying to attach a cytotoxic agent to the Fc glycan to make antibody–drug conjugates. In the process, they discovered that a small molecule, 2-fluorofucose, could block fucosylation. Seattle Genetics now has two afucosylated antibodies in phase 1 studies. One of them targets B cell maturation antigen, expressed on plasma cells. The rampant expansion of these cells causes multiple myeloma. The afucosylated antibody boosts ADCC, depleting the plasma cell population.

Seattle Genetics's other antibody uses afucosylation very differently. The agonist antibody targets CD40, present on macrophages and dendritic cells. Rather than deplete them by ADCC, it binds Fc receptors on neighboring cells to promote crosslinking and clustering of CD40's ligand on these cells, boosting CD40 signaling and antitumor immunity. Thus afucosylation can be a novel form of cancer immunotherapy. "Because of the potent activity of this drug, we're dosing it much lower than typically," says Seattle Genetics senior vice president for translational research Dennis Benjamin.