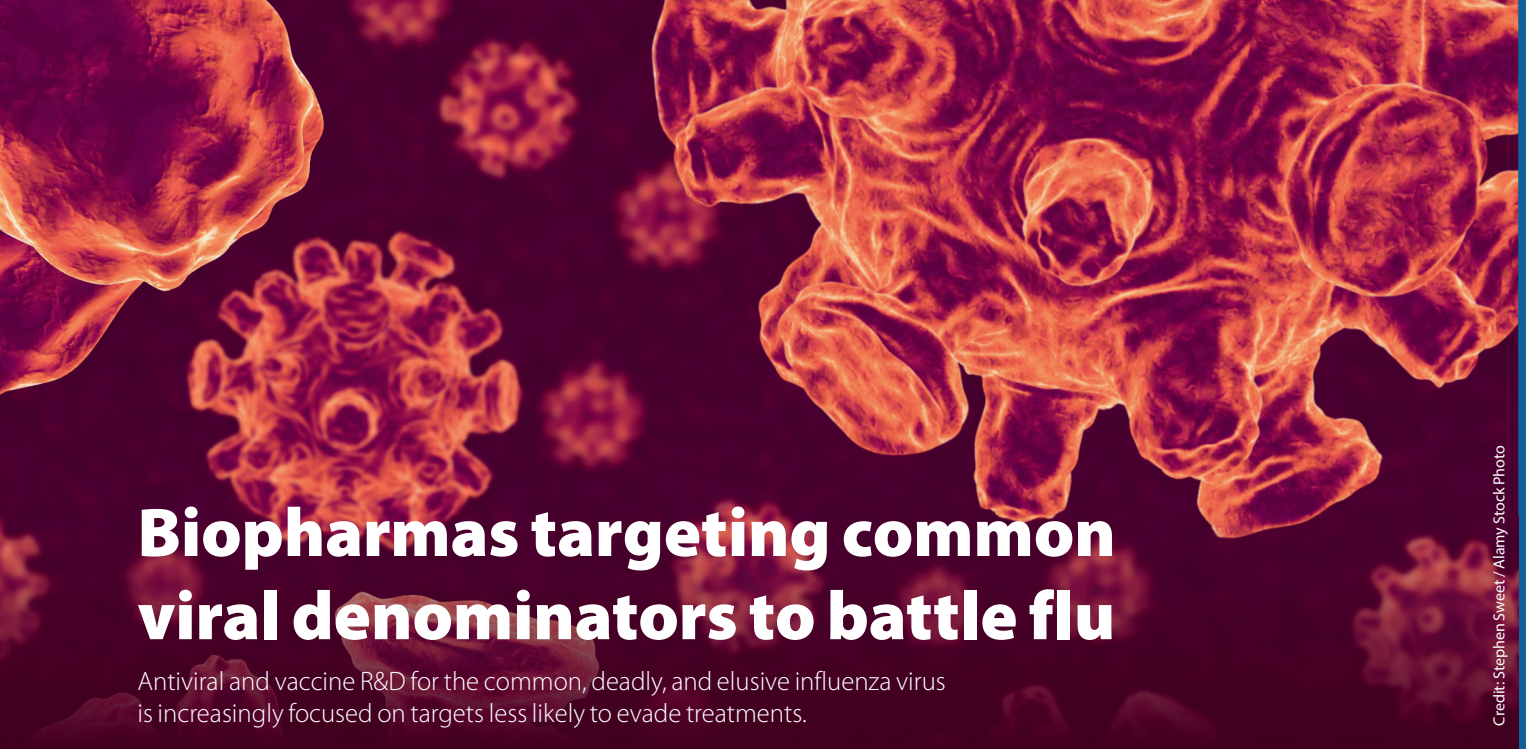

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Biopharmas targeting common viral denominators to battle flu

Antiviral and vaccine R&D for the common, deadly, and elusive influenza virus is increasingly focused on targets less likely to evade treatments.

Chris Morrison

Flu is a deadly, annually recurring epidemic, killing hundreds of thousands of people worldwide in a typical year, in particular those in vulnerable populations such as the immunocompromised or the very young and very old. Despite the severity and ubiquity of flu, however, there are only imperfect and limited treatment options. The best flu defense remains seasonal vaccines, which must be designed half a year before researchers know exactly which strains of the ever-changing virus will strike. These guesses, like choosing a wrench from a toolbox before knowing the size of the nut to be tightened, can misfire and erode the public's confidence in the vaccines, dampening their use. As such, drug and vaccine makers are laboring to develop an arsenal against flu targets that remain the same from year to year.

