

Testing times: centres will soon be deciphering small genomes alone.

Forces for collaboration falter with human genome in sight

Paul Smaglik, Washington

The cooperation that characterized the international Human Genome Project (HGP) is shifting rapidly towards competition as the project's members vie to decipher the genetic codes of other species.

Leaders of US sequencing centres have described the fragmentation of the consortium as inevitable — especially as the group nears its goal of publishing a draft version of the human genome.

But other researchers wonder if the consortium is breaking up prematurely. They believe a historic opportunity has been lost to build and maintain a distinctively collaborative approach to genomics.

Most of the human genome was sequenced at four centres in the United States and one in the United Kingdom. But many other universities and centres in America, Europe and Japan also took part. The links between the partners have been breaking up more rapidly than some of them had hoped.

Ironically, one of the things driving the sequencers apart is the whole-genome shotgun sequencing technique that once brought them together. The announcement in 1998 by Celera Genomics, based in Rockville, Maryland, that it would use the technique to sequence the human genome before the HGP, helped to galvanize the publicly funded consortium.

Whole-genome shotgun sequencing lends itself to a centralized approach, as any facility with enough sequencers can break the genome into millions of pieces, read them and reassemble them. In contrast, the HGP divided the genome into small segments, assembling the pieces soon after they were read.

The US National Institutes of Health (NIH) tacitly acknowledged the merits of Celera's approach when it revised its plans to sequence the mouse. Initially, the NIH considered applying the same clone-by-clone




Gene shift: Lander says partners will compare notes, not share projects.

technique used by the HGP. But the National Human Genome Research Institute has decided instead to sequence most of the mouse genome by the shotgun method, using the clone-by-clone approach only to build a map to help piece the shotgun data together.

The validation of Celera's technique — and the build-up in the number of sequencing machines at each major centre to prevent Celera from taking the lead — means that individual centres will soon be able to decipher small genomes on their own. The UK Wellcome Trust's Sanger Centre, near Cambridge, is taking on the zebrafish genome alone (see *Nature* **408**, 503; 2000), and the US Department of Energy's Joint Genome Institute in California sequenced 15 bacterial genomes in an October "Microbial Marathon" that also served, in effect, as a declaration of independence.

Richard Gibbs, director of the sequencing centre at Baylor College of Medicine, Houston, says that the loosening of the consortium was inevitable. But he thinks this is happening too quickly. "It makes most sense to enjoy the fruits of its efficiency as long as possible," he says.

Bob Waterston, however, director of the sequencing centre at Washington University in St Louis, says that working alone makes projects easier to manage.

Eric Lander, director of the Whitehead Institute at the Massachusetts Institute of Technology, does not foresee the consortium disbanding completely. Instead, he suggests it will move from sharing projects to discussing the  strategies and technologies. ■

Faster sequencing slows down release of mouse gene data

The whole-genome shotgun technique that has been adopted by members of the Human Genome Project (HGP) is affecting the consortium's ability to follow through on its promises over data release.

Before the high-throughput technique was taken up by the project, consortium members had agreed to place new data on a public database every 24 hours. HGP members had used this standard to differentiate the public project from the private one run by Celera Genomics of Rockville, Maryland. Celera intended to release its human data only on publication.

But the publicly funded centres are now using the shotgun technique to sequence the mouse and other organisms. And they are finding that this makes it difficult for them to stick to their agreement to release sequencing data immediately.

The HGP's initial sequencing methods lent themselves well to daily data release, because scientists could continually combine small fragments of deciphered DNA into larger ones. But shotgun sequencing is more problematic, as the technique requires that the small sequence traces produced daily are not assembled until relatively late in the procedure. And the small pieces are shorter than the HGP's agreement specifies for sequence release.

There is no agreement yet on how to deal with shotgun data. Baylor College of Medicine at Houston, one of five sequencing centres that worked originally on the mouse genome, has placed its own small amount of shotgun data on its website. But the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, is not releasing data on its web page. And the institute — along with Washington University in St Louis and the United Kingdom's Sanger Centre, near Cambridge — is sequencing the bulk of the mouse genome.

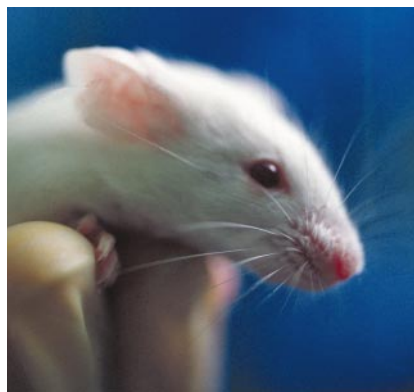
The Whitehead has instead given its data to repositories in Europe and the United States. But these repositories cannot yet accommodate shotgun data. The sequenced mouse fragments have therefore not been made public, even though the total genome of the animal has been sequenced once over.

