

Animal intelligence

Use of animals for testing early in the drug-development process aims to provide vital information to make new drugs safe and effective — and the process is being constantly refined.

Hannah Hoag finds out what is involved.

The decision to carry a drug through to human clinical trials depends on many factors, but safety tops that list. Scientists abandon a huge number of molecules early in the pipeline because of safety concerns — only about 0.1% of compounds that enter preclinical testing move on to clinical trials. The animal-testing phase is a critical piece of the preclinical development of any medicine.

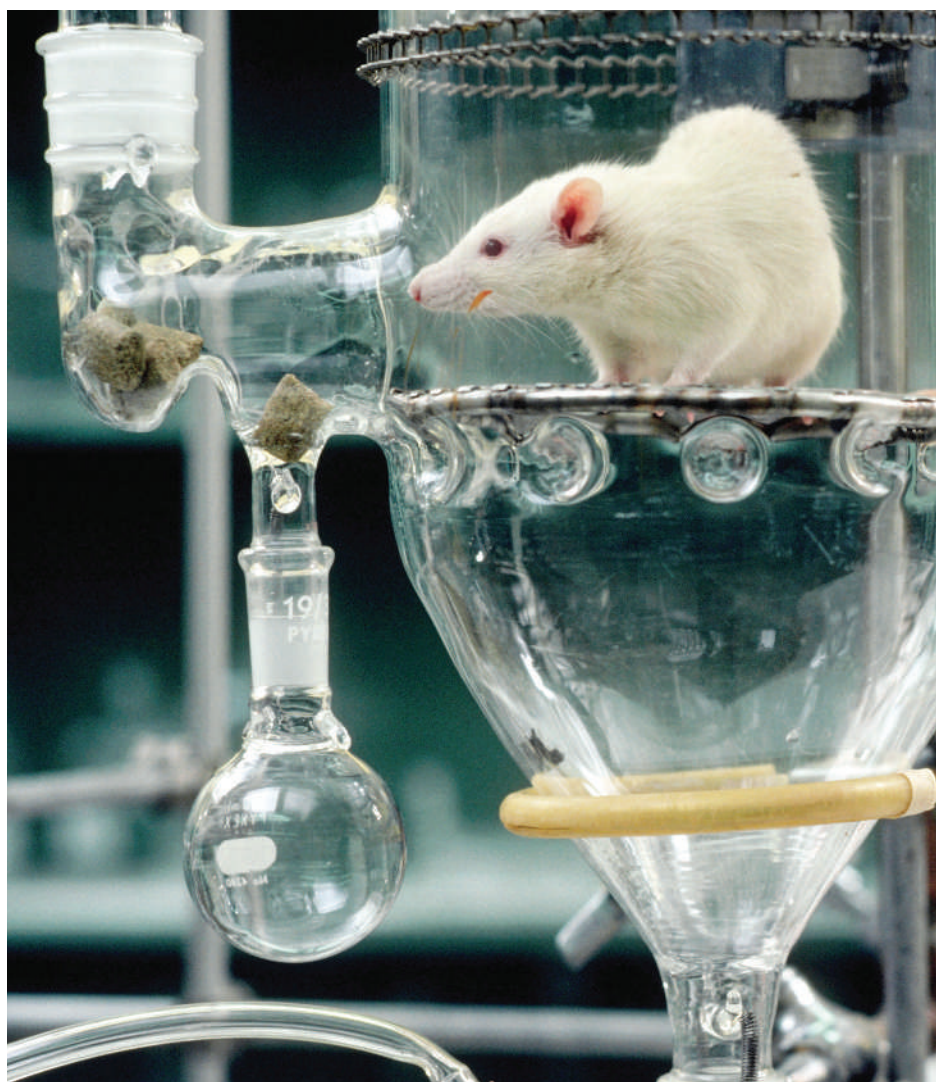
The recent TGN1412 trial, which provoked an extreme reaction in the subjects taking the drug, shows that even now that process isn't a safe bet (see *Nature* **440**, 855–856; 2006). And the highly publicized withdrawal of a handful of blockbuster drugs from the market in recent years has pushed pharmaceutical companies to introduce safety tests earlier in development and to devise novel tests that will allow scientists to halt drugs sooner.

Traditionally, animal-safety studies are done just before clinical trials. The studies reveal a drug candidate's features and its action in the body, but they are costly and labour-intensive. Recently, in an attempt to save time and money, the drug industry has begun to conduct animal studies during the very earliest stages of drug discovery. By doing this, the companies hope to eliminate poor or unsafe compounds earlier in the process. These studies use far fewer animals, or even unconventional drug-discovery animal models such as zebrafish or roundworms, to help scientists decide which compounds to promote to the development stage.

Taking a lead

The involvement of a pharmacologist or biologist with a toxicology background usually starts during 'lead identification', when drug candidates are being picked out, and 'lead optimization', when they're being tweaked (see *Nature* **439**, 886–877; 2006). Early safety studies in animals are becoming more routine. "It gives a discovery scientist the confidence to either take the molecule forward in the discovery chain or drop it and prioritize other molecules," says Geeta Sharma, associate director for biology at GVK Bio, a contract organization in Hyderabad, India, that provides chemical, biological and clinical services.

During these early stages, scientists concerned about a drug candidate's pharmacokinetics — its absorption, distribution, metabolism and elimination — work closely with medicinal chemists to find the right molecules to pursue. These molecule-builders make a series of slightly different structures and send them for



Clear value: early tests aim to weed out harmful drugs.

safety evaluation in animals. The results are then sent back to the medicinal chemists so that they can tweak the molecules further. "The key thing is the rapidity with which the data are generated, which then cycles back to our colleagues and partners in medicinal chemistry and affects the next series of structures," says Michael Silber, head of safety and technical services at Roche's Palo Alto facility in California.

