several viral hemorrhagic fevers, plague, and tularemia, are in the pipeline, according to Fauci. However, for second- and third-tier threat agents, it is "not appropriate" to seek specific vaccines or antitoxins for each of them, meaning investigators will be encouraged to seek "broader" countermeasures, he says.

Many of these NIAID programs—in part, anticipating the impact of the proposed BioShield initiative—invite and will benefit from greater industry involvement, Fauci suggests. As specific projects move forward, NIAID expects to produce small lots of new vaccines at its on-campus pilot plant, while considerable bioterrorism countermeasures research will be done at other facilities being built on the NIH campus, at Fort Detrick (Frederick, MD), or in still-coalescing 'centers of excellence' that will also serve as 'regional hubs' to respond to 'bioterrorism events,' he says.

Amid these primarily federal and academic research-oriented activities, the BioShield plan is intended to give NIAID flexible authority to expedite reviews and contract arrangements with the private sector. Moreover, Fauci says, "It establishes a secure funding resource for purchase of critical biomedical countermeasures…[including those] that no one may ever use."

Some researchers are calling for even broader, longer-term efforts to thwart bioterrorism. "Bioterrorism is not a short-term problem," says Stanley Falkow of Stanford University (Stanford, CA), who recommends studying microbial pathogenesis very broadly "rather than taking a limited look at microorganisms that might be used in a bioterrorist attack. We can't just study a small 'table' of organisms."

New broad-spectrum antimicrobial agents of any sort represent one of the principal gaps—and opportunities—to which Fauci alluded. Falkow calls the situation for conventional antibiotics "dismal" and "almost a state of emergency." Cassell from Eli Lilly, who chaired the ASM meeting in Baltimore, agrees, saying that the challenges for those seeking new antimicrobial agents "remain formidable." There are "lots of new promising technologies, a significant investment in research over the past decade, and a plethora of targets," she says. "Yet we've come up empty-handed…and this lack of success has dampened enthusiasm and investments."

For now, government and academic researchers are "driving this sector, but industry will come back eventually," says Martin Rosenberg of Promega (Madison, WI), a biotechnology company. "Not only large pharma, but some of the small and mid-sized companies are getting out of antimicrobial research. I think industry gave up too soon on new technologies to develop new products."

Jeffrey L. Fox, Washington, DC

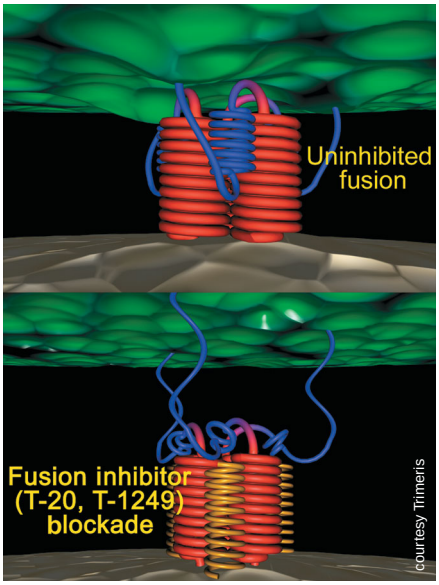
US FDA approves new class of HIV therapeutics

Fuzeon (enfuvirtide), the first in a new class of HIV drugs called 'fusion' or 'entry inhibitors' received final FDA approval in March, making it the first commercially produced synthetic peptide drug. One week later, drug makers Hoffmann-La Roche (Nutley, NJ) and the Durham, NC-based Trimeris, citing the complexity of this technological feat, set the price for Fuzeon treatment at a record-breaking $20,000 a year, with available treatment limited to 15,000 patients in 2003. Despite Fuzeon's status as a breakthrough HIV therapeutic, it remains unclear how many of the 300,000 patients resistant to or intolerant of current HIV treatments will have the insurance or personal wealth to pay for the drug.

"The financial community sees this as an important new drug but opinions diverge as to the number of patients that this drug will be right for," says Michael King, managing director and senior equity research analyst at Banc of America Securities. "Whether the number of patients is 5,000, 50,000, or 100,000, is still unknown."

Fuzeon, also known as T-20, is a 36-amino acid nonglycosylated synthetic peptide that blocks HIV infection by preventing the virus from entering the cell. The peptide mimetic blocks the interaction of HIV envelope glycoprotein 41 with the cell by binding the cell receptor and preventing the fusion of viral and target cell membranes.

