SPOTLIGHT ON GENETICS

The changing role of model organisms in genetics

Advances in sequencing technology are giving researchers access to a wide range of genomes, from microbes to mammals. What does the future hold for traditional models?

"The only people we'll go after are those who think at a systems-wide scale, rather than classically trained reductionists."

Eric Schadt, Mount Sinai School of Medicine

EVOLUTIONARY BIOLOGIST Thomas Hunt Morgan may have immortalized the role of *Drosophila melanogaster* in genetics research, but the fruitfly was not his first choice of experimental model. Seeking a short-lived organism that could be easily bred in the laboratory under changing conditions, he tried the mouse, rat, pigeon and even a plant louse before settling on *Drosophila*. A century after Morgan's seminal work on sex-linked inheritance, scientists still use the fruitfly to investigate and demonstrate basic genetic principles. But it is far from the only tool available to modern geneticists.

Techniques for sequencing genes and genomes have developed at ever-increasing rates, and the turn of the 21st century was dotted with announcements of successful genome-sequencing projects, from yeast in 1997 to the tomato in May this year (go.nature.com/Zpz7sB). "What you're seeing is a dramatic expansion in the number of organisms and strains you can study," says Eric Schadt, chair of the department of genetics and genomics sciences at Mount Sinai School of Medicine in New York. The ease with which sequencing technologies can be applied to all manner of species presents a potential conundrum for researchers: should they continue to work on the established models or start afresh with some of the myriad organisms now available?

Advances in sequencing technology could lead to a revolution in research on the fruitfly *Drosophila melanogaster*.

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The Big Five

The well-established 'big five' model organisms for genetics research, as described by Michael Snyder, director of Stanford University Center for Genomics and Personalized Medicine, are yeast, mouse, the nematode *Caenorhabditis elegans*, thale cress (*Arabidopsis thaliana*) and *Drosophila*. Snyder says the number one reason for working with these standard models these days is the wealth of biological information available about them and innumerable proven experimental techniques. His lab tests virtually every technical process on yeast before applying it to other model organisms or humans. "You have this vast database that lets you make connections you wouldn't otherwise make, and discover things you wouldn't normally look for," he says. "That's hard to beat."

Stéphane Noselli, director of the Institute of Biology Valrose (iBV) in Nice, France, who works primarily on *Drosophila*, agrees: "You can answer so many difficult questions with this small organism, from gene function to cell biology and physiology. It's a complete system."

Researchers at contract research organization KeyGene, based in the Netherlands, use *Arabidopsis* to validate new techniques and technologies for crop breeding. "*Arabidopsis* provides us with an ideal test system because it has a small genome that has been sequenced to a high level of accuracy and isn't expensive to use," explains chief scientific officer Michiel van Eijk.

The quantity of genetic information available for these standard model systems is just one of their advantages. They are all relatively sturdy organisms, and — with the exception of the mouse, whose maintenance is more complicated — they are inexpensive and easy to grow in the lab.

Emerging models

While basic cellular or biological problems are more easily solved with standard organisms, established models have been less useful in other, more complex areas. A lack of suitable systems for modeling ageing, for example, has encouraged researchers to branch out. Anne Brunet, Snyder's colleague at Stanford University, works on the killifish *Nothobranchius furzeri*. These fish live in African ponds that regularly dry out, so they complete their life cycle in a couple of months – perfect for studying the ageing process. Eugene Berezikov, one of the first recruits to the European Research Institute for the Biology of Ageing, which opened at University Medical Center Groningen in the Netherlands in January this year, is developing genomic tools to analyse the flatworm *Macrostomum lignano*. The worm's regeneration capabilities make it an ideal ageing model, while its small size, physical transparency and simple culturing techniques mean it can

