NATURE|Vol 464|1 April 2010

THE HUMAN RACE

What was it like to participate in the fastest, fiercest research race in biology? **Alison Abbott** talks to some of the genome competitors about the rivalries and obstacles they faced then — and now.

In many people's minds, May 1998 marked the real start of the race to sequence the human genome. In that month, Craig Venter announced that his upstart company, Celera Genomics in Rockville, Maryland, would sequence the genome within two years. The publicly funded Human Genome Project, which had been plodding along until that point, had a competitor — and each side assembled and prepped its team.

The shotgunner

Venter was willing to flout convention, and he recruited **Gene Meyers** to help him.

As a mathematician at the University of Arizona in Tucson, Meyers had developed a technique for blasting a genome to pieces and reassembling the sequenced debris. But he despaired of ever using this 'whole-genome shotgun sequencing' method on the human genome. The field was signed up en bloc to sequencing the genome piece by consecutive piece to avoid gaps, and Meyer's algorithms had been scorned for being error-prone and unworkable.

At Celera, Meyers never felt he was on the 'wrong side'. He arrived before the computers and furniture did, yet little more than a year later the group had lined up most of the 120-million-base-pair genome of the fruitfly *Drosophila melanogaster* (E. W. Meyers *et al. Science* **287,** 2196–2204; 2000), proving that the shotgun technique could work. The human genome came next.

Meyers still feels sore about his early rejection — "it hurt deeply" — and expresses a gleeful triumph that the technique is now standard in genomics. The academic world was hypocritical, he says. It castigated him for pushing the technique and joining industry, then sneaked him job offers at the first inkling that he might have been right.

When Myers left Celera in 2002, he was looking for a new direction. He eventually found it in neuroinformatics, a field that provides its own computational challenges. Advances in microscopy combined with sophisticated genetic techniques now make it possible to observe how individual neurons behave when genes are turned on and off. Doing this across an entire mouse brain allows biologists to observe development in unprecedented molecular detail — if, that is, they can make sense of the vast numbers of high-resolution images. Meyers is tackling this data challenge at the Janelia Farm Research Campus in Ashburn, Virginia. "Sequences: been there, done that," Meyers says. "Cell-resolution models of nervous systems or developing organisms: daunting but looking more and more doable."

> **"It was an incredible moment, seeing everyone stand up. We felt we had saved the day."** — Jane Rogers

The mega-manager

The huge sequencing effort of the Human Genome Project was biology's first foray into the world of 'big science'. It required big money, and a level of teamwork that came as a major sociological shock to participating scientists. These were the problems with which **Jane Rogers** had to contend as manager of the Human Genome Project for the Wellcome Trust Sanger Institute near Cambridge, UK.

In 1998, Rogers was part of a small posse of senior scientists from Sanger who persuaded governors of the Wellcome Trust to inject more momentum into the project by doubling the

LEFT TO RIGHT: R. MERHAUT; WELLCOME IMAGES; C.-C. ZHU; VO TRUNG DUNG/CORBIS SYGMA; T. FUJIYOSHI

Left to right: Gene Meyers, Jane Rogers, Robert Millman (top), John Sulston and Todd Taylor.

Sanger centre's budget so that it could sequence a full one-third of the genome. The trust's senior administrator, Michael Morgan, revealed the decision to scientists at that year's genome meeting at Cold Spring Harbor Laboratory in New York. The scientists were demoralized by Venter's recent announcement that he was entering the race, and Morgan's news brought the crowd to its feet. "It was an incredible moment, seeing everyone stand up," Rogers says. "We felt we had saved the day."

Back home, Rogers had to cajole and coerce scientists who were used to working in their own small groups into working together on a central project, using standardized methods and procedures. There were emotional moments, she concedes with some diplomacy.

Rogers, one of very few women involved at a high level in the Human Genome Project, developed a taste for big science. After finishing the major sequencing, the Sanger Institute reverted to principal-investigator-led research groups focused on the genomics of human health. But Rogers set about lobbying the UK Biotechnology and Biological Sciences Research Council for funds to establish a centre for sequencing plant, animal and microbial genomes. She now heads the council's Genome Analysis Centre in Norwich, UK, which opened last year— a management challenge that, for her, matches the buzz of the Human Genome Project.

The patent pioneer

Robert Millman believed he'd landed in patent-attorney heaven when he joined Celera as head of intellectual property in 1999. It was Millman's task to work out which of the company's intended products — the human genome sequence, its constituent genes, and the software and algorithms to analyse it — could be patented.

In earlier days, Millman had been a street artist, performing outrageous feats of escapology in his free time. Life at Celera turned out to be similarly challenging. He enjoyed the buzz of testifying in front of Congress with Venter, helping to shape the US patent office's policies in gene patenting. Academics scorned Venter for making a business out of the human genome, but Millman remembers that although Venter "revelled in his bad-boy image, he didn't always act like he really believed in patents and he didn't make my life easy". Millman found himself caught between Venter's academic principles and his business drive, and thought that the company could have pursued patents more aggressively.

