Personalized medicine prompts push to redesign clinical trials

Three prominent cancer organizations are on a quest to redesign clinical trials, saying that additional testing before and during trials will highlight individual differences in drug response and detect successful targeted therapies faster. Their call comes as the US Food and Drug Administration (FDA) in March released its guidelines for personalized medicine.

Traditional clinical trials test for safety first and efficacy later, but that approach fails to take advantage of continuing advances in pharmacogenomics, experts say. "Clinical trials need to be designed so that you know if a drug is working within the first few patients," says William Hait, director of The Cancer Institute of New Jersey.

According to a new model proposed by the American Society of Clinical Oncology, the American Association for Cancer Research and the Association of American Cancer Institutes, early clinical trials should include ongoing analysis of patients' tissue and blood samples. If a drug fails, scientists can determine whether it doesn't work because the target is inappropriate, or because genetic differences stop the drug from hitting the target in some individuals.

Such a design may have prevented the failure of the lung cancer drug Iressa: those trials were well underway by the time researchers identified a mutation in the EGF receptor that underlies the positive response in a small subset of patients (*Nat. Med.* **11** 107; 2005)

Before entering the clinic, scientists should understand the biology of the drug and its target, says Hait. "Then you can begin to predict how a mutation could alter that interaction," he says. Some drug designers are trying to create 'irresistible inhibitors,' compounds that will bind to a target regardless of mutations.

The guidelines also recommend unbiased testing, such as blood-based proteomics assays, to see whether those who respond to the drug show a particular profile. Once researchers identify likely 'responders,' they can design a second clinical trial using only this population. Such a trial is currently underway for Iressa at the Massachusetts General Hospital in Boston.

The organizations plan to test the new design with a small-scale trial of EGF receptor inhibitors for non–small cell lung cancer. James Doroshow and colleagues at the US National Cancer Institute are also trying to designate money to include blood and tissue analysis in clinical trials. Their proposal is expected to be reviewed in June.

Experts hope drug companies will develop diagnostic tools along with new drugs, but at a workshop in April, Janet Woodcock, the FDA's acting deputy commissioner for operations, said that the business model and regulatory path for such markers is not clear. "And I'm not sure it's clear to the FDA either," she said.

The FDA's new guidelines encourage—but don't require—companies to submit data on the impact of genetic variation on drug responses. In March, the FDA also issued dosing recommendations for Asians taking the cholesterol drug Crestor, after research showed this group metabolizes the drug differently. Although such differences are becoming increasingly apparent, the agency says it does not plan to ask for specific studies in ethnic subgroups unless there is a reason to suspect significant clinical differences.

Emily Singer, Boston

Sports law could even the score for women in science

When Harvard president Lawrence Summers said in January that innate differences might account for the low numbers of women in science, he didn't just anger advocates of gender equality—he also energized them. Some have begun wielding a powerful US law that bars sex discrimination in education.

One group has gathered 6,000 scientists' signatures to support using the 1972 law, dubbed Title IX, to address gender discrimination on campuses. Members of the Association for Women in Science, Society of Women Engineers and other organizations plan to deliver the signatures in May to US Senators Ron Wyden and George Allen, who have in the past held hearings on women in science.

Title IX is best known for increasing funding for women's sports, but it also addresses discrimination in employment, admissions and other areas. The law could be used to require institutions to examine—and correct—gender bias in hiring and allocation of resources such as lab space, says Jocelyn Samuels, a Title IX expert at the National Women's Law Center in Washington, DC.

The General Accounting Office (GAO), a government oversight agency, last year examined four federal agencies including the US National Science Foundation (NSF) and the Department of Energy. These agencies should ensure that those who receive funds from them comply with the law, the GAO suggested.

Jim Ketsdever/Contra Costa Times

Fair play: A law known for its impact on women's sports may create equal opportunities in science.

"The laws are on the books … they are just not being used," says Donna Nelson, a chemistry professor at the University of Oklahoma who also studies diversity in science.

Samuels says it might require action by the US Congress—or a high-profile lawsuit—to have Title IX fully applied to the sciences. In the meantime, the GAO report may change how the NSF administers grants.

"NSF is taking that report seriously, there may be compliance reviews coming down the line," says Alice Hogan, director of ADVANCE, an NSF program that provides $19 million in grants each year to address institutional barriers to women's scientific advancement.

A report due out at the end of the year by the National Academy of Sciences may provide yet more impetus. The academy is examining Title IX compliance in tenure, hiring, promotion and resource allocation at 89 universities. Another report by the RAND Corporation will examine gender differences in granting decisions at a few US science agencies and is expected this summer.

A Supreme Court decision in April may also support efforts to boost Title IX. That decision held that retaliation against people who complain about Title IX violations is illegal.

These reports may bring more attention to the issue, but some advocates say many institutions already have the information they need to move ahead. "We have studied this problem to death, we have analysis paralysis," says Nelson. "I think many women are ready for some action."

But the stir around Summers' comments has undoubtedly renewed interest in the topic on campuses. "It's given us more focus and credibility," says Sue Rosser, a dean at the Georgia Institute of Technology and co–principal investigator on the ADVANCE grant there.

Meanwhile, Summers has expressed contrition for his remarks and since charged two task forces to look into the status of women at Harvard—those reports are expected in May.

Charlotte Schubert, Washington DC