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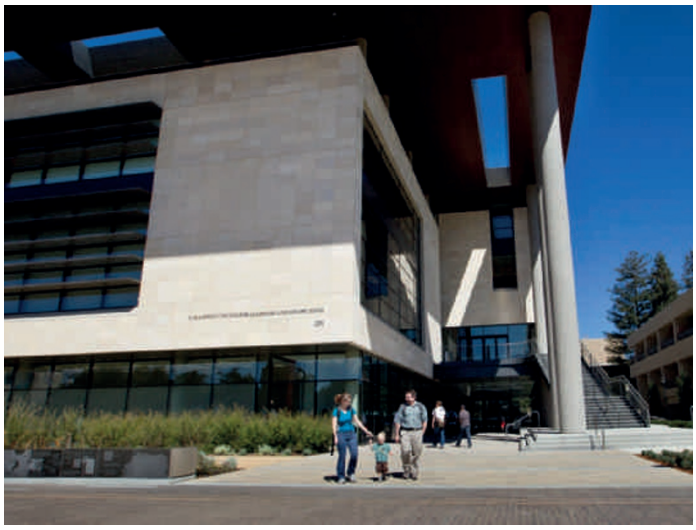
be easily handled in the lab.

The challenge of new models is that researchers start with little established biological knowledge. According to the NCBI's PubMed database there have only been 10 research papers published on *M. lignano*, and just eight on *N. furzeri*; a stark contrast to the figure of 15,477 for *D. melanogaster*. However, Brunet says the hard work that goes into developing a new model organism is worthwhile — as well as providing a valuable new experimental model to a range of scientific communities, it can also be an excellent career move. "Dario Valenzano, who was a graduate student when he jumpstarted the *N. furzeri* project, has set up the model entirely from scratch, developing the first linkage map and creating the first transgenic lines," she says. "He's now likely to focus on this in his own lab."

Advances in sequencing technologies could soon resolve the dearth of data for new models. The availability of cheaper, faster sequencers — Life Technologies now offer a bench-top model that can sequence a genome in a day at a cost of US$1,000 — has led to a plethora of ambitious projects that aim to reveal the genomes of everything from microbes to mammals over the coming years. In October 2011 a group of international researchers published the first findings from the 29 Mammals Project (go.nature.com/omuX3z), an initiative launched in 2005 to identify functional elements of the human genome by comparing it with those of other mammals. The project, led by the Broad Institute in the United States, has sequenced the genomes of 24 mammals, including the rhesus macaque, rat and cow, adding to the five pre-existing sequenced mammalian genomes (human, chimpanzee, mouse, dog and opposum). The Chinese genomics institute BGI, which operates a network of the world's biggest genome-sequencing centres, is involved in over 20 sequencing projects. It aims to sequence 10,000 microbial genomes, 1,000 plant and animal genomes and 10,000 vertebrate genomes, in collaboration with numerous institutions worldwide.

Researchers considering a move to a new model organism need to have a thorough understanding of its biology, says iBV's Noselli. "It involves a lot of investment," he says. The developmental biology department at the Pasteur Institute in Paris, France, now uses *Drosophila*, chick, zebrafish and the emerging vertebrate model organism amphioxus, a fish-like marine animal also known as the lancelet, but this only came about after years of investment in a solid research base of mouse genetics.



Stanford University, where all biology students take programming courses.

In with the old

Although sequencing is opening up a vast array of research avenues, Schadt at Mount Sinai cautions that adapting existing technologies for novel organisms is going to be "a much longer road than we appreciate". He argues that the best short-term use of new tools is to give geneticists a more sophisticated view of existing model organisms; in fact, he believes the field is heading for a revolution in *Drosophila* studies. He and his colleagues have just recruited additional staff to expand on promising work in a *Drosophila* lab at Mount Sinai. "It would be really difficult to develop it all from scratch in a new system," he says. "It's hard to justify."

Both Schadt and Guilio Superti-Furga, scientific director of the Center for Molecular Medicine (CeMM) in Vienna, Austria, predict that technological advances will encourage researchers to further study wild-type strains of existing mutant models, rather than moving straight into new systems. New mutations in established model organisms are also attracting interest. "Some groups are using genome-wide association studies to identify every potential disease risk gene, and making mouse models for each of them," says Christine Van Broeckhoven, professor of molecular biology and genetics at Antwerp University and a director at life sciences research institute VIB in Belgium.

KeyGene's van Eijk adds that researchers will continue to revert to model organisms when faced with the unknown. "Once each technological barrier is broken, there are more questions," he says. "It will always be the case that a limited number of model species stay ahead."

