to help reverse exhaustion in immune cells already committed to that dysfunctional fate.

Consider TOX targeting. As the recent papers from Wherry, the LJI team and others showed, “blockade of TOX blunts exhaustion, but it does not reprogram effector function,” notes Schreiber. As such, he says, TOX inhibition in combination with checkpoint inhibitors may not substantially improve upon the efficacy of existing immunotherapy regimens, and other strategies that truly refresh T_{EX} cells in the body are still desperately needed.

To that end, Vijay Kuchroo, an immunologist at Brigham and Women’s Hospital in Boston, is performing a systematic CRISPR-based screen looking for targets that, when knocked out, can successfully reprogram T_{EX} cells. “If there’s any way to reverse exhaustion,” Kuchroo says, “that would be the greatest thing you could do.”

At the 2019 Society for Immunotherapy of Cancer and American Association for Cancer Research Tumor Immunology and Immunotherapy meetings, both in November, Mackall reported that transiently shutting off expression of the CAR transgene and giving engineered cells a rest could help convert exhausted pools of T cells into a functional population. “It’s quite elegantly simple,” Mackall says. For now, however, most of the clinical action centers around forestalling further T-cell dysfunction and keeping terminal exhaustion at bay.

That is part of the rationale for combining anti-PD-1 drugs with experimental agents directed against second-generation checkpoint targets, such as LAG-3 (lymphocyte activating gene 3), TIGIT (T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domains) and TIM-3 (T-cell immunoglobulin and mucin domain 3) — inhibitory receptors that are often expressed on cells showing signs of exhaustion. “There are lots of steps along the way where

cells will start to exhibit an exhaustion phenotype but can still gain functionality” after checkpoint blockade, explains Dario Vignali, an immunologist at the University of Pittsburgh School of Medicine.

In fact, T_{PEX} could be responsible for the proliferative boost of immunity that often follows [checkpoint blockade therapy](#), according to data published last year by [Haining’s group](#) and [Werner Held’s team](#) at the University of Lausanne in Switzerland. Yet these cells are not maintained and often veer toward terminal exhaustion. “This is one of the big problems that we have to fix today if we want to prolong patient survival and prevent the loss of response,” says Nicolas Poirier, CSO of OSE Immunotherapeutics, a company with a preclinical-stage bispecific drug candidate that combines a PD-1–targeted antibody with interleukin-7, a cytokine thought to help prevent exhaustion.

Fortuitously, breaking T-cell exhaustion also seems to be a beneficial byproduct of many cancer therapeutics initially designed for other purposes. Take TTX-030, for example. This human IgG4 monoclonal antibody from Tizona Therapeutics is a selective inhibitor of CD39, a cell surface enzyme found on regulatory T cells, myeloid cells and cancer cells alike that helps convert immune-stimulating ATP to immune-suppressive adenosine. CD39 expression is also a hallmark of T-cell exhaustion, though, and unpublished preclinical studies suggest that its blockade has the added bonus of restoring effector function, notes Tizona CSO Courtney Beers. In January 2019, AbbVie paid \$105 million in cash and bought an equity stake in Tizona to fund development of TTX-030. A phase 1/1b trial in patients with lymphoma and solid tumors is underway. □

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“I thought that it was pretty incredible that I can disappear and someone else can appear.” Chris Long, who, after having a bone marrow transplant from an older German donor, discovered the donor’s cells in many parts of his body. (*The New York Times*, 7 December 2019)

“Given the extremely low chimeric efficiency and the deaths of all the animals, I actually see this as fairly discouraging.” Stem cell biologist Paul Knoepfler at the University of California, Davis, about two pig-monkey chimeras created by Chinese scientists at the State Key Laboratory of Stem Cell and Reproductive Biology in Beijing that died within a week. (*New Scientist*, 6 December 2019)

“The proof in the pudding will be to look in the mirror.” Bill Andrews, proponent of an anti-aging clinical trial taking place in Colombia that is charging participants a million dollars for a gene therapy of injected telomerase. (*OneZero*, 4 December 2019)

“What the Chinese government is doing should be a warning to everybody who kind of goes along happily thinking, ‘How could anyone be worried about these technologies?’” Pilar Ossorio, of the University of Wisconsin Law School, speaking of the Chinese government’s push to develop facial recognition algorithms from DNA. (*The New York Times*, 3 December 2019)

Bayer makes first move into condensates

German pharma Bayer has signed a [\\$100 million](#) deal with Dewpoint Therapeutics to jointly pursue biomolecular condensates for drug discovery. The companies will combine Dewpoint’s condensates expertise with Bayer’s small-molecules library to discover drugs for heart diseases and gynecological indications.

Biomolecular condensates are liquid-like droplets of proteins and RNA that form in the cell, through a process called [liquid–liquid phase separation](#), to speed up or slow down reactions. They are transient, membraneless structures that coalesce and then dissolve in the cellular cytoplasm and nucleus. Scientists have known about them for more than 100 years, but a growing body of research suggests that they also have [critical roles in health and disease](#).

Interest in these so-called membraneless organelles has largely been catalyzed by links between these structures and the neurodegenerative disease [amyotrophic lateral sclerosis \(ALS\)](#). Researchers have found that proteins linked to ALS form condensates, and mutations in these proteins can make the condensates more viscous than usual. Sticky biomolecular condensates, moreover, can drive the formation of the inclusion bodies that are a hallmark of the disease. Biomolecular condensate biology has also been linked to [Alzheimer’s disease](#), [Huntington’s disease](#), [muscular dystrophy](#) and [cancer](#).

Dewpoint became the first company to publicly stake out a claim in this space, raising [\\$60 million](#) in series A funding in January 2019 to work on neurodegenerative and cancer applications. Dewpoint and Bayer are still deciding what targets to work on. But biomolecular condensate biology provides opportunities both to identify entirely novel targets and to think about new ways of modulating known but previously intractable targets, says Amir Nashat, CEO of Dewpoint and managing partner at venture capital fund Polaris Partners. “We’re going to start out very open minded and explore both options.” A few other firms focusing on biomolecular condensates are expected to launch soon.

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