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DARPA dreaming

Replicating the success of the US Defense Advanced Research Projects Agency (DARPA), in an organization devoted to energy research, will be easier said than done.

Everyone always thought DARPA was cool. Last month, in a major study on US competitiveness, the National Academies suggested that the federal government build a new one — ARPA-E — to address energy research.

But what exactly is DARPA — and is it really that special? And if it has a magic all of its own, could it be replicated in a different time and place, when confronting different challenges?

The answer is complex. There's more to the venerable Pentagon research agency than meets the eye. Notwithstanding various Hollywood depictions of DARPA, it has never had any labs or opulent premises of its own. What marks it out, instead, are subtle structural touches that any successful imitator would need to recreate.

Three or four facets of DARPA set it apart. One is the loyal patronage of a leader — President Dwight D. Eisenhower when it was set up in response to Sputnik, and presidents and defence secretaries ever since. Without this support from the top, DARPA would have been extinguished by suspicious rivals in the army, navy and air force.

Second, at least in its hey-day, DARPA was not 'mission-driven' in the manner of, say, the National Institutes of Health. Most people probably think DARPA's role was to meet the needs of the army, navy and air force, but nothing could be further from the truth. The armed forces had their own labs and programmes to do that. DARPA spun out ideas that the forces said they didn't want, or hadn't even thought of. Defence secretaries used it as an agent for the type of sea change that the rest of the Pentagon could be relied on to resist.

Third, the agency has no bureaucracy or infrastructure to speak of. Its annual budget of $3 billion is handled by a director, a deputy director, a handful of office chiefs and a few dozen programme directors, most of them on short tenure.

It does, however, operate an effective congressional liaison office. It is true that some of its work goes ahead without the usual scrutiny because it is secret, but most of it is open and subject to the usual oversight. The committee structure that oversees the Department of Defense is relatively simple, however, and a few champions on Capitol Hill can protect DARPA from meddling. Even then, some observers see a steady grinding down of the agency's soul. They say it is getting more like the National Science Foundation, more "fair". Everyone likes to be fair. But for DARPA, what counts is being agile.

That agility has brought remarkable success over half a century. DARPA concepts led directly to military innovations such as stealth materials and pilotless aircraft, helping to win the cold war. At the same time, it openly conducted pioneering public projects such as Arpanet, which grew into the Internet (apologies to CERN).

Some dissenters — who are given space in the academies' report, *Rising Above the Gathering Storm* — complain about government picking winners, and some even claim that the Department of Energy's sprawling network of laboratories has done just as well as DARPA, dollar for dollar.

But DARPA's track record of success fully justifies the National Academies' call for an ARPA-E. Unfortunately, the academies' report is silent on the obstacles that would need to be surmounted for such a body to work.

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The inside of ARPA-E would be the easy part — smart people recruited at high wages for short periods, backing whatever horse they fancy and cajoling their grantees to push the envelope harder while collaborating intensively. It's the exterior linkages that make the project hard.

The original DARPA had the iron-clad commitment of the defence secretary, the president and Congress. But energy secretaries are marginal figures in the federal government, and presidents may or may not find the time to pay attention. Congressional oversight of the Department of Energy, meanwhile, is a basket-case of greedy and conflicting interests.

ARPA-E is unlikely to fly in the way the academies suggests, unless the energy department is rebuilt from top to bottom. But in different contexts — other nations, for example, facing other challenges — the lessons of DARPA's success are there to be learnt. Their resonance can only grow as research agencies around the world get larger, more comfortable, more audited and more risk-averse. ■

A less toxic solution

Industry should get behind a European partnership that will explore alternatives to animal testing.

A public–private partnership established by the European Commission this week will boost the development of alternative methods to the animal testing of chemicals. More than 10 million animals are used each year in Europe to test chemicals for safety. Now Europe is getting serious about developing alternative approaches (see page 144). Chemical manufacturers and political leaders have joined the animal lobby in embracing the alternatives, partly because of the sheer cost of using animal tests to meet new chemical safety requirements.

The European Commission's enterprise directorate this week hosted a conference on these alternatives, jauntily entitled 'Europe Goes Alternative'. It has taken three years of delicate negotiations to get industry on board, but at the meeting six trade associations representing hundreds of companies signed up to a Commission-led

project with the stodgier name of the European Partnership to Promote Alternative Approaches to Animal Testing. More signatures are expected shortly.