The data should be available in about three weeks, once programmers have ironed out the technical kinks in the new databases, says David Lipman, director of the National Institutes of Health's National Center for Biotechnology Information.

The public project's switch to shotgun

sequencing will nonetheless require some changes to the HGP's original agreement, says Mark Guyer, assistant director for scientific coordination at the National Institutes of Health's National Human Genome Research Institute, which is managing the US end of the publicly funded mouse project.

Strict adherence to earlier agreements would have meant that the mouse data were not publicly available until the organism was sequenced three times over and then assembled — a milestone targeted for April. Setting up a database of mouse sequence fragments may be an interim solution. "If we had kept to our earlier policy, the data would not have been released for six months," says Guyer. **P.S.**



Shotgun success: the mouse genome has already been sequenced once over.

Publication deal for Celera sparks row over data access

Science magazine has released details of the terms under which it plans to publish Celera Genomics' paper on the human genome — and drawn sharp criticism over the limits that the terms set on data access.

Celera and *Science* have agreed that publicly funded scientists can download up to one megabase of data without signing a material transfer agreement. But privately funded users must sign such an agreement stating that they will not commercialize their results or redistribute the data.

The arrangement has potentially profound significance, some researchers say, because it could set a precedent for scientists to publish papers without unencumbered access to supporting data.

"What will happen if someone else from the academic sector says, 'I have an interesting result to report, but I can't give you all the data?'" asks Harold Varmus, president of the Memorial Sloan-Kettering Cancer Center and former National Institutes of Health director. Varmus was one of several scientists who advised *Science* on the terms. But the advisers are not all in agreement with the announced policy, he says.

When the agreement was announced, Bruce Alberts, president of the National Academy of Sciences, issued a brief statement of support, saying that it may serve as a



Bruce Alberts: deal won't work for private sector.

way to prompt more companies to make their genomic data available.

But this week, Alberts — who says that the statement reflected his own views, not those of the academy — backed off from this. In an interview, he said that the deal could work for publicly funded scientists, but that the terms for private ones appear unworkable. "The data

should be available both to the public sector and private," he says.

The agreement has drawn vocal criticism from some researchers. Ewan Birney, team leader of genomic annotation with the European Bioinformatics Institute in the UK, co-authored an open letter to bioinformaticians attacking the arrangement. He says it is problematic for computational biologists, because they work with large data sets, whose transfer is restricted by the agreement. "This deal is bad for bioinformatics, but palatable for single gene biology," Birney says. **P.S.**

► <http://www.sciencemag.org/feature/data/announcement/genomesequenceplan.shi>

Japan pins hopes on fast-breeder nuclear option

David Cyranoski, Tokyo.

Bucking the international trend towards ending programmes to build nuclear power plants that breed their own fuel, Japan is drawing up plans to reopen its prototype fast-breeder reactor.

The Monju reactor at Fukui, 500 kilometres southwest of Tokyo, has been closed since an accident in 1995, when sodium coolant leaked from a cracked pipe and burst into flames. There were no injuries, but local residents were angered by an attempt to cover up the incident.

Fast-breeder reactors can potentially use uranium fuel many times more efficiently than conventional reactors. But they are expensive to build, and only cover their costs if uranium is expensive, which it has not been. The United States, Britain, France and Germany have all halted their fast-breeder programmes in recent years.

The Monju reactor's reopening is part of a long-term plan released by the Japan Atomic Energy Commission last month.

Japanese officials argue that, because of its lack of fossil fuels and other natural resources, the country has no choice but to develop nuclear energy.

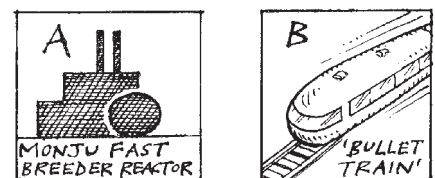
The Japan Nuclear Cycle Development Institute (JNC), which operates Monju, must gain approval from the local governor before it can prepare for the reopening. Officials say operations will resume in 2003 at the earliest and run for 20 years.

Their goal is to show that fast-breeder reactors can operate continuously and reliably, and to establish safe and effective techniques for handling sodium. The JNC says it plans to turn Monju into "an international centre for cooperation, open to researchers from Japan and abroad".

But not everyone is convinced that the JNC is adequately concerned about safety at the reactor. Critics complain about the absence of a properly independent safety commission, akin to the US Nuclear Reg.

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The central government is also



So if A goes critical, you can escape in B.



negotiating the possibility of passing a bullet train through Fukui, where Monju is located, arousing suspicions that the government is trying to buy off local criticism. ■

► http://sta-atm.jst.go.jp/jicst/NC/tyoki/siryo/tyoki_e1208/siryo.htm