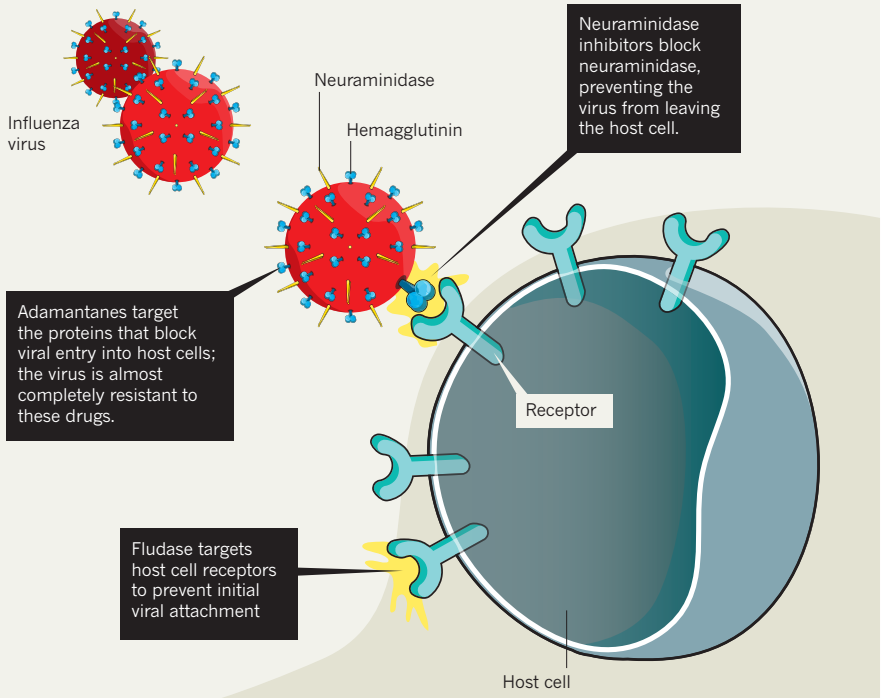
TAKING ON A TOUGH VIRUS

Flu drugs tend to stop working after the virus mutates enough to become resistant to them, and the arms race continues apace.



DRUGS

Lines of defence

Antiviral treatments are a critical component of an effective healthcare response to influenza, but drug resistance to the treatment-of-choice has public health officials searching for other options.

BY ROXANNE PALMER

The influenza virus has adapted to render the first generation of flu antivirals impotent, and there are signs of resistance to newer remedies. In late August 2011, the International Society for Infectious Diseases, based in Boston, Massachusetts, reported that 25 influenza patients in eastern Australia were infected with a strain of the notorious swine flu — influenza A (H1N1) — resistant to the widely used drug oseltamivir (Tamiflu), made by Roche, headquartered in Basel, Switzerland. The Australian case is the largest cohort of oseltamivir-resistant flu yet reported as scientists and pharmaceutical companies explore ways to outsmart the virus.

The good news is that resistance to antiviral drugs is not widespread in influenza strains for the upcoming 2011–2012 season — at least not yet. "Of the circulating strains of influenza in humans, we do not see resistance to oseltamivir," says Charles Penn, an antiviral drug expert with the global influenza program of the World Health Organization (WHO) in Geneva, Switzerland. Although resistance to oseltamivir was reported in as many as 1% of H1N1 flu samples collected during the winter of 2010–2011, says Penn, that level doesn't pose enough of a risk to warrant the WHO to change its treatment recommendations.

That doesn't mean that drug resistance is not a problem. Oseltamivir has successfully treated millions of patients since 1999, but mutations that confer resistance were described as early as 1998 — and given the ever-changing nature of flu, it can be hard to predict the trajectory of oseltamivir resistance. "In a span of two to three years we've seen a blossoming of resistance. At any time, the whole game can change," says Zachary Taylor, an infectious disease fellow at the Kaiser Permanente Fontana Medical Center in Sacramento, California. In part to safeguard against the possibility of such game-changing developments, drug developers are slowly filling the pipeline with alternative therapies (see 'Drugs to treat influenza infection'). Each drug come with side effects, which make them only worthwhile for those whom the flu could be potentially lethal — the elderly and the immunocompromised.

