non-profit, applauds the company for exploring the interconnectedness between tumors, the immune system and neurons in an unbiased, systematic fashion. "There's lots of feedback going on, and it's often unclear what's the chicken and what's the egg," he says. "This exciting platform allows you to appreciate that complexity, but at the same time still take the reductionist approach that you need in drug development."

Cygnal has disclosed one target identified in this way: CYFIP1 (cytoplasmic FMR1-interacting protein 1), a protein involved in regulating synaptic connectivity between neurons. Dysregulation of CYF1P1 has been implicated in autism, schizophrenia and other neuropsychiatric disorders, and lab experiments detailed at the 2019 International Conference on Molecular Targets and Cancer Therapeutics in Boston showed that knocking out CYFIP1 markedly delayed cancer initiation. However, the effect on tumor maintenance was much less pronounced — and "this target is not Cygnal's primary focus for the moment," Huang says.

"We shared this target at the meeting to illustrate how we use our platform to discovery new biology," she explains. The same platform also helped the company pinpoint α6-subunit-containing nicotinic acetylcholine receptors and the purinergic receptor P2X 2, among other synaptic proteins, as potential candidate targets, patent filings show.

Collectively, the targets discovered to date reveal that "as tumors become really deranged and they get more advanced, there's a selection for tumors that are expressing these nerve functions because it gives them a growth advantage," Huang says. "So what we've identified are targets that are neural in origin — that is, they were first described in neural systems — that are now acting like oncogenes in tumors."

Huang intends to announce two development candidates later this year. For now, she would only say that one is a small-molecule drug aimed at a neurotransmission target with expression levels that are amplified across multiple tumor types and are predictive of patient survival in various cancers, including those of the uterus and bladder. The other candidate is an antibody drug directed against an undisclosed target.

Few if any other companies beside Cygnal and Divide & Conquer have publicly disclosed plans to develop drugs targeting neuron–cancer interplay, but there are a handful of ongoing academic efforts. Monje, for example, will begin a human trial early this year that builds on her team's 2017 finding from mouse xenograft models that pharmacologically blocking the release of a neuron-secreted adhesion molecule into the tumor microenvironment can hamper the proliferation of brain cancer. Her team is planning to give patients with high-grade gliomas a small-molecule drug called aderbasib, an inhibitor of ADAM (a disintegrin and metalloprotease) enzymes. Incyte previously tested the drug for breast cancer before suspending further development.

Timothy Wang, a gastrointestinal cancer researcher at the Columbia University Medical Center in New York City and a member of Cygnal's scientific advisory board, also has a pilot study ongoing to test whether presurgical treatment with bethanechol (Urecholine), an activator of muscarinic acetylcholine receptors typically prescribed for bladder problems, can help patients with pancreatic cancer. The trial — run jointly with oncologists Susan Bates of Columbia and Paul Oberstein of New York University — has accrued five patients so far, and, according to biomarker analyses, "there are some very encouraging findings," says Wang. In 2018, he and his colleagues showed that cholinergic nerves, as mediated by muscarinic receptors, regulate the progression of pancreatic tumors in mice.

Earlier research from Wang's lab had additionally found that PLX7486 — an experimental small molecule from Plexxikon (a subsidiary of Daiichi Sankyo) that impedes nerve growth signaling by blocking tropomyosin receptor kinases — inhibits tumor development in mouse models of gastric and pancreatic cancers. Plexxikon had launched a clinical trial to test whether the same is true in patients. The study was stopped, however, for business reasons — "much to my own disappointment," says Gideon Bollag, the company's CEO.

"We were never able to properly explore the role of nerves in cancer growth," Bollag says. "It's nice to see that others are pursuing that link." ❐

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Digital drug fortunes falter

The fortunes of Proteus Digital Health tumbled at the end of 2019 when a multi-million-dollar funding round from Tokyo-based Otsuka Pharmaceutical didn't close as anticipated, reportedly causing the company to furlough many employees. Otsuka's cancelled investment in Proteus, the company that is behind the first FDA-approved digital pill and that was once valued at $1.5 billion, is likely related to a disappointing clinical trial in schizophrenia. The trial used a digital pill that combines Otsuka's antipsychotic aripiprazole with Proteus's ingestible sensor, which sends a signal to an external patch linked to a mobile phone app to track when the pill is taken. The drug–device, called Abilify Mycite, gained FDA approval in 2017 with the dose-tracking app. The trial in question was to investigate whether the digital pill would promote better outcomes by quantifying the number of hospitalizations. But the trial was terminated last November after it recruited only 2 out of a target 790 patients. Schizophrenia is a difficult indication because patients whose symptoms include paranoia and delusions are likely to reject it. For other indications, digital medicines may prove more acceptable, as evidenced by an open-label pilot trial in patients with uncontrolled hypertension and type 2 diabetes and another in patients with hepatitis C virus, where Proteus's digital device promoted adherence and improved outcomes. For Proteus to achieve its aim of implanting an ingestible tracking device into prescription medicines, it needs to prove to therapeutic companies and investors that the system results in improved outcomes and may potentially extend a drug's patent protection, but this may be an uphill struggle. Despite Proteus's recent layoffs, two clinical trials of the digital pill in schizophrenia are still active. Another digital therapeutics company, Pear Therapeutics, recently ended its partnership with Novartis's generics company Sandoz when the large pharma stepped away from their commercialization agreement.

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