Genomics down under

A talk with John Mattick, Director of the Australian Genome Research Facility, and Co-Director of the Institute for Molecular Bioscience

EMBO Reports (ER): Who funds the Australian Genome Research Facility?

John Mattick (JM): It is funded by the Federal Government.

ER: That is the only financial support?

JM: Yes, it was set up with a A\$10 million [Australian dollars] (6.46 million Euro) capital grant. The headquarters are in Brisbane, which concentrates on high-throughput DNA sequencing; the Melbourne division concentrates on high throughput genotyping and mutation detection for genetic epidemiology and positional cloning projects.

ER: Are you doing only high-throughput analysis or annotating too?

JM: Mainly the former. The difficulty is that the Australian Government did not provide the AGRF with funds to actually undertake genome projects of its own. We do assist some of our clients with informatics and annotation, but we recommend that the groups involved in researching the species get heavily involved in the annotation and data mining. We are well served in this respect by the Australian National Genome Information Service in Sydney, which provides web-based access to a wide range of genomic and protein databases and software tools.

ER: So the 10 million dollar...

JM: ...was only for equipment, for robotics, high-throughput sequencing and so forth. Recently, the Australian Government announced a new A\$10 million per year program in medical genomics starting in 2000 with A\$4.2 million. The first round of those projects is yet to be selected. Until now, however, the AGRF has operated simply as a sophisticated

service facility. One of the strengths of the facility is that it provides genomic services for people working across the whole spectrum of biological research, in microbiology, plant, animal and human biology. So, for example, somebody may call up and say 'Can you do a 100 000 ESTs for us?'

ER: This is done as a service?

JM: Exactly, they pay for it at base costs for academic organizations that are publicly or philanthropically funded. Basically, the idea is that people apply for grants to do genome projects through the conventional granting agencies—the National Health and Medical Research Council, the Australian Research Council and so forth—and then use those funds to

have the national facility do the work. This means that AGRF has to be operated in a business-like manner, but it also means that at this stage, the AGRF has been unable to act in a strategic way. The other problem is that there have been few funds available to Australian groups to do this type of work. I feel that the framework for genome research in Australia has not been as well thought out as it might be, partly because its importance has until recently been poorly appreciated, even within the scientific community. But, this is probably the case in many places.

ER: And that had nothing to do with medical genomics research?

JM: Yes and no. The National Health and Medical Research Council were strong supporters of the establishment of the AGRF, but initially there were no funds for genome-scale projects available. The situation is still pretty bleak, especially in the non-medical areas, although there are reasonable funds available in the area of agriculture and livestock. I have pointed out for some time that it is illogical to fund a genome facility but not genome research, and I think the establishment of the Program in Medical Genomics has been partly a response to this. In the meantime, we have used some of our reserves to fund some lead projects in-house, just to get something moving—for example, we are currently sequencing a psychrophilic archaea isolated from Antarctica, in collaboration with Dr Rick Cavicchioli from the University of New South Wales.

ER: And what will the medical genome program look like?

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JM: The intention is to fund perhaps five to eight projects a year, ranging from sequencing of pathogens and model organisms to high-throughput genetic epidemiology. The high-throughput work will be done by the AGRF. The results will go back to the laboratories, which is a good arrangement in many ways, although building critical mass in key areas of genomic science and bioinformatics will be difficult. Nonetheless, this is a welcome improvement in terms of the activity in genomics research in Australia.

ER: Australia is just a minor player in genomics research.

JM: Yes—unfortunately.

ER: And do you see Australia being an important player in genomics research with a budget of US\$6 million in genomics research plus your sequencing facility? You are competing with the USA and their biotech industry, the EU and Japan.

JM: Under the present circumstances, no. The Program in Medical Genomics is a step in the right direction but at the present level of investment, Australia cannot really compete as well as it could. On the other hand Australia has the advantage that its research base is strong; in genetic epidemiology, we're one of the world leaders. My feeling is that, and I've written about this in the Australian papers, unless that situation is improved rapidly, Australia will struggle to be the significant player in biotechnology that it wishes to be.

ER: Are there signs that the government is improving funding and support?