In the end, Millman patented 150 genes and proteins that were considered likely drug targets, a handful of 'SNP' patterns linked to disease, and technologies linked to shotgun gene sequencing, none of which Celera fully exploited. Frustrated, Millman says that when he left the company in 2002, he didn't want to hear the suffix '-omics' ever again.

He obviously changed his mind. Millman has since been involved in start-up companies that are pursuing other hot new biotechnologies, including, in 2004, Alnylam Pharmaceuticals in Cambridge, Massachusetts, which has led the way in RNA-interference technologies for regulating genes. In his current position at the venture-capital company MPM Capital in Boston, Massachusetts, he has invested in firms exploring epigenetics and stem cells. Gene patenting, however, remains controversial, even though patents are no longer granted for sequences alone and now require information about a gene's function and utility. Millman still sports his colourful clothes and his red ponytail. Occasionally he yearns to don his straightjacket and ride his unicycle across a tightrope, but, these days, he resists.

> **"The race made for a crazy and irrational time."**
> — John Sulston

The freedom fighter

Whenever Celera put out a bullish press release to reassure shareholders that it was winning the race, **John Sulston** went on television to explain that, actually, it wasn't. "I was a reluctant media star," he recalls. Sulston never worked directly on the human genome, but his work sequencing that of the nematode worm at the Sanger Institute paved the way for the Human Genome Project — and he became one of its most righteous political and scientific champions.

Sulston fought to ensure that sequence data were released daily into the public domain, helping to establish principles at a 1996 strategy meeting on human-genome sequencing in Bermuda that are still largely followed by the genomics community. And he put the kibosh on a compromise with Celera, proposed in 1999, because the company was not prepared to release data early enough to satisfy the public effort's principles. In retrospect, Sulston still thinks it was right to fight. "Otherwise the biological databases that we have today would have collapsed — everything could have ended up in the hands of an American corporation. The race made for a crazy and irrational time."

Yet his battles over the ownership of biology haven't stopped. Now emeritus at the Sanger Institute, he is a part-time faculty member at the University of Manchester's Institute for Science, Ethics and Innovation, which is engaging patent attorneys in heated debate about ownership issues in biology, such as the extent to which donors of biological material deserve compensation. Sulston thinks that the biology should be able to be exploited by businesses but that better checks are needed to stop basic researchers from becoming secretive.

The diplomatic coder

When **Todd Taylor** moved to Japan from the United States in 1998, he was a molecular geneticist in need of employment. Taking a chance, he presented himself as a bioinformatics expert to the RIKEN Genomic Sciences Research Complex in Yokohama, newly created to allow Japan to contribute to the Human Genome Project. Then he started reading up like crazy.

The centre was collaborating on chromosome 21 with another Japanese group and two German teams. He soon found himself as the centre's English-speaking representative at its meetings, and experienced the occasionally sharp edge of international tensions.

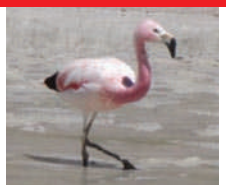
The Japanese side was not well organized at first, he says, and sequenced some parts of the genome assigned to its partners. He recalls a meeting at the Sanger Institute when one of the Germans, beside himself with anger, shouted that by doing so the Japanese had wasted German taxpayers' money.

Once the Japanese groups hit their stride, they bid for the unassigned chromosomes 11 and 18. The researchers flew over to Washington University in St Louis to negotiate with the rival US contingent. "We stepped off the plane and went straight into a three-hour meeting where no one even offered us a glass of water," Taylor remembers. After some fairly hostile bargaining, they came away with a compromise — the long arm of chromosome 11, the short arm of 18 and no dinner invitation. "It was crazy to split the chromosomes that way, but at least I got two *Nature* papers," he jokes.

Taylor, now a recognized bioinformatician, works at the RIKEN Advanced Science Institute that replaced the former genome centre. His group has shrunk from 70 to 20 people. One of his main projects is with the International Human Microbiome Consortium, developing software for analysing the hundreds of microbial species in the intestines of healthy Japanese people. But these and other international efforts cannot rival the Human Genome Project, says Taylor, who calls it "a once-in-a-lifetime project, something the likes of which we probably won't see again. Not that we all wouldn't mind working like that together again. I'd jump at the opportunity." ■

Alison Abbott is *Nature*'s senior European correspondent.

See Editorial, page 649, and human genome special at www.nature.com/humangenome.



M. EUGENIA FARÍAS

VOLCANIC LAKE TEEMS WITH LIFE
Flamingos and microbes thrive in hostile waters.
go.nature.com/kikEKu

What's in a name? Fly world is abuzz

Proposed reorganization of *Drosophila* fruitfly genus might throw out its most celebrated member.

The star subject of genetic research — the *Drosophila melanogaster* fruitfly — may lose its name.