Infectious disease in general and flu in particular is not a hotbed of venture capital investment like oncology. Nevertheless, in the past several years an influx of capital from government agencies such as the US National Institutes of Health and philanthropies including the Bill and Melinda Gates Foundation has rekindled industry efforts in flu antivirals and vaccines. The biopharma industry's flu pipeline is therefore growing, and dealmaking in influenza may also be picking up in what has been an under-the-radar field compared with other virology hotbeds such as hepatitis B and hepatitis C. Furthermore, influenza has also become a proving ground of sorts for a handful of novel therapeutic modalities, including prophylactic mRNA-based vaccines.

Antiviral opportunities

It is two decades since the most widely known antiviral drugs for flu—Roche's Tamiflu (oseltamivir) and GlaxoSmithKline's Relenza (zanamivir)—reached the market. Both target neuraminidase, an enzyme that has a key role in the viral life cycle (**Fig. 1**). However, while these drugs represented an important advance, in some cases the reduction in the duration or severity of flu infection from therapy is small, and resistance to the drugs has been reported, underlining the need for improved alternatives.

As part of this search, drug companies have moved beyond neuraminidase. In 2016, Osaka, Japan-based Shionogi & Co. struck a deal with Roche for global rights (outside Japan and Taiwan) to baloxavir marboxil, an inhibitor of polymerase acidic endonuclease, an enzyme the flu virus uses to replicate; financials were not disclosed. The US Food and Drug Administration (FDA) approved the drug—a pill taken just once—for uncomplicated flu in people aged 12 and older in October 2018 under the name Xofluza. And in March 2019, Roche asked the regulator to approve the drug in high-risk populations; a decision is expected in November 2019. Xofluza is effective against a variety of flu strains, including those that have become resistant to Tamiflu.

Other large biopharma companies are pursuing next-generation flu antivirals too. Among them is the virology behemoth Gilead Sciences, which has a long history in the field, having discovered oseltamivir, which it licensed to Roche in 1996 for $10 million upfront plus milestones and royalties. In July 2019, Gilead said it licensed three preclinical antiviral programs from Novartis, "including investigational agents with the potential to treat human rhinovirus, influenza, and herpes virus." A Gilead spokesperson described the company as "broadly interested in serious viral respiratory infections" but declined to detail the flu asset in the Novartis deal. Gilead paid Novartis an undisclosed upfront fee and is on the hook for up to $291 million in development and commercial milestone payments related to the programs, plus royalties (**Table 1**).

Also signalling its interest in the area, Merck & Co. inked a flu alliance with Cocrystal Pharma, an antiviral-focused structure-based drug design specialist in January 2019 (**Table 1**). Merck is funding the collaboration's R&D efforts and could pay up to $156 million in upfront and milestone payments. The collaborators have not disclosed the targets they are exploring together, though Cocrystal is separately developing its lead preclinical candidate CC-42344, an inhibitor of the PB2 subunit of flu RNA polymerase. Daria Hazuda, vice president of infectious diseases and vaccine discovery at Merck & Co. and CSO for the company's exploratory science center in Cambridge, Massachusetts, said Cocrystal's platform gives it insight across multiple strains of influenza virus, so the companies can identify targets "that are most conserved and that are, in principle, the hardest for the virus to mutate to generate resistance to small molecules."

Johnson & Johnson has also added several flu antivirals through business development. In 2014, it licensed pimodivir (formerly VX-787) from Vertex Pharmaceuticals for $30 million upfront plus milestones and royalties. Pimodivir inhibits the PB2 unit of the influenza RNA polymerase (**Fig. 1**) and is in two global phase 3 studies: one is testing the drug in hospitalized adults with complicated influenza A infection and the second is treating high-risk patients in the outpatient setting, said Jason Chien, vice president and head of respiratory infections R&D at J&J's Janssen pharmaceuticals unit. It is notable that these trials are evaluating pimodivir with standard of care, which is typically Tamiflu, which also points to the emerging possibility of combination therapy in flu. J&J also picked up the phase 1 candidate AL-794 (now known as JNJ-5806), which targets flu RNA polymerase, via its $1.75 billion acquisition of Alios BioPharma in 2014—a deal that was driven by the private virology company's expertise in discovering nucleoside

analogue antivirals against respiratory syncytial virus, flu, hepatitis C and other viruses. A 2013 pact between Janssen and the Scripps Research Institute has so far yielded multiple preclinical candidates. In late 2018, researchers from the two organizations reported that a multi-domain antibody targeting hemagglutinin and delivered by AAV gene therapy protected mice from flu infection (*Science* **362**, 598–602; 2018)— potentially forming the basis for a human vaccine. And in March 2019, a separate group of researchers from the two organizations reported that a small-molecule inhibitor of a highly conserved region of hemagglutinin was effective against a group of common flu strains in preclinical studies (*Science* **363**, eaar6221; 2019). The compound mimics the binding of broadly neutralizing antibodies against that viral protein; although such antibodies have been considered as flu-fighting therapies, an orally available small molecule has many practical advantages over a biologic (Janssen discontinued the latter program because although it was scientifically interesting, it was not effective against influenza B, said Chien).

