Taylor Schreiber, CEO of Shattuck Labs, is looking forward to learning those results. If Merck's vibostolimab works about as well as Genentech's tiragolumab, he says, "you can at least make the conclusion that effector competence is not inhibiting the effect of targeting TIGIT — and that is the main thing you'd be worried about." Conversely, if Arcus's humanized IgG1 mAb domvanalimab, with its Fc-disabled region, shows near-equivalency to the other agents, then it's the TIGIT-blocking function of these antibody therapies that likely matters more than any Fc–FcγR co-engagement. Initial phase 1 data from the domvanalimab trial are anticipated at the next SITC meeting in November.

For his part, Schreiber is still debating whether to include an Fc-inactive IgG4 linker protein or an afucosylated IgG1 with enhanced Fc activity in Shattuck's TIGIT-directed therapy, a bifunctional fusion protein now in preclinical toxicology testing. He plans to decide after seeing both the Merck and Arcus data. "That will be informative," Schreiber says.

Rosen, the Arcus CEO, isn't too concerned about such comparisons, though. That's because his company is not focused on the same strategy of dual checkpoint inhibition that others are pursuing. On top of TIGIT and PD-1 blockade, Arcus is planning to take a three-pronged attack on tumor immunosuppression with a small molecule drug designed to block signaling of adenosine, an anti-inflammatory metabolite. "That's going to be the place where we bring benefit to patients and provide something that adds to the field," Rosen says. The company is now testing a triplet regimen of its own experimental drugs: the TIGIT inhibitor domvanalimab, the PD-1 inhibitor fully human IgG1 mAb zimberelimab and the small-molecule dual adenosine $A_{2A}/A_{2B}$ receptor antagonist etrumadenant in patients with PD-L1-high NSCLC.

In a similar vein, iTeos is planning to evaluate its anti-TIGIT agent, EOS-448, together with its small-molecule $A_{2A}$ receptor antagonist EOS-850, plus or minus chemotherapy, in the coming year. Likewise, Compugen is positioning its anti-TIGIT therapy, COM902, alongside the company's inhibitor of poliovirus-receptor-related immunoglobulin (PVRIG), a related co-inhibitory receptor that competes with DNAM-1 and TIGIT for binding to the CD122 ligand.

Only by blocking both receptors, PVRIG and TIGIT, can "you actually release the arrest of the system and get sufficient immune stimulation," says Compugen president and CEO Anat Cohen-Dayag. "More than that, there is an intersection between these two pathways and the PD-1 pathway," she adds. "This is a triple pathway story and you need all the relevant pieces in the axis." In phase 1 testing, Compugen's anti-PVRIG drug, COM701, showed early signs of efficacy, both on its own and combined with BMS's PD-1 inhibitor Opdivo (nivolumab). Now, with COM902 still undergoing early clinical testing, Compugen has partnered with BMS to begin evaluating the triple blockade strategy through the combination of COM701, Opdivo and BMS-986207, another anti-TIGIT drug that has already completed the safety portion of a first-in-human study.

Other companies hope to carve out niches in the increasingly crowded anti-TIGIT arena by testing their experimental inhibitors in less common tumor types, or through the use of TIGIT-pathway-specific biomarkers for patient selection. "We're being very careful in exactly how we design these studies," says Mereo CEO Denise Scots-Knight. "We're looking for white space here."

Beyond cancer, some academic groups have also begun to consider situations in which therapeutically augmenting TIGIT activity with an agonistic antibody could be beneficial for patients. Nicole Joller, a T cell immunologist at the University of Zurich in Switzerland, points to the example of severe COVID-19 infections, in which many people experience excessive proinflammatory cytokine storms. "That is a setting where this could be helpful," she says. "You could definitely target TIGIT in anything that's marked by excessive inflammation, be it autoimmune or infection-mediated," Joller notes.

Vijay Kuchroo, from Brigham and Women's Hospital in Boston, says that he and fellow immunologist Dario Vignali, of the University of Pittsburgh School of Medicine, are now shopping around the idea of forming a company focused on advancing checkpoint agonists for treating autoimmunity. Few large drug firms seem to be pursuing this strategy, although Janssen scientists publicly presented in vitro data last year on the immunomodulatory effects of an agonist TIGIT-targeted human IgG1κ mAb called TGTB227. According to spokesperson Kellie McLaughlin, the company is "in the process of evaluating the potential of TGTB227 relative to other assets in our portfolio." She declined to comment on future development plans. ❐

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## Moderna loses key patent challenge

A dispute over a key technology used in Moderna's highly anticipated COVID-19 vaccine came to a head in July when Arbutus Biopharma fended off a claim by the vaccine maker. The patent clash over the delivery system used in Moderna's mRNA-1273 vaccine could hamper the biotech's ability to price the vaccine competitively, as well as affect its margins versus those of other companies developing coronavirus vaccines. Moderna previously held a limited sublicense to Arbutus Biopharma's lipid nanoparticle (LNP) formulation, which is used to deliver messenger RNA drugs into cells. But since 2018, Moderna has filed three inter partes reviews (IPRs) with the US Patent and Trademark Office seeking to invalidate Arbutus's LNP patents. The first two IPRs resulted in wins for Moderna — invalidating one of Arbutus's patents in full and partially invalidating another. However, on 23 July the US Patent and Trademark Office's Patent Trial and Appeal Board (PTAB) delivered a decisive win for Arbutus in the third IPR, rejecting Moderna's argument that the Arbutus patent known as the '069 patent should be revoked because it describes obvious concepts. "To the extent it is believed the PTAB erred in their decisions, Moderna may further pursue these matters," the company said in a statement, adding that they were "not aware of any significant intellectual property impediments for any products we intend to commercialize, including mRNA-1273." Though it is still unclear whether Moderna's vaccine development efforts use the LNP technology in question, the PTAB's ruling increases the pressure on Moderna to seek a sublicense on the technology. The '069 patent is licensed to Genevant Sciences, a maker of LNPs for RNA-based therapeutics, and Arbutus would receive 20% of any revenue received by Genevant for sublicensing the patent. Analysts at investment bank SVB Leerink called the decision a "disappointing turn" for Moderna in a note to investors.

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