Nobel rewards two laboratory revolutions

London. This year's Nobel Prize for Chemistry has been awarded to Michael Smith for his work on site-directed mutagenesis, and Kary B. Mullis for the invention of the polymerase chain reaction (PCR). Both techniques have already revolutionized the procedures used in research laboratories and biopharmaceutical companies.

Site-directed mutagenesis uses mismatched synthetic DNA fragments (oligonucleotides) to alter specific nucleotides along a sequence of DNA. This produces predictable changes in the amino-acid sequence of the translated protein, and makes it possible both to work out the how the different parts of a protein contribute to its function, and eventually to design proteins. PCR also uses oligonucleotides, but in a cycle that lets an extremely small amount of DNA be amplified exponentially. Site-directed mutagenesis and PCR are often combined.

"We were in a unique position to develop site-directed mutagenesis", says Smith, who works at the University of British Columbia in Canada, referring to work carried out with his colleagues. "We had information on duplex stability with mismatches, and at the time one had to be a chemist to make oligonucleotides."

"Few genomic sequences were known, but I was on sabbatical in Fred Sanger's lab, and so had the sequence of the bacteriophage ΦX-174, which was relatively easy to work with because it was single stranded DNA." The prize is "a great honour" he says, because "there are so many scientists doing good things".

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Michael Smith: "in a unique position to develop site-directed mutagenesis".

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Kary B. Mullis: "if the finding's important, it should get the prize".

Kary Mullis, who is now a freelance consultant based in La Jolla, California, was stirred but not shaken by news of his prize: "From what people told me, I figured it would happen eventually, and it might as well be sooner rather than later."

Mullis says that the prize recognizes the significance of a finding and not the work of individuals during their lifetime. "Whether I'm a maverick, weirdo, or whatever, if the finding is important, then it should get the Nobel prize."

Alan Fersht, a 'protein engineer' who is professor of organic chemistry at the University of Cambridge, says he is delighted that gene technology had been honoured by the chemistry prize. "This is modern organic chemistry; for both techniques you need chemistry to make the oligonucleotides and enzymes to finish it off." He says that "site-directed mutagenesis has totally transformed my science".

Peter Little, a molecular geneticist at Imperial College, London, describes Smith and Mullis as a "surprising pairing of winners", but adds that "there was no doubt that they should win the Nobel prize". He welcomes the award for PCR because "it has changed the way molecular biology is done", and made the public more aware of the possibilities of DNA analysis. He says that site-directed mutagenesis is "an incredibly important tool" and that "we have not yet had time to see its full effects on medicine".

Alec Jeffreys, who invented DNA-fingerprinting in his laboratory at the University of Leicester, has used PCR for many applications — including its first use to identify a murder victim. He says he now finds it impossible to conceive of a molecular genetics laboratory without PCR. "Like all good scientific ideas, it's exquisitely simple and, in retrospect, obvious", he says. "I'm sure that thousands of people like myself are kicking themselves that they didn't think of it." **Kimberley Carr**

Prize lifts prospects for gravity wave detectors

London. The Nobel Prize for Physics has been awarded to Joseph Taylor and Russell Hulse of Princeton University for their discovery of binary pulsars. This is the second time that the physics prize has gone to research on pulsars — rotating neutron stars that send a lighthouse-like beam of radiation sweeping through space.

Pulsars were discovered in 1967 by Anthony Hewish of the University of Cambridge and his student Jocelyn Bell. Their observation of oscillations from pulsars at radio frequencies confirmed that when a star explodes in a supernova, electrons can fuse with protons in a highly dense, imploding core to create a compact body composed only of neutrons. Some neutron stars were predicted to have a strong magnetic field, which would cause them to emit intense beams of radiation at each magnetic pole. If the star rotates, the beam appears to turn on and off when viewed from Earth.

While the implications of this discovery lay primarily with stellar and nuclear physics, Taylor and Hulse's observation of a pulsar (PSR1913+16) circulating a companion in a binary system confirmed an important prediction of Einstein's theory of general relativity: that a rotating mass should emit gravitational energy as waves in much the same way as a rotating electric charge emits electromagnetic radiation. This had never been shown experimentally, because the amount of energy emitted is so small.

In 1919, Arthur Eddington provided confirmation of Einstein's theory that a gravitational field represents a curvature of spacetime. Taking the opportunity offered by an eclipse, he observed that light rays from a star are "bent" by the Sun's gravitational field, as the theory predicted.

Taylor and Hulse reasoned that they should be able to detect gravitational waves from their binary pulsar because of the close orbits of the pair — as the binary loses orbital energy, the pulsar's orbit spirals inwards and the period decreases. By 1978, Taylor's group had confirmed that the orbit of PSR1913+16 decreased by the predicted amount of 75 microseconds per year (within errors of 20 per cent).

It was this quantitative agreement (now with much tighter error margins) that provided the compelling test of the theory, says Clifford Will of Washington University, in St Louis, Missouri, who is a specialist on tests of general relativity. He says that the discovery of a binary pulsar was somewhat fortuitous, in that it would have been undetectable had the signal been slightly weaker. But he praises Hulse's persistence in pursuing his observations instead of rejecting them as instrumental artefacts.

Hulse says he was more disappointed than excited when he first noticed that the pulsar's period appeared to vary between observations. He says that with further observations, he became convinced that this variation was not an instrumental artefact, and that he eventually realized it was due to the presence of a companion body.