Other companies are attempting to target host proteins to hobble the flu virus. Provention Bio's PRV-300 is an anti-TLR3 antibody that the biotech licensed from Janssen as a potential treatment for ulcerative colitis. In May 2019, it was announced that the drug met safety and tolerability endpoints in an early-stage trial in ulcerative colitis, but it was not effective. Provention says it may pivot toward flu and other viral infections, since excessive TLR3 signaling—triggered by the presence of viral RNA—contributes to morbidity and mortality in animal models of severe influenza. Finally, Atriva Therapeutics' lead candidate ATR-002, a MEK inhibitor, entered phase 1 in May. Atriva says ATR-002's inhibition of MEK—a well-trodden target in various cancers—interferes with formation of functional flu virus particles.

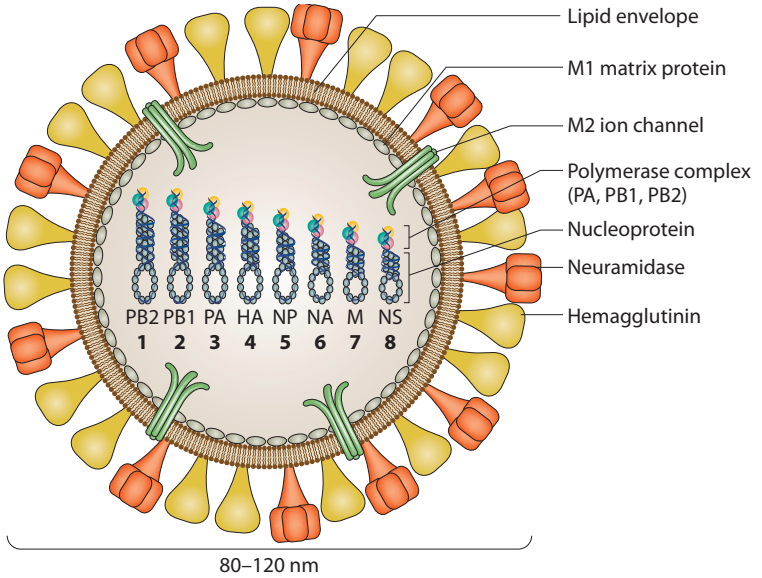

Fig. 1 | Structure of the influenza A virus. All three distinct types of flu virus (A, B, and C—of which A infects humans most virulently) are RNA viruses that code for 11 proteins, including hemagglutinin (HA) and neuramidase (NA) which are spike-like proteins found on the surface of the virus. Influenza A's subtypes comprise 18 HA and 11 NA variations, the H and N numbers the viruses are identified by—for example, H1N1. These viruses can be further subdivided into various strains.

Platform potential

Emerging technology platforms may provide new approaches to fighting the flu virus, or enable improvements in existing vaccine strategies. For example, an mRNA vaccine would take only 3 months to design and manufacture, compared with 5–6 months for conventional seasonal flu vaccines, which are typically produced in chicken eggs. This would give the World Health Organization more time to make a more accurate prediction for the strains that should be covered by each season's vaccine.

Moderna has used flu as a proving ground for its mRNA vaccine platform, although flu is not one of its commercial priorities. The first human studies of that technology read out in May 2019, showing that vaccines targeting H10N8 and N7N9—two strains of avian flu that crossed over into humans in recent years—were highly immunogenic and safe in healthy volunteers. During the company's September 2019 R&D day, the flu programs took a back seat to Moderna's cytomegalovirus vaccine mRNA-1647, which is being moved into phase 2. The flu vaccines, similar to other public health-oriented vaccines against Zika virus and chikungunya, will only advance subject to external funding, the company says. In 2013, Janssen allied with Curevac on an mRNA flu vaccine; although that partnership has dissolved, CureVac's CV7301 mRNA influenza vaccine remains in preclinical development. And in August 2018, the mRNA platform company BioNTech teamed up with Pfizer to develop mRNA vaccines against seasonal flu, in a deal worth $120 million upfront, including a $70 million investment in BioNTech. The partners expect to begin a clinical program by the end of 2020.