Next come formal animal studies, which are carried out under laboratory practices that comply with industry standards and follow regulatory agency guidelines. "These formal safety assessments form the basis of filing with regulatory agencies to show that the molecule is safe," says Kevin Stark, Amgen's senior director of strategic operations.

Such tests lay the groundwork for human clinical trials. The US Food and Drug Administration (FDA) requires data showing that "the drug is reasonably safe for use in initial, small-scale clinical studies". At the very least, a company must provide a pharmacological profile, including absorption, distribution, metabolism and elimination; determine acute toxicity in two animal species; and conduct short-term toxicity studies, usually lasting 28 days, to mimic human use. The term ADME-tox describes this battery of tests. The goal of ADME-tox testing is to maximize safety and efficacy predictions so as to minimize drug-development costs.

"We are trying to understand what the drug does to

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normal animals, typically a rodent and non-rodent species, and making sure there is a therapeutic window,” says Scott Biller, head of chemical discovery at Novartis. “It is probably the most important aspect of the preclinical development phase — to characterize the toxicity of your molecule relative to efficacy.”

Drugs typically fail in the preclinical phase because of poor pharmacokinetics or toxicology. “Poor bioavailability, poor blood levels and too short a half-life are a major cause,” says Jon Mirsalis, director of preclinical development at SRI International, a contract research organization in the business of discovering and developing new medicines. “Poor pharmacokinetics probably kills 60–70% of the drugs that die in preclinical. The other 30% die for toxicology reasons.”

Quest for data

New tools, such as genomics, proteomics and the use of biomarkers (physical or molecular indicators of treatment efficacy or disease progression), promise to improve clinical success rates. “It has to do with cost, reducing animal use and getting better data early on. If you are confident that this drug is going to shut down enzyme X, you had better have some data that that is happening, and if you can’t show that, you had better not move the drug forward,” says Mirsalis.

Toxicogenomics continues to flourish as a predictive tool. Using tools such as microarrays, this relatively new genomics approach looks for changes in gene expression in live animals in the days following treatment, rather than waiting for the physiological and biochemical changes that might occur two to four weeks after treatment begins. The speed of testing helps identify compounds with toxic liabilities before too much time and resources have been invested.

Novel animal models that will detect failures earlier are slowly being introduced. In its Critical Path Initiative, the FDA called for new animal models to test the safety of novel drug candidates, estimating that a 10% improvement in predicting failures would save US\$100 million per drug in development costs.

One trend is for improving current animal models and adding to their complexity. But emerging *in vivo* models that use species such as roundworms, fruitflies and zebrafish are also gaining ground. Although these animals have long been a mainstay of biological sciences, they remain relatively novel to the pharmaceutical industry.

Zebrafish may provide opportunities to accelerate the process of drug discovery (L. I. Zon and R. T. Peterson *Nature Rev. Drug Disc.* 4, 35–44; 2005). Their tiny size,



Jon Mirsalis: looking for skills and leadership.

large numbers, rapid development and transparent bodies make them suited to high-throughput screening.

Although less established than traditional mammalian models, zebrafish are easier to use, faster and inexpensive, says Nina Sawczuk, co-founder and chief executive of Zygogen, a biotech company based in Atlanta developing zebrafish models of human disease and toxicity for use in drug discovery. “The drug companies we’re talking to are very interested in using zebrafish for toxicity screening early to validate targets and prioritize compounds,” she says. Novartis recently established a Models of Disease Center (located in Cambridge, Massachusetts, and Basel, Switzerland) to develop zebrafish models of diseases for pharmacological studies, alongside the company’s development of mouse models.

How to stand out in a crowd

Whether it’s drug candidates or job candidates, choosing those with the greatest potential depends on a variety of factors. Job candidates with a PhD from a world-class institution will stand out, but without relevant work experience offers will remain scarce. Interpersonal skills and evidence of leadership are as important. “There are those who have a 4.0 and graduate *summa cum laude*, but the résumé is blank. They are not what we are looking for,” says Mirsalis.

Graduates in toxicology, pathology, biology and lab-animal science are popular. “They should have some knowledge of the behaviour of a molecule in living systems and the adverse effects it could cause,” says Stark. Maths graduates may find entry-level jobs doing biostatistical programming for ADME-tox groups.

“Experience at a discovery company definitely helps,” says Niranjan Reddy, director of human resources at GVK Bio. “For a junior scientist, it is more important to be able to handle animals and conduct experiments, whereas a senior position would require knowledge of a particular therapeutic area.” The breakdown of experience depends on where your talents will be focused. Weeding out drug candidates during the early stages requires a better understanding of the disease area, whereas ADME-tox studies require a solid understanding of animal models of disease and handling animals, says Silber.

Scientists carrying out formal safety and toxicity studies typically have a higher degree and several years of experience, perhaps as a postdoc in a toxicology lab. Veterinary qualifications are also common among this group, says Ken Batchelor, senior vice-president of GlaxoSmithKline’s centre of excellence for drug discovery, metabolic and viral diseases.

Hiring practices can be difficult to predict, but contract research organizations tend to fare well in a variety of economies — deCODE Chemistry in Woodridge, Illinois, recently doubled the size of its drug safety and metabolism team. Business at SRI has tripled in six years, boosting the preclinical development group from 35 to 95.

Elsewhere, both large and small drug companies are eager to fill spots in *in vivo* pharmacology, ADME and safety testing. “It’s an extremely rewarding area for scientists to be working in, to select and identify the needle in the haystack that ultimately turns out to be an important new medicine,” says Silber.

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Cheap and easy: zebrafish are gaining ground in toxicology labs.



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