Technically minded

As well as influencing which model genetic organisms will be used in the future, the vast quantities of data generated by collaborative genome-sequencing efforts is changing the field of genetics as a whole. Many leading departments are looking towards informatics-driven investigations and scientists are no longer being hired purely for their laboratory experience. Institutions list bioinformatic and statistical skills as key criteria when taking on new staff. "Investigators must be able to use all the new literature and databases," says CeMM's Superti-Furga. "The next generation of researchers require much more computational skill." Schadt agrees that geneticists need experience of a quantitative subject to be competitive in the field: "Ten years from now you'll be a dinosaur — extinct — if you don't". Knowledge of systems biology is also an asset, he adds. "The only people we'll go after are those who think at a systems-wide scale, rather than classically trained reductionists."

Many institutions have already embedded bioinformatics in their degree programmes. At Stanford University all biological sciences students now have to take programming classes, and the University of Washington set up an interdisciplinary computational molecular biology PhD more than a decade ago.

Robert Desnick, dean for genetics and genomic medicine at Mount Sinai, says computational genomics will be particularly important in research into human disease. Being trained in both computational genomics and biology is "going to pay off at every level of science," he says.

Practical experience of sequencing is also advantageous. For example, the New York Genome Center (NYGC), an independent biomedical research start-up scheduled to begin operations in 2012, is currently "aggressively recruiting lab technicians with experience with Illumina HiSeq technology," according to founding executive director Nancy Keller. The majority of the centre's initial 500 staff will be sequencing and bioinformatics professionals. NYGC's initial research focus will be human genomics, but it will also support the mouse genetics carried out at its founding institutions. "We expect that our focus and mission will evolve over time, and we are open to expanding in the future into other model organisms," says Keller.

Stanford's Snyder says it is important to recognise the intrinsic value of traditional models in translational research as they can help accelerate the discovery of clinically relevant findings. "What we know about the cell cycle was pioneered in yeast; neurobiology, from flies and worms," he says. "That background information can't be understated in terms of its value."

So while there is certainly a place within the genetics field for research and development involving new model organisms, the traditional ones are by no means redundant. ■

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Center for Genomic Science of IIT@SEMM

The Center for Genomic Science of IIT@SEMM (http://genomics.iit.it) located in Milan, Italy, is an outstation of the Istituto Italiano di Tecnologia. The Center benefits from state-of-the art technological platforms including a high-throughput cell-based screening unit, next-generation DNA sequencing and others.

The following post-doctoral positions are available:

Pos. 1, 2 Cancer Biology: Genome, epigenome and transcriptome dynamics in mouse tumor models; forward and reverse genetic screens for modifiers of tumor progression. The projects will involve work with animal models and advanced molecular/cellular biology. PI: Stefano Campaner (Pos. 1), Bruno Amati (Pos. 2).

Pos. 3 microRNA biology: miRNA-mediated regulatory loops and gene expression mechanisms controlling stem cell self-renewal and fate specification in the mouse mammary gland. The project will involve isolation of mouse primary cells, FACS-based cell purification, organoid culture and transplantation. PI: Francesco Nicassio.

Pos. 4 Drug Development: Quantitative chemical proteomics applied to the identification of cellular proteins targeted by selected drugs. Collaborative project with the group of Dr. Tiziana Bonaldi at the European Institute of Oncology (IEO).

Pos. 5 Computational Biology: Development of pipelines for the automatic analysis and integration of different genome-wide datasets (RNA-seq, ChIP-seq, DNA methylation, long-range DNA interactions, mutational analysis); development of statistical and visualization tools. Familiarity with the Linux environment, programming skills (especially in R) will be advantageous; previous experience in genomics is not mandatory. PI: Bruno Amati, with computational supervision by Mattia Pelizzola and Marco Morelli.

Pos. 6 Computational Biology: Meta-analysis of somatic mutations in cancer with the goal of identifying driver mutations and specific mutation patterns. Proficiency in using JavaEE technology, mySQL databases, the Hibernate object relations management framework, statistics or grid computing will be advantageous. PI: Heiko Muller.

