Cell-based tests tackle predicting safety of antibody drugs

The disastrous trial in the UK in March clearly illustrated one thing: the tests we rely on to predict how a drug will behave in people are outdated. Scientists in Europe are developing new tests to help get a better picture.

In the UK trial, six men suffered severe immune reactions to an experimental leukemia drug. Tests in animals revealed nothing extraordinary, and the investigators ruled out any possibility of contamination in the drug.

There are many unresolved questions about that trial (*Nature* **440**, 856; 2006), but the human body's response to the drug, based on a monoclonal antibody, proved particularly unpredictable.

Up to 30% of experimental drugs fail in clinical trials. Because of differences in immune makeup, animal models are likely to be even poorer at predicting the toxicity of protein-based therapies.

"These types of drugs make up more than 50% of new drug applications," notes Thomas Hartung, head of the European Centre for the Validation of Alternative Methods (EVCAM). "We can't use toxicology that is 60 years old."

In March, EVCAM approved six new toxicology screens based on cultures of human cells. Five of the tests detect pyrogenic contaminants in drugs—for instance, bacteria that can infiltrate injectable or intravenous drugs during manufacture and cause lethal immune reactions. The tests rely on cultured human white blood cells, and might replace two expensive current methods—the Limulus assay and testing on rabbits.

The new techniques improve on both methods. The Limulus assay picks up only a subset of bacteria, but these methods detect most bacteria, viruses and fungi.

Drugs not suitable for the Limulus test, such as monoclonal antibodies and other biological compounds, are typically tested in rabbits. But the tests only provide a simple yes or no for contamination and cannot quantify the amount of toxin. Because of species differences, the immune reaction in a rabbit may also not match the response in humans.

The sixth new test uses cultures of human cord blood and mouse embryonic stem cells to detect low levels of white blood cells—a common side effect of cancer drugs. The test will speed up phase 1 clinical trials of cancer drugs, explains Hartung. Because there is no assay to assess the right initial dose of experimental cancer drugs, scientists now start with a low dose in animals and incrementally increase it till they get an adverse response. Another 9 *in vitro* tests are in the final stages of peer review and 25 more are in the pipeline.

The tests might improve on existing technology, but their use is also limited.

"Cells are not as metabolically active in culture as they are *in vivo*," says Samuel Cohen, chair of microbiology at the University of Nebraska. Cells also don't provide a picture of general metabolism. Animal models are more accurate when the liver can detoxify a drug and alter its potency, for example.

Still, a systematic comparison of existing methods is necessary, says Hartung. "We're asking whether a method is actually doing its job and, if not, coming up with alternatives."

The European Commission in 1991 established ECVAM in response to protests against the misuse of animals in research. Its mission has since evolved to improving toxicology methods. By law, once the agency validates a new technique, scientists within the European Union are required to use it.

Gunjan Sinha, Berlin

Despite doubts, containment plans for pandemic take shape

As the H5N1 avian flu virus continues its relentless march westward, scientists are scrambling to prepare for the possibility that it will mutate into a form that can jump between—and kill—humans. Top among the strategies is a plan to snuff out an outbreak right where it begins, but few experts believe that will work.

Quarantine and other measures limited outbreaks of the severe acute respiratory syndrome in China, but won't contain influenza, says Yoshihiro Kawaoka, professor of virology at the University of Wisconsin in Madison (see page 489). "There's no way, it won't work. Influenza is different," he says.

In August 2005, epidemiologists modeled outbreaks in Southeast Asia and concluded that, given early warning and enough Tamiflu, a human outbreak can be contained (*Science* **309**, 1083–1087; *Nature* **437**, 209–214). But in February, Harvard University researcher Marc Lipsitch argued that the virus is likely to jump to humans multiple times, making containment nearly impossible (*PLoS Med.* **3**, e135).

"If [the jump] can happen in one place, it can happen in more than one place," Lipsitch says. "If it is introduced into more than one site, containment won't work."

Sabah Arar/afp/Getty Images

Free bird: Plans to contain a flu pandemic will most likely fail, experts say.

Still, the World Health Organization (WHO) is embracing containment in its strategy, and plans to fund it out of the avian flu monies pledged at a conference in Beijing in January. A draft containment plan released in March lays out guidelines for national authorities to investigate a cluster of ill people, as well as for launching a full-blown containment effort. The two-phase plan will focus first on tracing the chain of infection, giving antivirals to those closest to the ill, monitoring health and preparing hospitals for highly infectious patients. The second phase may include voluntary and involuntary quarantine, closing of schools, churches, public transport and borders, and the large-scale distribution of antivirals.

The pharmaceutical company Roche has donated 5 million courses of Tamiflu to be rushed to the site of an outbreak. The goal is to get the doses distributed within 21 days, a possible tipping point into chaos identified by the models.

Even the skeptics, including Lipsitch, say the plan is worth a shot. The strategy might buy time to make more vaccines, for instance, might slow the pandemic down, and might improve the infrastructure of the countries, notes Imperial College London epidemiologist Neil Ferguson, who published one of the August models.

"If there is a chance to stop a pandemic, we have responsibility to try it," adds Maria Cheng, a spokeswoman for the WHO. "It is a worthwhile effort, even if it fails."

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