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Southern California: Hot in interior. A few cloud patches on the coast, otherwise sunny. Highs 80s on coast, 92 to 102 elsewhere, except cooler beaches. Details, Page B10.

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New Drugs May Attack Flu, but Not in Time

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Besides the vaccines aimed at preventing flu, new drugs are on the way to treat it once it strikes. But it is not clear whether they will arrive in time to make a difference in thwarting the H1N1 flu pandemic.

New drugs are needed, researchers say, because there are now only four approved flu drugs that work by only two different mechanisms. And many strains of influenza are already resistant either to the two older drugs, amantadine and rimantadine, or to Tamiflu, a somewhat newer drug.

The H1N1 pandemic strain, or swine flu, is resistant to the two older drugs. There have been only sporadic cases of resistance to Tamiflu so far. But if such resistance spread, there would be only one effective drug left — Relenza, which is less convenient to use because it is inhaled rather than swallowed.

The new drugs closest to reaching the market are probably variations or combinations of existing drugs. At a conference in San Francisco last week organized by the American Society for Microbiology, researchers presented data on some of the new approaches.

DIFFERENT DELIVERY Peramivir is a drug that works the same way as Tamiflu and Relenza but is given intravenously.

Infusions would deliver a quicker jolt of drug to desperately ill patients. An intravenous drug could also be used by patients who cannot swallow Tamiflu capsules or inhale Relenza.

A study conducted in Asia showed that a single 15- to 30-minute infusion of peramivir was equivalent to a five-day course of Tamiflu in alleviating symptoms of the seasonal flu.

In the United States, peramivir is not likely to be used for routine treatment of

seasonal or pandemic flu, partly because most primary-care physicians do not administer intravenous infusions. It would be saved for seriously ill patients in hospitals, a need not always well served by existing drugs.

Dr. Frederick G. Hayden, a virologist at the University of Virginia, said intravenous administration "gives a high concentration in the plasma rapidly and makes a lot of sense." But he said peramivir did not appear to work that well against infections resistant to Tamiflu.

BioCryst Pharmaceuticals of Birmingham, Ala., which is developing peramivir with federal financing, is planning a clinical trial of hospitalized patients to seek regulatory approval. But it is hoping that in the meantime the government will stockpile the drug and allow it to be used during the pandemic under a so-called emergency use authorization.

STRENGTH IN NUMBERS A three-drug combination is the standard treatment for H.I.V. and AIDS. Adamas Pharmaceuticals of Emeryville, Calif., hopes a triple combination will also work for flu.

The company's combination consists of two existing flu drugs, amantadine and oseltamivir (Tamiflu), as well as ribavirin, an antiviral drug that is part of the standard treatment for hepatitis C. The three drugs work by different mechanisms to gang up on the virus.

In tests done using cell cultures, the triple combination was more effective than any combination of two of the drugs, Mark Prichard of the University of Alabama at Birmingham, reported. This was true even against viruses that were resistant to Tamiflu or to amantadine. In a sense, the combination seemed to reverse the resistance to those drugs.

Why does this work? "We frankly

don't know," Dr. Prichard said.

Adamas plans to present data from tests in animals soon and is just starting testing in people. So the drug will not be approved for use this flu season.

Since all three drugs are already on the market, a doctor could conceivably prescribe such a combination. Adamas executives caution, however, that they use doses that are different from what is commercially available. The doses were chosen to get the best efficacy and to minimize side effects, like the anemia that can be caused by ribavirin.

GO FOR THE HOST Most antiviral drugs aim at the virus — trying, for instance, to disable an enzyme produced by the pathogen.

NexBio, a small San Diego company, is aiming at the host. It has developed a drug that breaks down the sugar on human respiratory cells that acts as the flu virus's landing pad. This makes it harder for the virus to attach to and infect the cells.

The advantage of blocking a human molecule is that it does not usually mutate. So it is harder for the virus to become resistant to the drug. When a drug attacks a viral protein, the rapidly reproducing virus can develop a mutation that changes the protein in a manner that confers resistance to the drug.

The danger of aiming for the host could be increased side effects. Molecules in the body are not there just to serve as doorways for viruses. They usually have some function, which could be disrupted by a drug. The sugar to which the flu virus attaches, called sialic acid, has various functions in the immune system and in metabolism.

NexBio says its drug, called DAS181 or Fludase, is inhaled and does not spread much beyond the respiratory tract, minimizing side effects.