Pos. 7 Computational Biology: Analysis of imaging data from genome-wide siRNA screens; bioinformatic analysis of an ubiquitin-dependent signaling pathway. Proficiency with statistics, programming (R, C++ or Python), automated image analysis or analysis of large datasets will be advantageous. PI: Mark Wade

The positions will be subject to Post-doctoral contracts and require a PhD degree with or without post-doctoral experience. Candidates should be proficient with the relevant methods and technologies. Applications should be e-mailed to positions_semm@iit.it and should include a CV, the e-mail addresses of 3 referees and a short statement on professional skills and interests (1 page max). Candidates should indicate in the title to which of the above position(s) they are applying, and should ask three referees to send their reference letters directly to the same e-mail address. Selected candidates will be initially interviewed by Skype.

Application deadline: July 9, 2012

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The qualified candidate should have a Ph.D. in a related field, highly experienced with immunology, cell and molecular biology and biochemistry.

Experience with gene expression profiling, multiplex PCR is a plus. Effective written and verbal communication skills are required.

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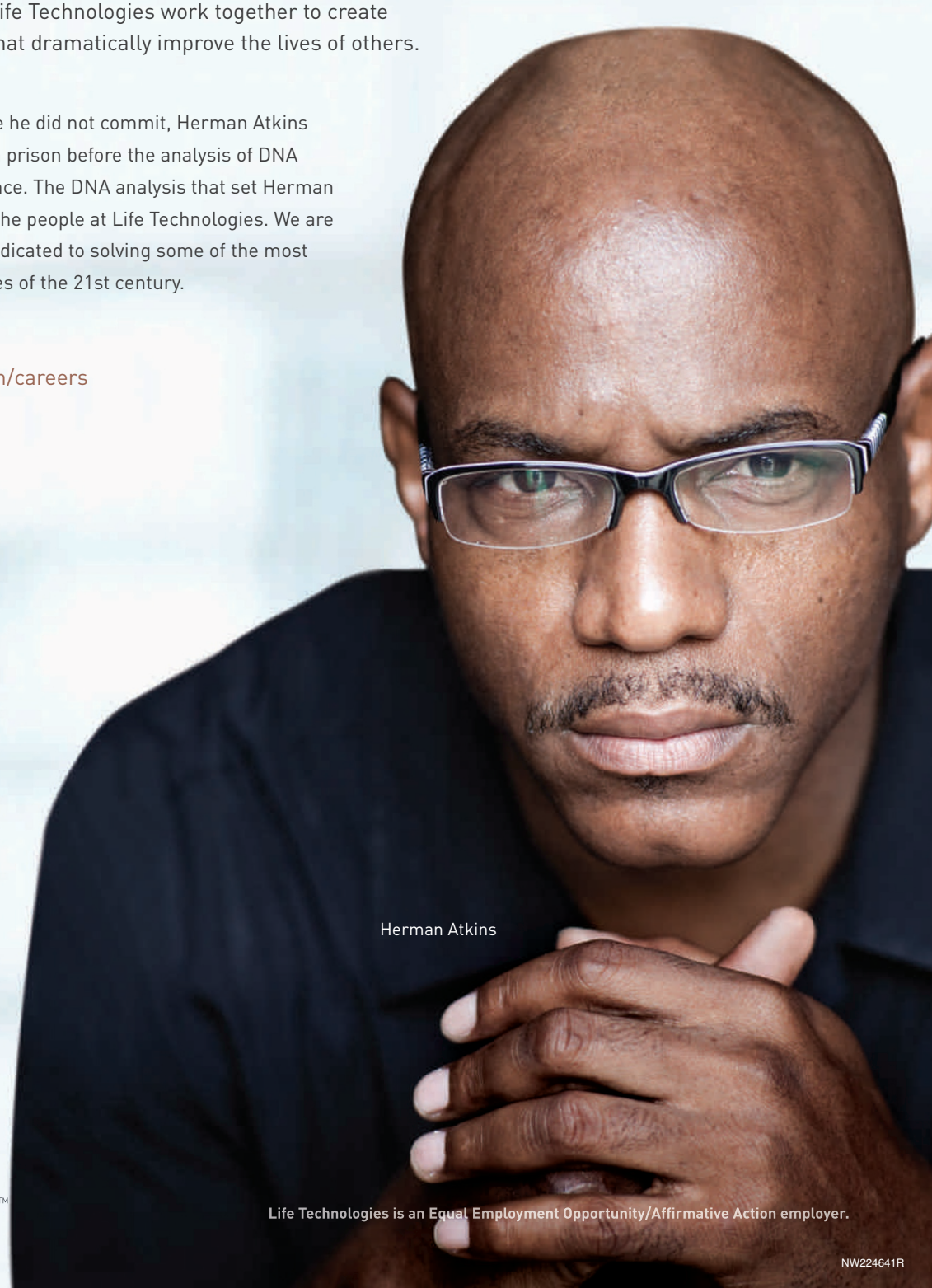