Given the wily history of the influenza virus, any sudden appearance of drug resistance is certain to concern public health officials. The first antiviral drugs to combat the disease — the adamantanes, which target the M2 channel protein to block virus entry into host cells — are now essentially useless. The US Centers for Disease Control and Prevention (CDC) found that 100 % of seasonal H3N2 flu in the 2009–2010 season and 99.8% of 2009 pandemic H1N1 flu were resistant to adamantanes.

Oseltamivir belongs to a class of drugs called neuraminidase inhibitors. These agents block the active site of a viral protein called neuraminidase (N), thereby arresting the influenza virus' ability to leave the host cell after it proliferates. The most common way for the influenza virus to evade oseltamivir is via the H275Y mutation (also known as H274Y) of neuraminidase, which replaces a single histidine amino acid with a tyrosine. This alteration interferes with the drug's ability to bind to the protein — a problem acknowledged by the maker of oseltamivir. "There remains a medical need and room for additional treatment options, especially for the management of severe infections and for improved pandemic preparedness," says Klaus Klumpp, Roche's top virologist. Klumpp says the Roche is supporting research into new therapies targeting viral replication as well as other mechanisms, but notes that these efforts are preclinical.

Fortunately, viruses with the H275Y mutation are still susceptible to a different neuraminidase inhibitor: zanamivir (marketed by UK-based GlaxoSmithKline (GSK) as Relenza). Zanamivir, the first neuraminidase inhibitor discovered, is generally administered by oral inhalation; its side effects include dizziness and nose irritation.

The WHO recommends using zanamivir to treat patients afflicted with oseltamivir-resistant flu strains, and it's already a viable alternative to oseltamivir. Zanamivir was actually the first neuraminidase inhibitor on the market, but its cousin oseltamivir was approved shortly afterwards and captured a larger market share. In January 2011, GSK began a double-blind study comparing intravenous zanamivir with oral oseltamivir. The study, which has enrolled 462 adolescents and adults, is due to be completed in September 2013.

While zanamivir remains an arrow in the quiver to be used in case of an oseltamivir-resistant strain, another drug

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DRUGS TO TREAT INFLUENZA INFECTION

Clinical name	Type of drug	Brand name and manufacturer	Status
Oseltamivir (oral)	Neuraminidase inhibitor	Tamiflu (Roche)	Commercially available in most countries
Zanamivir (inhaled)	Neuraminidase inhibitor	Relenza (GSK)	Commercially available in most countries
Peramivir (intravenous)	Neuraminidase inhibitor	Rapiacta, in Japan); Peramiflu in South Korea (BioCryst)	Available in Japan and South Korea; in Phase III testing in U.S.
DAS181 (inhaled)	Fusion protein	Fludase (NexBio)	Phase II testing in U.S.
ADS-8902 (adamantine, ribavarin, oseltamivir) (oral)	Triple combination	N/A (Adamas)	Phase II testing in U.S.
Amantadine (oral)	Adamantane	Symmetrel (Endo Pharmaceuticals)	Commercially available; not recommended for influenza due to resistance
Rimantidine (oral)	Adamantane	Flumadine (Forest Pharmaceuticals)	Commercially available; not recommended for influenza due to resistance

targeting viral neuraminidase is already available in Asia and might be useful for patients who can't tolerate the other neuraminidase inhibitors. This third neuraminidase inhibitor — peramivir, developed by BioCryst Pharmaceuticals of Durham, North Carolina — is available in Japan (as Rapiacta) and South Korea (as Peramiflu) but is still undergoing clinical trials in the United States. Its known side effects are similar to those of oseltamivir — diarrhea, nausea and vomiting. As an intravenous drug, peramivir can be administered to very sick or hospitalized patients who wouldn't be able to swallow oseltamivir or inhale zanamivir. In October 2009, the US Food and Drug Administration issued an emergency use authorization (EUA) for peramivir for people unable to take oseltamivir or zanamivir. The peramivir EUA expired in June 2010, and although the approval process has been fast-tracked in the United States, general approval of the drug is still several years away; the phase III clinical trial is not expected to be completed until May 2013.

