Table 1 | Small-molecule influenza therapies approved and in development

Drug	Company	Target	Status
Tamiflu (oseltamivir)	Roche	Neuraminidase	Approved 1999
Relenza (zanamivir)	Vaxart/GlaxoSmithKline	Neuraminidase	Approved 1999
Rapivab (peramivir)	CSL	Neuraminidase	Approved 2014
Inavir (laninamivir)	Vaxart/Daiichi Sankyo	Neuraminidase	Approved 2010 (Japan)
Xofluza	Roche/Shionogi	RNA polymerase	Approved 2018
Avigan (favipiravir)	Toyama Chemical/Fujifilm	RNA polymerase (PB1 subunit)	Approved 2014 (Japan)
JNJ-3872, pimodivir	Vertex/Janssen (Johnson & Johnson)	RNA polymerase (PB2 subunit)	Phase 3
JNJ-5806, AL-794	Alios BioPharma/Janssen (Johnson & Johnson)	RNA polymerase	Phase 1

to block the membrane fusion and thus stop infection.

Using this as a starting point, teams at Janssen, the pharmaceutical arm of Johnson & Johnson, and the Scripps Research Institute decided to focus on CR6261, a broadly neutralizing anti-HA antibody isolated from the polyclonal response of a healthy immunized person. (CR6261 is so called because it recognizes a conserved region (CR) of the HA stem, potentially conferring activity across influenza strains.)

The team screened ~500,000 compounds to identify chemical agents capable of displacing a computationally designed peptide that recognizes the same part of the HA molecule as CR6261. After medicinal chemistry to optimize these hits for stability and solubility, a benzylpiperazine, JNJ-4796, was selected as the small molecule that best mimicked the binding of CR6261 to the HA stem.

Broadly neutralizing antibodies have the potential to protect, at least in theory, against a wide range of influenza strains and subtypes. Early results with broadly neutralizing antibodies have been unpromising, however: MHAA4549A, Roche's monoclonal antibody against HA, was suspended after it fared worse than placebo or Tamiflu-only treatments (see results from clinical trials NCT02293863 and NCT02623322). That said, several companies are now pursuing broadly neutralizing monoclonal antibodies against neuraminidase as a target, including Janssen, Otsuka, AstraZeneca and Roche, with the last two of these entering phase 2 efficacy testing.

Small-molecule drugs against influenza have a somewhat checkered history. Companies marketing neuraminidase inhibitors courted controversy in the 2000s as governments spent billions of dollars stockpiling Tamiflu to combat an anticipated 'bird flu' pandemic. When the pandemic failed to materialize, politicians accused Roche of gouging healthcare systems and overselling the drug's efficacy against flu infection; in some patients, Tamiflu curtails the duration of influenza symptoms by less than a day.

One of the key problems with small-molecule neuraminidase inhibitors like Tamiflu and Relenza is the rapid emergence of resistant influenza strains. Similarly, other drugs, like the small-molecule Symmetrel (amantadine) and its derivative Flumadine (rimantadine), a cell-cycle inhibitor that is thought to also target the flu virus's M2 ion channel, are now no longer recommended by the US Centers for Disease Control because of high levels (30–50%) of resistance in treated patients.

As neuraminidase is a surface protein, small molecules binding to it were originally thought to be more likely to induce viral escape mutants than drugs targeting intracellular proteins, like the viral polymerase, particularly if directed to conserved regions. However, in the pivotal trial that led to the approval of Xofluza in the United States, virus variants with amino acid substitutions conferring reduced susceptibility to the drug emerged in nearly 10% of patients (*N. Engl. J. Med.* **379**, 913–923, 2018). Much of that reduced susceptibility was associated with a change to a single amino acid (isoleucine at position 38) that is conserved in 99.9% of influenza A and B strains.

Even so, Frederick Hayden, professor emeritus of medicine at the University of Virginia School of Medicine and a veteran of influenza antiviral research, says he is "pretty upbeat" about arrival of the RNA polymerase inhibitors. More compounds directed at a range of different targets means that clinical researchers can explore new paths. The clinical research community "hasn't had the tools until recently," he says, to properly test whether drug combinations can increase the potency of treatments and reduce the risk of resistance.

Charles River Labs hit by hackers

Cyber-thieves infiltrated the servers of one of the largest contract research organizations in the world and made off with client data, in just the latest incident to highlight the cybersecurity threat in the biotech and pharma industry. Charles River Laboratories said in a regulatory filing on 30 April that a "highly-sophisticated, well-resourced intruder" had broken into its computer systems in March and copied data from about 1% of its customers. Because the company focuses on preclinical and drug discovery work, the data stolen would not have included patient data. In an update to clients posted on its website, Charles River said it did not believe any of the data were deleted, corrupted or altered. The company has now closed the access point that led to the breach, set up monitoring systems and implemented a remediation plan. One of the Charles River customers affected was Nivien Therapeutics, a now-defunct start-up that tried to develop a pancreatic cancer drug. In a post on Medium, Nivien CEO Nathaniel Brooks Horwitz said, "The cyberattack exposed the identity of our therapeutic target and potentially valuable structure–activity relationship data: how the structures of our molecules affect their function—and therefore their therapeutic application. Were we still in business, the breach may have jeopardized our endeavor." Last year, the US government's National Counterintelligence and Security Center cited biotechnology as a key hacking target, stating in a report that "biomaterials, biopharmaceuticals and new vaccines and drugs" are "of particular interest" to foreign hackers.

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"**Someday I will be on TV. So many people will come.**" Prabhat Soni, who runs a private business out of a townhouse in Brooklyn, New York, expresses confidence that his stem cell practice, which charges $5,000 for one injection of amniotic cells, is poised to grow. (*ProPublica*, 7 May 2019)

"**We really need to have very significant clinical trials.... But it's hard to get funded, because there are a lot of doctors already doing it. What if we find out it doesn't work? Then you've got a very large revenue stream that's going to disappear.**" Susan Solomon, CEO of The New York Stem Cell Foundation, comments on a burgeoning cottage stem cell industry that still lacks clinical data. (*The New York Times*, 13 May 2019)