The text of the partnership agreement is rather bland, merely committing companies to agree that reduced use of animals in safety testing is a good idea. But it also commits the signatories to develop an action programme aimed at developing alternative methods. The Commission wants this action plan, which will be based on the sharing of information and the joint development of new approaches to testing strategies, to be in place by spring 2006.

It will need to be. Barring last-minute delays, controversial legislation on chemical testing will get its first reading in the European Parliament this week. The proposed Registration, Evaluation and Authorization of Chemicals (REACH) law would require regulatory approval for all chemicals sold in Europe — including some 30,000 compounds that have been around so long that they've never been registered before. Tests that do not require animals might greatly reduce the costs to industry of obtaining approval.

Scientists at the European Centre for the Validation of Alternative Methods (ECVAM) in northern Italy — which was set up by the European Commission to develop alternatives to animal testing — argue that animal tests are badly flawed. They say the new drive for alternative methods will improve the science of toxicity testing. And public safety demands that the new tests are shown to be better predictors of toxicity than the existing methods.

To this end, ECVAM scientists want chemicals manufacturers to provide more information, including data on compounds that have been tested but not brought to market. Companies are reluctant to share this information for proprietary reasons. But it should be possible to derive shielding arrangements that will enable outside toxicologists to access it, without the release of commercially sensitive information about the products that were tested.

The action plan also calls for the sharing of the compounds themselves. These could be used to compare the efficiency of a new test against existing animal tests. It took ECVAM nearly a year to gather enough compounds to prove the value of its new *in vitro* skin irritation test, for example. The action plan would lead to simple procedures for material transfer that respect industry's concerns over proprietary information.

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Perhaps the most difficult point in the action plan concerns its call for the release of more information on the performance of animal tests: how robust, reproducible and relevant are they? The data so far give grounds for concern. Yet industry has been resistant to this.

If the gold standard of animal tests against which new tests are to be compared turns out to be made of tin, the political fallout would be considerable. Public trust in the ability of regulatory authorities and industry to address safety issues would be damaged. But in the interests of a thorough, economically viable and scientifically valid product-safety testing regime, information about the methods used in the past needs to be shared, and fairly investigated. ■

Flu in circulation

An interim US rule on safeguards may not, on its own, be enough to contain the 1918 flu virus.

The US Centers for Disease Control and Prevention (CDC) has published an interim rule placing the reconstructed 1918 flu virus on its list of select agents, and outlining provisions for its safe handling. But these are just the first steps that need to be taken to assure the public that the virus is in safe hands.

The interim rule, which was published in the *Federal Register* on 20 October, means that the virus may be shared with laboratories in the United States that have registered with the agency (see page 134). Some sharing is needed to accelerate progress in understanding its virulence — but it will also increase the risks of an accidental release. The classification of the virus is welcome, although some virologists would argue that it is overdue, given that the existence of the strain was well known months in advance of its publication (T. M. Tumpey *et al. Science* **310**, 77–80; 2005).

The 1918 flu virus is hard to contain and is capable of spreading rapidly between people. The researchers who work with the reconstructed virus point out that current flu vaccines and drugs provide good protection from it — but these are in short supply, and the threat of an accidental release is real.

The risks of such release during the physical shipping of the virus will be reduced if laboratories choose to construct it themselves, on the basis of the published sequence. But that still leaves the risk of an escape from labs that work with it.

The CDC has ruled that enhanced biosafety level 3 laboratories can work with the virus, rejecting calls for a tougher, level-4 requirement that would have restricted the work to a handful of laboratories. That decision seems justifiable, in the interests of rapid research.

But uncertainty continues to cloud the question of access to the virus for laboratories abroad, where the CDC's writ doesn't run. Already, a biosafety level 4 lab in Winnipeg, Canada, has announced plans to reconstruct the virus.

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No one will question the motives or the security arrangements at the Canadian lab, but the question of international regulation for this and other reconstructed viruses remains fraught. There is no international regime for the mandatory regulation of virus reconstruction, and it is hard to imagine how one could be put together in the time available.

In 1994, however, the World Health Organization (WHO) brokered an agreement restricting the smallpox virus to just two laboratories across the world. National governments should ask the WHO to examine the need for a broader agreement between member states to oversee the distribution of potentially dangerous, reconstructed viruses such as 1918 flu. ■