THE VIRTUE OF VARIETY

Other pharmaceutical companies, cognizant of fears of resistance to neuraminidase inhibitors, are exploring a variety of ways to attack flu. One drug making its way along the pipeline is DAS 181, an oral antiviral drug developed by NexBio in San Diego, California, under the trade name Fludase, which is now in phase II clinical trials. The drug is a fusion protein, which is created by combining genetic sequences that encode two or more other proteins into a single protein. It aims to prevent infection by inactivating viral receptors on cells in a patient's respiratory tract, making it harder for the virus to latch onto host cells. A study by NexBio published in 2009 reports that Fludase was effective against 11 oseltamivir-resistant strains of the H1N1 virus — including a couple of variations that showed signs of reduced sensitivity to zanamivir. In September 2011, NexBio presented results from the phase II trial at the Interscience Conference on Antimicrobial Agents and Chemotherapy in Chicago, Illinois, that showed Fludase had cut the level of virus in patients' blood after just the second day of treatment, much as zanamivir and oseltamivir do. However, viral load has not been found to correlate with clinical severity of a flu patient's illness, and its use as a surrogate endpoint is controversial.

Any single flu drug has drawbacks. A mixture of treatments might be a better strategy to combat the virus — and in some cases, overcome resistance. Adamas Pharmaceuticals, based in Emeryville, California, for example, has been developing a three-drug combination treatment strategy of oseltamivir, amantadine — an adamantane drug thought to be obsolete — and ribavirin (another antiviral drug commonly used to treat hepatitis C infection). In cell cultures, the three drugs worked better than any pair, and were even able to inhibit viral activity in strains of influenza resistant to oseltamivir.

Nobody knows for sure how the three drugs work together. Adamas researcher Jack Nguyen speculates that each drug can take out the viruses that slipped past the others — a one-two-three punch combo. "After each stage you have fewer and fewer viruses making it through the cycle," Nguyen says. It may also be possible that oseltamivir's binding to neuraminidase causes other proteins on the virus' surface to change shape and become more susceptible to the other drugs, Nguyen adds.

In April 2010, Adamas released the results of a pilot study of its three-drug combination in seven patients with weakened immune systems. Five of the six patients that received the triple treatment responded by day 10 of therapy. The lone patient that was given only oseltamivir did not respond after 20 days. "This pilot study was an important first step in validating that the combination of three antivirals can provide a virologic and clinical benefit to patients at risk for complications of influenza," says Janet Englund, a clinical investigator who led the trial at Seattle Children's Hospital in Washington. The US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland is recruiting 720 people for a phase II trial testing the efficacy of Adamas' triple combination therapy versus oseltamivir in patients with severe medical conditions, such as heart or lung disease, which make them more susceptible to serious complications from a bout of the flu.

More options are being explored. Recently researchers at the Scripps Research Institute in La Jolla, California, infected mice with a fatal dose of influenza, then gave some of the animals compounds that inhibited their ability to produce cytokines — cell signalling molecules that summon T cells and other immune system effectors to the site of infection. Mice that received these cytokine blockers plus the antiviral drug oseltamivir had a much higher survival rate (96%) than the other experimental groups that received only the cytokine-blocking compound (82% survival); oseltamivir alone (50%); or no treatment at all (21%). This suggests that much of the damage caused by flu is not due to the virus itself, but to an overenthusiastic response from a person's immune system. 'Cytokine storms', triggered by an overproduction of immune signaling molecules, can cause significant damage to tissue. Indeed, the phenomenon is thought to be responsible for a large proportion of deaths during the 1918 influenza pandemic.

Still, targeting the patient instead of the virus has its risks. "When you start tweaking the immune system, you have to wonder about whether you're under correcting or overcorrecting the immune response," explains Dean Blumberg, head of paediatric infectious diseases at the University of California, Davis. Overcorrect, and you exacerbate the problem of cytokine storms; under correct, and you run the risk of leaving the body defenceless against pathogens besides influenza.

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Blumberg says some patients shrug at the idea of using antiviral drugs at all, figuring that once contracted, the disease will simply run its course. In most cases, it will. In fact, neuraminidase inhibitors usually only shorten the duration of illness by about one day, and that's if the drug is taken within 48 hours of the first sign of flu symptoms. Yet Blumberg says that personally, "as a doctor and as a parent" he usually recommends a course of antivirals, to cut down on the length of illness.

With no signs of an avian or swine flu pandemic looming, the need for a wide spectrum of antiviral treatments might seem over cautious. But when warring against viruses, carefully laid preparations made in peacetime may serve well in the thick of the fight. ■

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