

Safe in their hands?

Britain's restructuring of research funding and the budget announced last week are welcome. But a cloud still hangs over basic biomedical science.

Every country with any interest in biomedical science and its applications wants to boost 'translational research': the work required to shift biological insights discovered in laboratories towards their application in the clinic. Britain is no exception, and given its scientific and industrial strengths, it is well placed to do so, as part of a drive to deliver the greatest economic return from its scientific investment.

The 2008–09 budget announced last week was fully consistent with this general goal. With a tough review of government spending yet to be completed, Tony Blair's government has nevertheless committed to a growth in science funds of 2.7% above inflation, with increased incentives for industrial innovation.

But beneath the surface, all is not well for Britain's future commitment to basic biomedical research. To consider the money first, the allocated funds have to pay for the new initiatives to boost translational research. But they also have to cover other government commitments, including more realistic compensation to universities for the costs of all government-funded research. These will make substantial claims on the budget of the Medical Research Council (MRC), so the basic biomedical research that it has long supported seems bound to take a hit.

Basic science is vulnerable for another reason: changing organization. Last year, the government announced the removal of funds from the National Health Service trusts that currently control them so the money could be more transparently and rigorously deployed as a dedicated research budget under the auspices of a new National Institute for Health Research (NIHR), working alongside the MRC. Above these bodies sits the Office for Strategic Coordination of Health Research, chaired by John Bell, professor of medicine at the University of Oxford.

This is all to the good. But here too there are devils in the detail. The NIHR will not materialize until 2009 at the earliest, a year later than originally envisaged. There are major negotiations ahead about who has what responsibility for enhancing translational and clinical research and developing the necessary infrastructures. Translational

research is, after all, very different from basic research in terms of its organizational and regulatory requirements and associated costs.

There is no doubt about Bell's belief in basic research. But this top-level development requires healthy cooperation between the various parties involved. It also requires strong leadership at the MRC to protect the interests of basic research. But the MRC's chief executive, Colin Blakemore, and the Department of Health research director, Sally Davies, are reportedly not communicating on such matters. Furthermore, the MRC has been somewhat marginalized in developing bids to the Treasury in the spending review. And its clout is further reduced by the fact that Blakemore's term as MRC chief executive will come to an end later this year, with no replacement in sight.

The MRC faces other challenges, too. Last October saw its appointment of a chair, John Chisholm, who has a strong track record in privatizing defence research laboratories. He has recently sent signals that have left MRC researchers dumbfounded. To judge by recent statements, he views biomedical research as being applied research by definition, and sees fundamental research to be all but irrelevant. A review of MRC governance that he commissioned, to be considered by the MRC's council this week, leaves open the possibility that the representation of basic science on that governing body will be weakened. And it is anybody's guess whether Blakemore's successor will be a sufficiently forceful champion of fundamental research among the various fiefdoms competing for leverage and budgets within the new structures.

In short, despite a seemingly strong environment for Britain's basic biomedical research, an unfortunate combination of issues leaves it looking vulnerable. Translation is one critical route to the biomedical future, but equally important for the MRC are the people responsible for fundamental discoveries, including some with little idea about applying their knowledge outside their labs. Unless Britain's new biomedical hierarchy demonstrably commits itself to such people, it risks losing not only some excellent scientists, but also its ability to retain and attract those very industries on which the country's science-based economic strategy depends. ■

Mutant mice galore

A new consortium will fulfil a genomics dream — provided it gets the support it deserves.

The purpose of sequencing the mouse genome was to further the career of *Mus musculus* as the biologist's favourite model of human disease. The task was completed in 2002, a year after the human genome. To exploit the new knowledge, a catalogue of mutant mice had to be created in the service of biomedical science.

The outstanding questions were just how many genes needed to be individually mutated in mice, and how to set about it.

Some five years later, genetic technologies have developed so fast that the questions have virtually answered themselves. The community at large, in the form of the newly created International Mouse Knockout Consortium, has now declared that each and every one of the 20,000 or so genes in the mouse genome will be systematically targeted and mutated in embryonic stem cells. And all this is only the beginning.

The consortium is now taking requests from the community for genes to be targeted, with the gaps to be filled in later. Soon, if all

goes according to plan, anyone will be able to order an off-the-shelf mutant mouse to test any biological hypotheses or develop any disease model.

The consortium formally launched itself earlier this month with the signing of a cooperation agreement between three funding agencies that together are committing several hundred thousand dollars to the cause over the next five years or so: the European Commission, the US National Institutes of Health and Genome Canada. The signing took place during a two-day meeting organized by the European Commission at a lakeside chateau in Genval, a village just outside Brussels, where delegates from around the world were able to discuss the implementation of the ambitious plan and to dream about the next steps.