JM: There are some good signs. Two of the state governments, Queensland and Victoria, are now investing heavily in biotechnology and in basic research infrastructure. But at the present time, the Federal government still does not seem to fully understand how important this is. For example, they announced a few months ago a new 'initiative' in biotechnology—A\$30 million over five years, that's US\$4 million a year. Compare this to the \$1 billion for biotech in Singapore or the new £650 million Irish initiative. But I think the winds are starting to blow in the right direction.

ER: What about co-operation; are you as a region co-operating with other countries, particularly with Singapore?

JM: We're trying to. I was just talking to Frank [Gannon] about the Asian-Pacific International Molecular Biology Network, the A-IMBN, which is an umbrella organ-

ization that is shaping up to be a kind of Asian EMBO. It's still early days and the problem is that we do not yet have government support for A-IMBN in the region, primarily because it does not sit easily under the umbrella of APEC [Asian-Pacific Economic Cooperation]. Nevertheless, like EMBO and EMBL, this could be an important vehicle by which we can provide a constructive framework for science and technology applications and cooperation in molecular biology and biotechnology.

ER: So how is the biotech industry in Australia doing?

JM: Well, not bad—it is starting to take off. There have been a substantial number of start-up companies established in Australia over the last few years, some of which are doing quite well. We're also starting to see the development of strong biotech clusters in Melbourne and Brisbane.

ER: Mainly in medical research?

JM: Yes, primarily. A good case would be Biota, which recently developed and then sub-licensed to Glaxo-Wellcome an anti-flu drug called Relenza, which has been approved in Europe, Australia and the USA. And this was one of the first examples, if not the first example, of rational drug design based on crystallographic structures of the virus neuraminidase—Australia is very strong in crystallography and structural biology. There is a whole range of companies at different stages of maturity. The problem in Australia is that the tax rules have until recently not been very favourable for this sort of high-tech risky investment.

ER: And you probably need something like a high-risk investment market?

Big investment houses in Australia are starting to see the considerable value in biotech

JM: That's right, and in fact the Australian government recently looked at the situation in Britain, Europe and the USA and has now adjusted the tax rules to make it more favourable for investment in high-tech industry. Also, the big investment houses in Australia are now starting to see the considerable value in biotech and starting to invest in risky high-technology start-ups.

ER: Science also profits from the stock market. The establishment of NASDAQ and the Neuer Markt in Germany have boosted high-tech start-ups there.

JM: Yes, and if you plot the rise in All Ordinaries index over the last couple of years, and then you plot NASDAQ, and then you plot the genomic companies, even the NASDAQ curve goes flat. So the biotech companies, particularly the genomic companies, are out-performing NASDAQ by a long way, which again is out-performing ordinary companies by a long way. The technology sector as a whole is growing quickly. And Australia is in a fortunate position as it now has substantial national savings because of the institutionalized superannuation or retirement funds and so there's billions of dollars available there. And if some of those funds could be harvested to invest in high technology, with the appropriate mix of strong basic research and middle-stage investment, then Australia has a chance. Australia is one of the top six or eight countries in the world in terms of research and scientific publications. But my concern is that without really informed and solid investment in genomics and associated areas, we are going to miss a huge opportunity. For a country like Australia that wants to build a more sophisticated, high-tech future, it has to go with its strengths in medical, biological and agricultural research, and it has to go quickly when new trends emerge. It's not too late, but it's late in the day.

ER: There are genomics companies, particularly in the USA now, which started a debate about the use of results... as there was the debate about Celera trying to sell all genomic information. Do you see any problems in regard to patenting or buying services—particularly with companies in the USA?

I think industry is now driving the research agenda, more than the universities or research institutes

JM: Well, it's interesting that you bring that up. I'll make two comments. One is that much of the innovative research is now being done in industry, particularly in the USA, although it must also be said that

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this has been underpinned by massive public investment. And Celera has been far more influential than anyone else. The second thing I have to say is that we've just made an agreement with Celera: all of Celera's human, mouse and *Drosophila* databases, including all of their tools and polymorphic information, are now being made available to Australian scientists and researchers.

ER: In industry and academia?