Early clinical trials showed that Fuzeon decreased viral loads more effectively when administered as part of the highly active antiretroviral therapy (HAART), a combination therapy that treats the patient with a cocktail of three or more antiviral drugs including protease inhibitors and two classes of reverse transcriptase inhibitors. The peptide, which is administered as a twice-daily subcutaneous injection, was shown to be, when used with HAART, twice as likely to achieve undetectable plasma levels of HIV, with minimal toxicity, in patients who were receiving the antiviral cocktail or were resistant to at least one drug in each of the three classes of antiviral drugs as compared to patients receiving an individualized treatment regimen without Fuzeon. The requirement that the drug be used in combination with others raises the total treatment cost to about $30,000 per year.



Fuzeon keeps HIV out of the cell by blocking the fusion of viral and cell membranes.

In 1999, the US-based unit of Roche Pharmaceuticals agreed to partner with Trimeris to develop and commercialize Fuzeon worldwide. Roche paid $10 million up front to co-develop and market the AIDS drug in the US with Roche holding exclusive marketing rights in the rest of the world. The deal is worth $58 million in cash to Trimeris as the product is developed and sold.

The approval of Fuzeon, however, requires Roche to produce the drug at a rate no pharmaceutical company has ever produced a synthetic peptide. Essentially, Fuzeon is a biological molecule that is manufactured synthetically, much like other small-molecule drugs. It cost 800 million Swiss francs ($565 million) to develop Fuzeon with 50% of the cost associated with clinical trials and 1% with research. The high price tag of drug production is largely attributed by Roche and Trimeris to the complexity of the 110 step manufacturing process and the 42 kilograms of raw materials required to produce 1 kilogram of purified drug—contrasting sharply with the six to eight steps required to manufacturer one small-molecule inhibitor or the

six steps it takes to make Lipitor, a cholesterol-lowering drug which leads product sales worldwide.

The success of Fuzeon, therefore, is largely dependent on managing the risk associated with potential capacity problems, an uninterrupted supply, and a better understanding as to the patient market. Typically, shareholders are better served when the manufacturing process is simpler, minimizing the risks associated with capacity and supply interruptions.

Even so, analysts are optimistic. "I think that [the] financial community is confident that despite the complexity of producing the drug, Roche can overcome the barriers and successfully increase their manufacturing capacity and overcome the production challenges to treat a very sick population," says King. "As they upgrade their Boulder [CO] plant, throughput will increase."

Nevertheless, Trimeris and Roche admit that capacity will be constrained in 2003 with their current Boulder-based manufacturing facility able to supply only 10,000–15,000 patients. "Because of the complexity of Fuzeon manufacturing, we anticipate that the demand will exceed the supply," says Heather Van Hess spokesperson for Roche. "We are ramping up production by increasing the essential manufacturing equipment at our Boulder plant."

Limited production has required Roche and Trimeris to institute a Progressive Distribution Program designed to provide the drug on a first-come, first-served basis, and uninterrupted access for the patients receiving the drug while production is constrained. Until supplies of Fuzeon increase, Roche will distribute the drug through a single pharmacy, Chronimed/StatScript (Minneapolis, MN). The company hopes to be able to provide Fuzeon to 35,000–40,000 patients by 2005 using a more traditional distribution network. "It is very important to be able to promise AIDS patients an uninterrupted supply of Fuzeon once they start treatment," says Robin Fastenau, spokesperson for Trimeris. "In response we have initiated a program where a six-month backup supply of drug will be stored for each person receiving the drug."

Roche and Trimeris do not consider Fuzeon suitable for the treatment of the 36 million people infected with HIV and living in underdeveloped countries. "Fuzeon is not suitable for the developing countries because it is not considered a first-line treatment for the disease," says Van Ness. "There is a lack of infrastructure and the patients are not HIV-drug experienced. The treatment regime requires that the drug be used in combination with other AIDS drugs."

The cost is still a huge consideration. "The drug is expensive to manufacture and the cost will need to be amortized in the richer countries before it is available in the underdeveloped countries," says King. Gilead Sciences announced in early April that it would provide access to Viread (tenofovir disoproxil fumarate), the company's once-a-day antiretroviral medication for HIV, at no profit in every country in Africa and in 15 countries in other parts of the world for $39 for a 30-day supply, or $1.30 per day.

As successful clinical trials in Europe, Canada, and Switzerland lead to global approval and increased use of Fuzeon, Roche will need to evaluate novel methods to improve manufacturing of the drug. When asked why the unmodified peptide drug was not produced in simpler biological production systems, Roche indicated that its "team of experts" had looked into the possibility and had concluded that it was not an "appropriate system."

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