This is an anticipated repercussion of a decision last week by the London-based International Commission on Zoological Nomenclature. It had spent more than two years debating a petition that would have protected the hallowed name while opening the way to a major reorganization of the *Drosophila* genus, which includes at least 1,450 species.

The commission, which oversees the naming of all species, rejected the petition, setting the stage for a likely renaming of *D. melanogaster* and hundreds of related species. Among biologists who study various fruitfly species to link genes to traits, the 1 April ruling was no joke.

"Oh my God," says Therese Markow, a geneticist at the University of California, San Diego, who was reached in the Sonoran Desert, where she was collecting fruitflies. Markow, who is director of the university's Drosophila Species Stock Center, added that extensive name changes could "wreak havoc" in the *Drosophila* literature and databases.

The naming debate began when a US scientist filed a petition with the commission to designate *D. melanogaster* as the *Drosophila* type species — the accepted standard of the genus (see *Nature* **457,** 368; 2009). Kim van der Linde, an ecologist at Florida State University in Tallahassee, wanted to ensure that the name *D. melanogaster* would not change if the genus were divided, as she and other scientists advocate. The genus is extremely large, and genetic data suggest that some of its member species are more closely related to flies outside the genus than they are to other *Drosophila* species.

INDIANA UNIV.

Drosophila melanogaster faces genus reassignment.

In the end, the commission voted 23 to 4 to reject van der Linde's petition. The designated type species will continue to be *Drosophila funebris*, described in 1787 by Johann Fabricius. But the proposal forced the taxonomic world to face the possibility that the genus in its present form may be untenable.

In their written opinions, commission members gave several reasons for voting against the new proposal. Many called it premature because the science about the organization of the *Drosophila* genus remains unsettled. Others sought to limit the naming disruptions that would occur if the genus were split. *Drosophila melanogaster* fits within a subgenus called *Sophophora*, which includes some 350 members. Splitting this group off to form a new genus would require fewer renamings than would be needed if *D. melanogaster* became the type species for *Drosophila*. In that case, roughly 1,100 species would be pushed off into new genera.

"It was very difficult for the commissioners," says Ellinor Michel, the commission's executive secretary. "It was a question of celebrity, as everyone knows *D. melanogaster*."

If a researcher were to use current data to publish a revision of the *Drosophila* genus, *D. melanogaster* would probably become *Sophophora melanogaster*. Van der Linde says that if she and her co-authors from the petition can agree, they may present the case for the change. "Something needs to happen," she says.

But even if the celebrity fly is renamed, Michel noted, it may still be referred to by its original name. ■

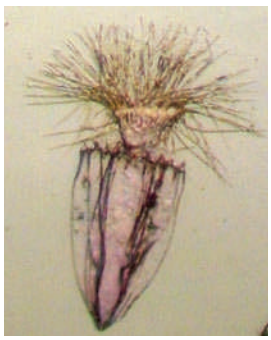
Rex Dalton

Animals thrive without oxygen at sea bottom

Living exclusively oxygen-free was thought to be a lifestyle open only to viruses and single-celled microorganisms. A group of Italian and Danish researchers has now found three species of multicellular animal, or metazoan, that apparently spend their entire lives in oxygen-starved waters in a basin at the bottom of the Mediterranean Sea.

The discovery "opens a whole new realm to metazoans that we thought was off limits", says Lisa Levin, a biological oceanographer at Scripps Institution of Oceanography in La Jolla, California.

Roberto Danovaro from the Polytechnic University of Marche in Ancona, Italy, and his colleagues pulled up the animals during three research cruises off the south coast of Greece. The species, which have not yet been named, belong to a phylum of tiny bottom-dwellers called Loricifera. Measuring less than 1 millimetre long, they live at a depth of more than 3,000 metres in the anoxic sediments of the Atalante basin, a place so little explored that Danovaro likens his team's sampling to "going to the Moon to collect rocks".



R. DANOVARO

Some loriciferans live in anoxic sediments.

Researchers have previously found multicellular animals living in anoxic environments, but Danovaro says that it was never clear whether those animals were permanent residents. The new loriciferans, which he and his team reported this week (R. Danovaro *et al. BMC Biol.* doi:10.1186/1741-7007-8-30; 2010), seem to "reproduce and live all their life in anoxic conditions", he says.

The researchers identified an adaptation that helps these loriciferans to survive in their environment. Instead of mitochondria, which rely on oxygen, the creatures have organelles that resemble hydrogenosomes, which some single-celled organisms use to produce energy-storing molecules anaerobically.

Angelika Brandt, a deep-sea biologist at Germany's Zoological Museum in Hamburg, says that the work by Danovaro's group is "highly significant". The discovery of metazoans living without mitochondria and oxygen, she says, suggests that animals can occupy niches that once seemed too extreme. ■

Janet Fang

Correction
The News Feature 'The human race' (*Nature* **464,** 668–669; 2010) misspelt the name of the architect of whole-genome shotgun sequencing. It should be Gene Myers. This error has been corrected online in the HTML and PDF versions of this story.