Table 1 | Selected recent influenza development deals during 2018–2019

Date	Licensor	Licensee	Financials ($ millions)	Deal summary
August 2018	BioNTech	Pfizer	$425 (including $120 upfront of which $70 was an equity investment in BioNTech)	BioNTech signs $425 million deal with Pfizer to collaborate on the development of mRNA vaccines for influenza
September 2018	MedImmune (AstraZeneca)	Vir Biotechnology	$343 (including 10 upfront)	Vir Biotechnology licenses VIR-2482 from MedImmune
January 2019	Cocrystal Pharma, Inc.	Merck & Co.	$156	Cocrystal Pharma signs potential $156 million deal with Merck & Co. to develop certain influenza A/B antiviral drugs
July 2019	Vaxart, Inc.	Janssen Vaccines and Prevention B.V. (Janssen)		Vaxart partners with Janssen to evaluate the use of its oral vaccine platform for the development of an oral vaccine for Janssen's universal influenza vaccine program
July 2019	Novartis	Gilead	$291	Gilead signs partnership deal with Novartis to develop three preclinical antiviral programs against three undisclosed targets to potentially treat rhinovirus, herpes and influenza viruses
July 2019	Roche	Sanofi		Roche licenses Sanofi OTC rights to Tamiflu

Universal goals

The seasonal flu vaccine market, estimated at roughly $3–4 billion worldwide, is supplied by only a few companies, including CSL Ltd, Sanofi, AstraZeneca's MedImmune unit and GlaxoSmithKline. Although seasonal flu vaccines aren't perfect, they tend to be free for most vulnerable people and do often reduce the severity and duration of infection and its spread to others.

So far, a universal flu vaccine that would remain effective year after year has proved elusive. In mid-2019, for example, GSK abandoned development of GSK3277526A, the company's only disclosed universal flu vaccine candidate, after it flunked a mid-stage clinical trial. But several efforts are ongoing. Among these, Janssen is working with the US Biomedical Advance Research and Development Authority (BARDA) on a universal vaccine candidate, said Chien. In May 2018, the NIH's National Institute for Allergy and Infectious Disease began a clinical trial for M-001, a universal flu vaccine candidate from the Israeli biotech BiondVax Pharmaceuticals. And in October 2019, the NIH awarded up to $132 million to researchers from Icahn School of Medicine at Mount Sinai to fund development of a universal vaccine targeting a conserved region of flu hemagglutinin. "Hemagglutinin looks like a mushroom and while the head of the mushroom changes frequently, the stalk is much more conserved," said Peter Palese, chair of microbiology at Mount Sinai and one of the vaccine's architects. "The stalk is much more functional, and so it has functional restraints," he said, because it's what the virus uses to enter a host cell.

The Mount Sinai vaccine has also received funding from GSK and the Gates Foundation, and has begun phase 1 testing. The NIH funding is a lifeline—given the high safety and efficacy bars that vaccines must clear, the FDA requires large and expensive clinical programs with up to 50,000 subjects, said Palese. Other groups, including one at Johnson & Johnson, are targeting highly conserved regions of the virus to create universal vaccines, he notes, and those vaccines are emerging from several platforms—they can be expressed in a virus or, in the case of several biotech approaches, messenger RNA.

A July 2019 report issued by the Sabin Vaccine Institute pointed to a confluence of advances in vaccine manufacturing and computational biology that "make the current moment a more promising time than ever to marshal resources toward the goal of dramatically reducing the threat of influenza" with a universal vaccine. In August 2019, the Gates Foundation, alongside the non-profit Flu Lab, announced the winners of its Grand Challenge for Universal Influenza Vaccine Development, which together earned $12 million in grants.

One of the winners was the Oregon Health & Science University, which landed $1.7 million to repurpose its existing vaccine HIV and tuberculosis vaccine platform toward flu. The technology incorporates viral antigens into a benign cytomegalovirus to prompt an immune response, and has been licensed to Vir Biotechnology, which calls the platform 'immune programming'. Vir was launched in 2017 with $150 million from investors led by the Gates Foundation and Arch Venture Partners, and has raised $500 million from private investors in total, and recently filed to go public on the NASDAQ. The company is already pursuing development of the antibody VIR-2482 for the prevention of flu, which it licensed from AstraZeneca's MedImmune in September 2018 for $10 million upfront and up to $343 million in milestones. VIR-2482 targets a conserved region of influenza A hemagglutinin. Under a deal with the antibody engineering company Xencor, Vir has extended the antibody's half-life so that a single dose will last an entire flu season, the company says. Data from a phase 1/2 clinical trial in high-risk populations should be available in the second half of 2020.

Ongoing work in viral sequencing and structural analysis has contributed to the promise of creating a universal vaccine, said Palese. New vaccine technologies like mRNA are emerging and demonstrating long-lasting and effective immune responses, and better adjuvants are being developed, he says. "It might sound incremental, but these are real differences. I'm very hopeful that in a fairly short period of time there will be real progress toward a universal vaccine."

Chris Morrison is a writer for the biopharma industry.