Although Taylor stresses that he and Hulse had no intention of "setting out to work on relativity", he explains that the

discovery of evidence that gravitational waves from astrophysical systems have observable consequences provided the impetus for proposed gravity-wave detectors, such as the proposed Laser Interferometer Gravitational Wave Observatory (LIGO) in the United States, and the Franco-Italian detector Virgo. Both are huge interferometric systems designed to detect gravitational waves produced from astrophysical events as they wash over Earth.

Hewish, whose discovery earned him the Nobel prize in 1974, says that Taylor and

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Joseph Taylor and Russell Hulse: persistence rewarded.

Hulse's prize should brighten the prospects for these expensive projects, which have fought for survival for years. LIGO's director Rochus Vogt of the California Institute of Technology says that the award is "an endorsement by the Nobel committee of the importance of gravity waves", and "will definitely help [LIGO] in the long run".

Meanwhile, Hulse himself switched to research on plasma fusion at Princeton soon after completing his thesis. One reason, he says, was the lack of long-term opportunities in astrophysics. **Philip Ball**

SSC faces last ditch challenge in Congress

Washington. Three hotly disputed research programmes were each given full funding at a joint meeting last week designed to iron out differences between representatives of the US House of Representatives and Senate.

The conference agreement on the Energy and Water budget bill allowed $640 million for the Superconducting Super Collider, $110 million for the Integral Fast Reactor (IFR) programme and $36 million for the B Factory to be built at Stanford, California. The outcome means a certain reprieve for the IFR, which the House had voted to shut down (see *Nature* **365**, 99; 1993), and that work on the B factory can start immediately.

But the funding for the SSC was still set to face a last gasp challenge in the House earlier this week. SSC supporters were confident that the challenge would fail for procedural reasons, despite the unpopularity of the project in the House. The entire budget, comprising 13 separate bills, is set to be agreed by today (Thursday).

Colin Macilwain

French gene laboratory gets a new lease of life

Paris. Uncertainty over the future of the Généthon laboratory near Paris has ended, following a decision by the French Muscular Dystrophy Association (AFM) to launch two long-term research programmes, one to identify disease genes, the other to work out what they do, and how.

Généthon was set up in 1990 jointly by AFM and the Centre d'Etudes du Polymorphisme Humain (CEPH). It is based at AFM's headquarters at Evry near Paris, and has built a reputation as one of Europe's most advanced gene mapping centres.

Earlier this year, however, AFM announced that it would not support further long-term research programmes after Généthon completed its mapping programme this year. It said that it would instead seek to eliminate bottlenecks in gene therapy research by funding research groups and biotechnology companies (see *Nature* **361**, 671; 1993).

Under new plans, to be announced next month, Généthon II will identify genes using the laboratory's physical and genetic maps of the human genome. Its broader aim is to create a centre of excellence to develop improved positional cloning techniques to be made available to research groups worldwide. The programme will be headed by Jean Weissenbach, who published a 'second generation' genetic map of the human genome last year (see *Nature* **359**, 380; 1992).

Axel Kahn, director of the INSERM Laboratory on Genetics and Molecular Pathology at the Cochin Institute of Molecular Genetics in Paris, will lead Généthon III. This will work out the role and function of genes once they have been identified. In particular, it will test what happens when genes of unknown function are inserted into mice, develop less-empirical ways of assessing gene function, and create animal models for particular diseases.

Généthon II will begin immediately. The start of Généthon III will depend on whether AFM reaches its target of FF400 million (US$71 million) in a television appeal in December (last year it raised FF314 million in this way). AFM plans eventually to back research on vectors for gene therapy (Généthon IV) and clinical trials (Généthon V).

Bernard Barateau, the president of AFM, says that several companies, including Rhône-Poulenc Rorer, are planning to invest in Généthon II and III. The local authority has also made available to AFM land next to Généthon to help it attract biotechnology companies and other research groups to the site.

Private organizations and charities contribute significantly to the French genome effort. The government is keen to integrate such organizations into its national strategy for genome research. François Fillon, the minister of higher education and research, is said to be impressed by Généthon's approach; Kahn says he has also expressed an interest in funding AFM's new programmes directly.

But although GREG funds some research at Généthon, close collaboration between the government-backed programme and AFM has been blocked by a long-standing deadlock between Barateau and Piotr Slominski, the director of GREG. One solution may be that proposed by Fillon to appoint one research organization to take responsibility for co-ordinating each area of biological research.

It is not known if Fillon intends to include genome research in this scheme. But François Kourilsky, director general of the Centre National de la Recherche Scientifique (CNRS), says that CNRS could become the lead agency for genome research. If this were accepted, he says, he would bring together the opposing parties by "imposing fortnightly meetings".

Meanwhile, Slominski is taking comfort from the fact that Fillon has increased GREG's budget for next year. "This clearly shows his willingness to develop genome research", he says. **Declan Butler**

Bid to launch 'European PhD'

London. Scientists from the 12 member states of the European Communites (EC), as well as four non-EC European states, have set up an executive board to oversee the development of a European doctorate in biotechnology. A meeting in Luxembourg last week discussed how the new doctorate could be awarded to those completing a PhD programme recognized throughout Europe, and was told that it might form a prototype for similar programmes in other disciplines.

The initiative has been backed by Antonio Ruberti, the European Commissioner for research, who told the Luxembourg meeting that it was in line with the commission's attempts to increase the mobility of doctoral and postdoctoral fellows within the EC. In addition to the 12-member executive board, the development of the new doctorate will also come under the scrutiny of six scientific trustees, including Nobel laureates Renato Dulbecco and Werner Arber. □