interview

research focuses on vascular targeting. 'It needs to be validated *in vivo*.'

A possible addition to immunotherapy

Patients with well-differentiated prostate cancer are most likely to benefit from the combination of anti-PSMA therapy and treatment with microtubule-destabilizing agents. Rajasekaran believes this approach could reach clinical trials within four years, as it is based on 'well established chemotherapeutic agents that are used on a daily basis in cancer clinics.'

As in the laboratory work, where the researchers expressed PSMA in Madin-Darby canine kidney cells as a polarized prostate cell model was not available, 'one of the challenges in the animal model may be to generate tumors that are very well differentiated,' says Rajasekaran.

References

1 Milowsky, M. I. *et al.* (2004) Phase I trial of yttrium-90-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for androgen-independent prostate cancer. *J. Clin. Oncol.* 22, 2522–2531

2 Bander, N.H. *et al.* (2005) Phase I trial of 177lutetium-labeled J591, a monoclonal antibody to prostate-specific membrane antigen, in patients with androgen-independent prostate cancer. *J. Clin. Oncol.* 23 (Published online ahead of print April 18, 2005; 10.1200/JCO.2005.05.160)

3 Christiansen, J.J. *et al.* (2005) N-glycosylation and microtubule integrity are involved in apical targeting of prostate-specific membrane antigen: implications for immunotherapy. *Mol. Cancer Ther.* 4, 704–714

4 Christiansen, J. J. and Rajasekaran, A.K. (2004) Biological impediments to monoclonal antibody–based cancer immunotherapy. *Mol. Cancer Ther.* 11, 1493–1501

interview

John Anson of GE Healthcare

Interviewed by Steve Carney

How do you see the balance of high throughput versus high content screening developing over the next ten years and do you think that companies will adopt a more focused approach to screening with high quality information compared with a mass screening approach?

I think the balance is already changing Steve, and if you look across the industry it is very much company-specific. Clearly, some companies have invested in factory-based approaches to screening and this approach will continue to be an important part of the drug discovery philosophy. That isn't consistent across the industry and we've talked to other companies who are going in a slightly different direction and, as you point out, they are looking at perhaps greater quality within their big compound collections, reducing the number of compounds they want to put through their high throughput screens. Down from where it is today at the multiples of millions in some cases, to the level of, maybe one to two hundred thousand or fewer. Now, at that sort of level, the application of high content screening becomes pretty attractive. As you look across the industry different companies are taking different approaches. If I were to predict where the trend would go, I would see it developing in the direction of high-content at the expense of high speed and high numbers, since from what we're seeing with the quality of data that you can generate in a in a high content screen, it potentially allows you to make better quality decisions in the pre-clinical drug development process.

John Anson

Head of Product Development, Lead Discovery at GE Healthcare

John Anson is Head of Product Development, Lead Discovery at Amersham Biosciences, which is now part of GE Healthcare. He read microbiology at Kent University, obtaining a BSc in 1981. His doctoral studies were at Cranfield University, successfully completed in 1985. Following a period at the PHLS CAMR, Porton Down, John joined Amersham. In his career with Amersham and now GE Healthcare, stretching over 16 years, John has held a number of posts in project and programme management. More recently he has held the positions of Business Development Director, Vice President, Pharmacogenetics and Vice President, Business Development Bioassay Business, before assuming his current role in 2002.

1359-6446/05/$ – see front matter PII: S1359-6446(05)03520-8

interview

You've stated in the past that you see chemical genomics more as a research tool than a drug discovery platform. Do you see this changing in the future?

Chemical genomics is a very exciting opportunity for the academic community and what's interesting Steve, is we're now seeing people from Pharma moving into these more academic positions. They are taking up roles to run high throughput biology in academic institutions. So, by the very nature of the cross-fertilization between Pharma and academia, there is a good chance that the academic community will become more involved in drug discovery, but I don't think it's their primary focus at the moment. Their primary focus is about getting a better, fundamental understanding of disease biology and that, in itself, will contribute to enormously to the pharmaceutical industry and this is likely to continue for some time.

'Some companies have invested in an almost factory-based approach to screening'

Could you possibly outline the company philosophy on personalized healthcare: where do you think its going to go and where's it going now and where do you see it in the future?

Personalized healthcare is a huge opportunity and the concept of being able to give the right therapy at the right time to the right individual is where we would like to be. The combination of really enabling diagnostic tools with focused therapies is a very exciting one. That's only part of the story and personalized healthcare can mean other things as well. I was particularly intrigued by the news story that came out recently about the 69 year old man who was given an islet cell transplant to treat his type I diabetes. That is also personalized medicine, that guy was treated and his very personal condition was cured. So, I think that personalized healthcare is really a very, very broad field and it can encompass a number of different aspects. The position of GE Healthcare is to be in the centre of this opportunity and really maximize its breadth of skills and technologies to be able to make a difference.

In what practical ways is GE Healthcare advancing the concept of pharmacogenomics, have you got some initiatives in place to drive along particular drugs, or particular therapeutic areas?

We do have a program where we're looking at the use of or the development and use of biomarkers. Clearly biomarkers are important and will continue to grow in importance for the identification of early identifiers of disease or disease progression. This permits the monitoring of disease progression and we believe that is an important and growing area as well. So, alongside our ability to run diagnostic tests in vivo and potentially in vitro, the potential to be able to exploit novel biomarkers is an area that we are interested in exploring as well.