The practicalities don't depend only on money. Databases are needed so that the consortium can efficiently share information and avoid duplication. The most important mutants need to be 'phenotyped', or characterized, to record the physiological effects caused by the lack of a gene. This means expanding and standardizing the activities of the 'mouse clinics' that have sprung up, mostly in Europe, to support previous research programmes. The question of how much phenotyping needs to be done during this phase, and on how

many of the chosen mutants, still remains to be resolved.

Grandiose as these plans are, they are but one major step towards the vision of offering an even fuller service to biologists. For example, most of the embryonic stem-cell mutants currently available are 'null' knockouts — the targeted gene simply doesn't function. But, at a greater cost, it is now possible to make 'null-first conditional-ready' mutants. In these, the gene is knocked out by default but can be re-established and knocked out at will in particular tissues at particular times. This flexibility is much more valuable to researchers.

This technology cannot currently be applied to all genes, but it is developing fast. A fuller service would require that more extensive phenotyping be done on each of the mutants. Moreover, a further database is required to document the differences between mouse and human gene function, to ensure a deeper understanding of mouse models of human disease. The full service will be costly.

This vision represents the fulfilment of mouse genome sequencing. Support for that project needs to be followed through: the mouse has already led to excellent insights into many human diseases, and the continuation of this approach will deliver many more. Budgets have tightened, but funding agencies that stay the course can be assured of ample returns on their investment. ■

Cut the climate antics

A long run of congressional theatre should close.

Last week, Al Gore made a triumphant return to Washington, testifying in the US Congress for the first time since his film, *An Inconvenient Truth*, turned the man who was almost president into an Oscar-winning environmental saint. He is now reckoned by almost everybody to have been right all along, and his star turn could mark the moment when Congress gives up arguing about whether climate change is real, and starts arguing about how to handle it.

The affair was suitably raucous, with a burst of camera shutters punctuating the former vice-president's every gesture and scribbling journalists packed in so tight they had to keep their elbows in front of them. Looking solid but progressive in a blue-checked shirt and blue tie, Gore called on Congress to be bold on climate change. "There is a sense of hope in this country that this Congress will rise to the occasion," he said. "We do not have time to play around with this."

Gore also made specific recommendations for action, suggesting changes that are probably too bold for any sitting politician but that may expand the outer bounds of what is considered feasible. They included freezing emissions levels immediately, then reducing them by 90% by 2050; a carbon tax and a cap-and-trade scheme; bans on incandescent light bulbs and new coal plants that cannot be made to capture and store carbon; corporate disclosure of carbon emissions; and tougher mileage standards for cars.

The leading Republicans in the committees where he spoke kept up their increasingly surreal insistence that climate change isn't happening. Joe Barton of Texas in the House of Representatives and James Inhofe of Oklahoma in the Senate not only presented increasingly threadbare arguments against climate change, but seemed to be trying

to take the lustre off the occasion by extensively negotiating how much time they would get to speak.

Inhofe was so determined to get his share of the time that he wanted Gore to respond to all his questions in writing only. He was overruled by Barbara Boxer, the Democrat senator from California who now runs what used to be Inhofe's committee in the Senate and clearly relishes it — at one point she brandished her gavel at him triumphantly. Gore responded to their questions with scientific lectures, deep sighs and offers of one-to-one tutoring in climate science.

More productively, most Republicans asked Gore substantive questions about policy approaches, notably on the challenge of convincing China and India to act, and on the possibility of a renaissance for nuclear power (Gore is wary of it, being an ardent fan of distributed micro-generation). Some Republicans seemed willing to make it their issue too. Republican stalwart Senator John Warner of Virginia said: "I am prepared to fight with you on this." In the House, Bob Inglis of South Carolina framed it as a Christian issue and said that efforts should be made to cut down emissions even without China and India because "you teach your children to do the right thing, even if no one is looking".

In the metro system beneath the Capitol complex, Boxer said that Gore was pleased with the Republican response. As she chatted with reporters, Gore dashed to an adjoining carriage. As the doors threatened to close on him, a Capitol worker reached out and held the door for him. Boxer watched in astonishment. "I've never seen them do that for anyone before," she said.

It was all good theatre, but the high jinks of the climate-change sceptics already seem outdated, and many in their own party are starting to ignore them with the serene expression seen on the faces of parents when their children throw a temper tantrum in public. This is the duty of all sensible politicians as they move forward on climate-change policy. The naysayers should be indulged no longer. ■