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Max Planck Institute for Plant Breeding Research

A new department of Comparative Development and Genetics at the Max Planck Institute for Plant Breeding Research (MPIPZ) is seeking a group leader in the area of:

Computational Modelling of Morphogenesis

The Department will operate under the direction of Honorary Professor Miltos Tsiantis and will investigate problems of plant development and evolution. The successful applicant will contribute to existing research projects and build independent research activity aimed at understanding plant morphogenesis and its diversity. The successful applicant will work with other research groups in the Department and will also participate in national and international Graduate Partner Programs and bids for external funding. Core funding is available to support activity of the group.

We are seeking a scientist with a PhD and an outstanding record of internationally competitive research accomplishments in computer science and its application in understanding morphogenesis, particularly through the use of geometric models. Experience with the effective and creative use of biological imaging data to support quantitative studies of development would be a strong advantage. A demonstrable ability to collaborate smoothly and synergistically in the context of interdisciplinary projects involving external collaborations is essential. Payment and benefits are according to the German TVöD. The position will initially be for five years. Exceptional candidates may be considered for a tenure track appointment pending review.

The Max Planck Institute aims to increase the proportion of women in so far underrepresented areas. Disabled applicants with equal qualifications will be given preferential treatment.

The Max Planck Institute for Plant Breeding Research (MPIZ) in Cologne (http://www.mpipz.mpg.de/2169/en) is one of the world's premier sites committed to basic research and training in plant science. The institute has four science departments, three independent research groups and specialist support, totaling 400 staff including externally funded positions.

Interested candidates are invited to send applications consisting of:
- a brief cover letter explaining their background and motivation for applying for this post,
- a statement of research plans (up to a page long),
- a full CV including the contact details three referees indicating the reference number by post to:

Max Planck Institute for Plant Breeding Research
Dept. of Developmental Genetics
Carl-von-Linné-Weg 10
D-50829 Cologne, Germany
e-mail: Christiane Wojtera, wojtera@mpipz.mpg.de

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Applications will be evaluated until a suitable candidate is identified.
For informal enquiries please contact miltos.tsiantis@plants.ox.ac.uk.

W225668R

Max Planck Institute for Plant Breeding Research

A new Department of Comparative Development and Genetics at the Max Planck Institute for Plant Breeding Research (MPIPZ) is seeking a group leader in the area of:

Bioinformatics

The Department will operate under the direction of Honorary Professor Dr. Miltos Tsiantis and will investigate problems of plant development and evolution. The successful applicant will contribute to existing research projects and build independent research activity in comparative plant biology using high throughput sequencing (HTS) datasets. S/he will be instrumental in building bioinformatics capability within the new department and will develop strong synergies with colleagues pursuing genetic and computational modeling approaches to study morphogenesis. S/he will participate in national and international Graduate Partner Programs and external funding bids.

We seek a candidate with a PhD and an outstanding record of internationally competitive research accomplishments in bioinformatics and the creative use of HTS datasets to shed new light on biological problems in genetics, development and evolution. Candidates must be highly interactive and willing and able to collaborate smoothly with both biologists and computational scientists. High-level expertise in gene expression analysis and regulatory genome annotation is of particular interest. Payment and benefits are according to the German TVöD. The position will be for five years in the first instance.

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Dept. of Developmental Genetics
Carl-von-Linné-Weg 10
D-50829 Cologne, Germany
e-mail: Christiane Wojtera, wojtera@mpipz.mpg.de

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