sels with an antibody caused massive clotting and killed the tumors. And in November, a University of Minnesota team led by S. Ramakrishnan reported in the *International Journal of Cancer* that it had slowed tumor growth in mice by targeting diphtheria toxin to tumor blood vessels using vascular endothelial growth factor, a protein that binds to a receptor that is plentiful in new vessels.

Thorpe notes that his work relied on experimentally engineered tumor cells, so it "didn't directly extrapolate to humans" as Ruoslahti's does. And many in the field favor the latter approach over others that use proteins, because the small peptides are easy to make and use and the technique can be tailored to many different tissues.

The path to clinical trials of the peptide-doxorubicin conjugate looks fairly clear, but oddsmakers know only too well that the favorite out of the gate will not necessarily be the first across the finish line. "We are in very early stages of anti-angiogenesis therapy," says Zetter. "We have to test them all, and go after the best." Where peptide conjugates finish will be apparent only after the race is run.

–Marcia Barinaga

INFECTIOUS DISEASE

Sequence Offers Clues to Deadly Flu

The Hong Kong "bird flu" that has killed four people, sickened more than a dozen, and prompted the mass slaughter of more than 1.5 million chickens in the last month is still perplexing to scientists. Researchers are trying to discover why this virus is so deadly and why, unlike most known avian viruses, it can infect human cells. Now, in a report on page 393, a team from the United States and Hong Kong provides the most careful look yet at the virus—a complete sequence of the genes that code for its surface proteins and partial sequences of the remaining genome. Although the sequence so far can't reveal all of the virus's biological tricks, it offers clues as to how the virus infects cells, and it lays the groundwork for understanding what makes the bird flu a killer.

This particular virus was isolated from a 3-year-old boy in Hong Kong, who died in May after coming down with a flulike disease that did not match any of the known human influenza strains (*Science*, 12 September 1997, p. 1600). It did, however, match a bird strain, called H5N1 because of the varieties of the proteins hemagglutinin and neuraminidase on its surface. H5N1 had infected and killed thousands of chickens in Hong Kong a few months earlier, but no one expected it to jump to humans.

To infect cells, viruses must attach to specific binding sites on the cell membrane, and human and bird sites are different enough that researchers assumed a single flu virus could not infect both species. Avian strains generally have to mix with human flu viruses in an intermediate host, such as pigs, to produce a new variety dangerous to humans. When H5N1 broke this rule, it triggered a public health alarm. Because people had never before been infected by the bird strain and therefore have no immunity to it, epidemiologists worried that the strain could trigger a pandemic.

By analyzing the DNA sequence of the virus, researchers led by Kanta Subbarao of the U.S. Centers for Disease Control and Prevention in Atlanta have now confirmed experts' first hunch: The virus is indeed derived from an avian influenza strain, evidently without an intermediate host. This is probably not the first time such a leap has happened, but it's the first time scientists have been able to observe it directly, says Subbarao.

The team members also have uncovered a possible clue to what makes the strain so deadly to both birds and people. When they sequenced the gene for hemagglutinin, they found an insertion that is common among especially virulent bird viruses but had never been isolated from a human. The insert codes for several additional amino acids right next to a crucial spot where cellular enzymes cleave the hemagglutinin protein. That cleavage helps the protein coat break apart, allowing the virus to infect cells.

Scientists suspect that the cleavage site is key to a virus's infectivity. The enzymes that cleave the most common protein are abundant in the digestive and respiratory systems of birds, and most flu strains can infect only those cells, says team member Michael Perdue of the U.S. Department of Agriculture's (USDA's) Southeast Poultry Research Laboratory in Athens, Georgia. But the extra amino acids may provide an easier—and less specific—target for enzymes, allowing the virus to infect other tissues, including heart, brain, and blood vessels.

APPLE DAILY/AP PHOTO

Chicken fever. The death of Hong Kong's chickens will help protect humans.

Virologist Robert Webster of St. Jude Children's Research Hospital in Memphis, Tennessee, suspects that the insert "allows the virus to become systemic. Instead of just replicating in the respiratory tract, it now can spread through the bloodstream." Poultry victims of the virus suffered general hemorrhaging and death within a few days. It is still not clear whether the virus works the same way in humans, however. None of the human victims hemorrhaged, although several had suspicious kidney failure, says Webster.

The virus isolated from the boy is deadly to chickens, however. The Subbarao team experimentally infected 24 chickens with it, and all but one died. That raises concerns for the USDA, says Perdue. If a human were to carry the flu back from Hong Kong, it could be devastating to U.S. poultry.

What the scientists still don't know is exactly how this flu strain manages to infect humans. To solve that question, Subbarao says, researchers are closely examining a range of avian flu viruses, hoping to pinpoint how this H5N1 strain is different. Webster says he and his colleagues have uncovered one potential clue. In work in press at *The Lancet*, he and his colleagues report that the hemagglutinin of viruses isolated from Hong Kong chickens in March contains a carbohydrate near the site where it binds to cell surfaces, but that molecule is missing from the H5N1 strain isolated from the boy. Webster says the change "may have great influence" on the virus's ability to bind to human cells.

However the virus has altered to allow bird-to-human infection, it still doesn't pass easily between humans. So far, there has been only one suspected case of transfer from one person to another: The toddler's doctor has antibodies to the virus but never got sick. And for now, there has been a drop in new infections—the latest individual became ill on 28 December. But epidemiologists are keeping a wary eye on Hong Kong, especially as the yearly flu season begins. Although no new cases have been reported, officials fear that a currently circulating version could mix with a strain more adept at infecting humans, sparking a pandemic.

The chances of that pandemic are greatly reduced, say most researchers, now that Hong Kong's millions of chickens in open-air markets have been killed. "The slaughter was absolutely essential," says Webster. "The big question is whether the stable door was shut in time."

–Gretchen Vogel