JM: No, just in academia. It means that any publicly funded research group in Australia can obtain access to Celera's databases and associated tools. The arrangements for intellectual property and publication are very comfortable. So we will be the first country in the world to have the use of the human and, just as importantly, the mouse genome sequence. I am particularly pleased about this, as I was involved in negotiating it. It means that not only the big institutes, but also hospitals and small universities in Australia can be looking at the unpublished data and this will accelerate the transition to genomics and computational biology in Australia. So I think that despite what we've said about the very poor investment in Australia into genomics and into research generally compared with other countries, this is a very good step in the right direction. It was announced, just before the end of June.

ER: What was Celera's incentive to give this information to the Australian research community?

JM: It's not for free, we're paying for it. But it's a modest cost by any standards. I actually think that Craig Venter, and this is a personal view now, is unfairly criticized and that much of the motivation for that criticism has come from politics and professional jealousy. He is a visionary who thinks outside the square. His sin has been to do it outside of the square and do it better. It is worth pointing out that about half of all the genomic data in the public databases that we all use has been generated by Craig Venter and his colleagues, either from TIGR or Celera. He certainly has revolutionized genome science and changed the way that people think, all the way from EST sequencing to shotgun sequencing. Craig Venter has just been unjustly demonized. And a lot of this goes all the way back to NIH wanting to patent his EST data. One of the hypocrisies and double standards here is that scientists in most universities and other public institu-

tions around the world are expected by their universities, and by their governments, to capture the intellectual property that is generated from their research, to assist the economy of the country and/or the finances of the university.

ER: This view is particularly strong in the USA.

Society now says, rightly or wrongly, we invest in research because we want to drive economic growth

JM: But it's true. Society says, rightly or wrongly, we invest in research partly because we want to understand our world and improve human condition, but also because we want to drive economic growth. So the people that do the research have a responsibility to protect their intellectual property, and we are under pressure to do so in Australia, like people are around the world. Scientists at the NIH, scientists at the universities in the UK, and elsewhere, have for ages been patenting genes or chemicals or new engineering designs, whatever.

ER: So why hasn't the Australian government seen these economic chances in the biotech area?

JM: I don't know. I think—I have to choose my words carefully here—the key people in our federal government do not seem to be interested in science and technology, or perhaps do not understand its relationship to the economy. They come from a background that has sympathy more with marketing than it does with the real top end of industry. I think the key people just don't see it, but we're working on it.

ER: Is there, as in Germany or Britain, a strong public perception against biotechnology?

JM: I think the political and social view of biotechnology in Australia is somewhere between the USA and Europe.

ER: You're more critical than in the USA?

JM: People tend to be more critical of biotechnology, but not as heavily as the extreme groups in Europe. Most people are open-minded in Australia, but many have been influenced by the scare campaigns of groups who have selected GM foods as a rallying point. There is certainly

almost no concern in Australia in terms of pharmaceutical development. There are groups who are expressing disquiet about some of the newer cloning technologies, which is understandable. But the general attitude in Australia is cautiously sympathetic to high technology. Australia is out there in the South Pacific on the edge of Asia; it wants to be a sophisticated country. Australian big cities are much the same as any big cities around the developed world, and the nation is now peacefully and interestingly multicultural, as a result of very strong post-World War II immigration. But the country is still somewhat remote and the government and even many people in the research agencies have been slow to appreciate the rapid pace of change that is occurring, and been slow to invest in it. And that's going to cost.

ER: Do you think genomics and proteomics research are now the driving force, the most important areas of research in molecular biology?

The next generation of biological science is going to be holistic and integrated

JM: I do, personally. And I'm not suggesting that it's all going to be done in one day or just on the basis of DNA sequencing. But I think we're undergoing a fundamental transition in biological science. The last half-century has been quite reductionist, necessarily, in terms of trying to identify the components of life. People felt their way, trying to understand the nature of DNA, the nature of proteins, protein structures, signal transduction pathways, and so on, but it was all very ad hoc. So the challenge is the integration of this information. What will happen is that computational biology and bioinformatics will assume a central importance. Biology is evolving into an information science. And what we're going to have to try to do is to reproduce *in silico*, with increasing accuracy, a four-dimensional representation of what happens in biology. So DNA transforms into RNA and protein, and they transform into metabolic, signal transduction and regulatory pathways. These in turn collectively transform into cell biology, which

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then transforms into developmental biology and physiology. We have to understand all these transformations if we are to understand the workings of cells and organisms, and the relationship between genetic information and phenotype, and how this is modified by environmental factors. It's not a matter of discovering components anymore, it's a matter of understanding how these components work together.

