



Peter S. Lu is the president and chief executive officer of Arbor Vita Corporation in Sunnyvale, CA. The company's focus is the use of PDZ domains in human therapeutics and diagnostics in oncology, neurology, and influenza. He also has patent applications in the area of influenza diagnostics and therapy.

## Early Diagnosis of Avian Influenza

THE CURRENT WAVE OF PANDEMIC AVIAN INFLUENZA LOOKS LIKELY TO SPREAD VIA MIGRATING ducks into North America by early fall of this year. Although this form of influenza A virus primarily targets wild birds and poultry, it can infect some mammals. In the few human cases that have been reported (usually only after intimate contact with domestic birds), the infection followed an unusually aggressive course and more than half of the victims have died (on 24 March 2006, the World Health Organization reported 186 human cases and 105 fatalities). The danger is that if the virus adapts sufficiently to allow serial human-to-human transmission, a global human pandemic may rapidly develop.

Vaccination, drug treatment, and containment are all under consideration for influenza preparedness (and are discussed in some detail in the special section in this issue), but their use cannot be optimized unless infection is quickly detected. Early stages of influenza, when transmission first begins, lack distinguishing clinical symptoms and thus require a biochemical test. Because such a test will most likely be used under diverse conditions, ranging, for example, from emergency rooms to airports, it needs to be as straightforward and robust as possible. It should give an answer quickly, ideally in about 5 minutes. It should not require special storage, reagents, instruments, or personnel, nor generate hazardous byproducts such as more virions. It should work on a sample specimen that is easy to obtain and should provide specific information that will distinguish an emerging pandemic strain from seasonal influenza. Perhaps the most challenging requirement is that the test should be resistant to the mutational changes that are characteristic of influenza, allowing us to detect today's virus, not just yesterday's.

Unfortunately, current detection technologies—PCR (polymerase chain reaction), viral culture, and immunoassays—fall short of these requirements. PCR, which analyzes the viral genome, is the most sensitive but is slow (minimum time, 2 hours), requires highly trained personnel, and can miss new viral strains. Viral culture is the gold standard for diagnosis but is even slower (minimum time, several days), is more difficult to perform than PCR, and requires special high-security labs to minimize the risk of release of virions that are formed during the test. Immunoassays, like those used for the familiar home pregnancy test, give rapid results and are easy to perform but currently lack the necessary sensitivity and specificity to distinguish avian from seasonal influenza reliably. The few such immunoassay-based tests that claim to detect avian influenza are purportedly insensitive and are thus unlikely to pick up newly evolving strains.

Is all lost? There are glimmers of hope. Our understanding of the avian influenza virus is growing rapidly, and some of these early insights may be leveraged to facilitate its early detection. Especially important are viral diagnostic targets, such as the abundantly expressed NS1 viral protein that may be used by influenza to inhibit interferon-related host defenses and contribute to its virulence. It appears that this protein exists in a specific form in avian influenza. It could therefore be detected in a rapid diagnostic test by agents that are capable of binding to it but not to the NS1 proteins of typical non-avian human influenza. Such target-based tests will not only permit detection of today's avian influenza but may also be able to detect tomorrow's.

Early diagnosis in the form of a quick point-of-care test is a vital element in our defense against avian influenza. Efforts to develop vaccines and drugs must surely continue, but we cannot rely solely on these interventions. Vaccination presently suffers from the inability to target tomorrow's influenza. Drug treatment can limit influenza's spread, but only when the infection is quickly identified. The power of containment is still our traditional first line of defense against an epidemic, but rapid identification of infectious individuals or animals is crucial to treatment and to containment strategies. Accordingly, we need to put a major effort behind the development of tests that are quick, sensitive, specific, simple, and inexpensive. This may also alleviate the need to extensively train the personnel who administer and interpret these tests. We may or may not need such a test this year, but we will surely have to have it in the future.

— Peter S. Lu