ER: But you still have to have the people who work on the components, who crystallize the proteins and look at the structure.

JM: Absolutely. But there is now another dimension to this. I'm not suggesting that we stop doing those things, but that we will value those things all the more when they are integrated into larger frameworks. Yes, you need to know the structure of this protein, you need to know the mechanism, what this protein is contacting, you need to know how organelles, the cytoskeleton work. But to understand the cell, you have to put it all together. People who work on this bit and that bit are all working on pieces of the puzzle, but the big issue is the puzzle itself. For example, some people think that structural genomics is working out the structure of every protein in the genome. So the Scop, Pfam and SMART databases that are cataloguing the universe of protein domains are becoming very important resources. In the end, the people sitting there, taking all the bits and putting it together will actually generate the next transition. The next generation of biological science is going to be holistic and integrated, whereas the last one was ad hoc and reductionist.

ER: People are talking a lot about proteomics and functional genomics, but, as far as I have seen, they are not yet at the point where they can do this. When will we be able to put together the structural data, the genetic data and the physiological data?

JM: It's hard to say, but my guess is within the next 10 to 20 years. It's interesting when you look back... when you think what has happened in the last 20 years. Many of the things that we predicted have happened, some have not, but the pace of change has been faster than anyone expected. We're currently building an A\$100 million institute in Brisbane that will be the largest research complex in Australia, and that will be well funded over the next ten years. In that institute,

we plan that at least 25% of all of our staff will be in computational biology, who will cover the whole spectrum on the informatics side of things and connect on a daily basis with the experimental divisions. They will create an informatic and integrative representation of genes, structures, pathways, cells and organisms. It will absorb information from all around the world, and help the experimental divisions reach new insights, formulate new hypotheses and forge new syntheses.

ER: Do you think co-operations with Celera will increase over time, as Celera increasingly invents into proteomics?

I see Celera as the vanguard of a new generation; it is an information company, not just a sequencing company

JM: Yes, I do. I see Celera as the vanguard of a new generation, not just of companies, but of science. Celera is an information company, not just a sequencing company. And that's not widely understood. So there are areas of mutual interest; we expect to work closely with them and happily so. It's a matter of defining that interest as we do with other industry.

ER: Pharmaceutical companies and biotech companies are putting more money into research than governments do. Do you still see governments being able to reap benefits in the way you mentioned before?

The Americans are quite happy to see Europe devour itself over what they see as essentially fruitless debates about irrelevant things

JM: Well, the national interests are going to be reaped in the end, really by how effectively the economies of different countries capture the output, whether it's publicly or privately funded. And to some extent, the unfortunate politics in Europe about GMOs is just retarding the uptake rate. I think the Americans are probably thinking privately that this is fantastic.

That's the impression I get from them. They are quite happy to see Europe devour itself over what they see as essentially fruitless debates about irrelevant things. But there is always a role for publicly funded research—for many reasons. One is that there are basic things that industry normally won't do, as it is too far from product development; they won't do the epidemiology associated with infectious diseases, for example. They don't usually play with new ideas, although there have been some notable exceptions to this. So publicly funded research provides a platform for industry development. The Americans understand this, which is why they have invested so heavily in basic research. Now I agree that industry in some countries is investing more than government, but one thing that publicly-funded researchers can do more easily than industry-funded researchers despite the breadth of the industry programs is to follow their nose. So you find in the USA, for example, that 70% of all patents that underpin US industry are generated by the university sector. The whole information technology industry grew out of universities like Stanford—from professors and graduate students who saw the future before anybody else did. Industry is not necessarily at the front of the boat. Celera is an exception to this. But there will be more from the start-up sector, which has a very dynamic interplay with the university sector. But in the end, it is about people's health, the economy and the environment. I think genomics and biotechnology have much to offer all three, and much more.

ER: Professor Mattick, thank you for the interview.

The interview was conducted by Holger Breithaupt. Photos by Doug Young.

DOI: 10.1093/embo-reports/kvd060