'The combination of enabling diagnostic tools with focused therapies is very exciting'

Now that you've merged and you're part of a significantly larger company, do you have a more holistic approach to the treatment of disease, since you can now provide the biomarker, the screening approach right the way through to diagnosis and imaging?

I think that you know that this is clearly part of the vision of GE Healthcare and it's very interesting for me to look at the various components of GE Healthcare. We've got the very strong GE Healthcare base which is focused on implementation of a lot of the hardware that is required to do much of the imaging-based diagnostic tests, such as MRI and ultrasound. Now obviously if you add that to the pieces of Amersham, then you know you're looking at the diagnostic imaging agents themselves, which go alongside the imaging instrumentation. More related to the area I work in, you know clearly we are focused within the discovery system's business on providing tools for researchers in pharmaceutical companies, biotech companies or in academic research – providing them with tools to get a better understanding of the disease or disease processes and also obviously providing them with the tools to help them screen and for test novel therapeutic compound. Also there is the protein separations business that we have which looks at the technologies and systems to facilitate the manufacture biopharmaceuticals. If you look at those in isolation you know they may look like rather unconnected pieces but if you think about the ability of this company to bring together these technologies, to be able to do molecular diagnostics at the level of the cell and at the sub-cellular level, and then at the other end of the process, to assist pharmaceutical and biotech companies in actually manufacturing the final product, you can see we are in a very strong position to facilitate and help our partners in the pharmaceutical world bring a lot of these therapies to market and to bring the provision of personalized health care to the fore.

Does your division operate as an independent unit within GE Healthcare, and if not, how is its direction and objectives determined?

GE Healthcare is split into two business units: GE Healthcare Technologies and GE Healthcare Bio-Sciences. Within the GE Healthcare Bio-Sciences business we have a group working on imaging agent development, which is a very strong business and part of the old Amersham Health business. We also have a division, called Discovery Systems, which is the business that I work in. That is the life science tools business, and then, as I previously mentioned, the protein separations division which both made up the old Amersham Biosciences as was. So those Amersham businesses rolled up make the GE Healthcare Bio-sciences business unit, but they are all connected up through the management organization to one person and that is Bill Castell. Bill Castell is leading the whole of GE Healthcare – he provides the leadership and the vision to bring the various parts of the businesses together, but yes we do operate as an entity, and we are measured on our performance, within the GE Healthcare organization as a separate P&L.

There have been a number of things in the press about your collaboration with various companies, particularly of public interest with Cellomics – can you give me some comments on how successful you see that as being and other things you would have done differently?

interview

We collaborate with a lot of companies. When we decided to get into the area of high content screening or high content sub-cellular analysis, we recognized that we were very strong in the in vitro screening area, we'd had a great franchise with the SPA technology, we built on that franchise with the LEADseeker technology and we had a very broad and strong portfolio to serve just about every single type of HTS assay the customers wanted to do. That wasn't really the case about five years ago when we looked at our portfolio in cellular analysis; we had a lot of the in-house skills: we had the biochemists, chemists, cell biologists and so on, but we didn't have a lot of the core technology. So the decision was made to invest in sub cellular analysis and what we decided to do was to look outside the organization and see where we could buy into existing technologies which we felt were either fully developed or certainly on the way to becoming potential products. So, around about 2000, we did a number of licensing deals and acquisitions that put us in a pretty strong position, fairly quickly, in the sub-cellular analysis area.

'We recognized that this game was not just about instrumentation'

In 2000 we acquired a company in New Jersey called Praelux, which brought us a technology that is still the fastest high content screening technology that is currently available. We also recognized that this game was not just about instrumentation, but to be a true player in high content screening, we had to be a provider of tools and technologies, so we looked at where we needed to build our strengths in the reagent field and we made a strategic decision to invest in GFP as a reporting agent for cellular analysis, so we stitched together a number of licensing deals to enable us to be in a position to commercialize that technology and we continue to do that as a business.

We also had a licensing arrangement and a research collaboration with a company called BioImage in Denmark. They have the intellectual property related to the redistribution of GFP within cells, so when proteins redistribute within the cell on treatment with drugs, for example, you can monitor that using GFP, and they have the IP around that area so we licensed that IP as well. We also invested in a company called Imaging Research Inc in Canada, which also had technology, hardware and a lot of software expertise in image analysis. So effectively over a 2 to 3 year period we pulled all these technologies together which has helped us develop the IN Cell platform, that is, the IN Cell 1000 and 3000, and it's the combination of the hardware of the 1000 and 3000, the enabling image analysis tools and the reagents that have really made a difference.

'Since becoming part of GE we have been given greater scope'

Now, in addition to that, we also recognize that we wanted to work with Cellomics because of some of their capabilities, particularly in data handling and storage. Cellomics have invested significant resource in building a strong position, particularly on the data management side, so the relationship with Cellomics is really about obtaining a license to their high content screening technology, but also to be able to work with them to supply our customers with some of their key tools in the area around informatics.

It's a tactical relationship at the moment with Cellomics, in terms of working with them to help to provide the customers who adopted IN Cell with a holistic approach to both data generation and data management and storage.

You have outlined a number of acquisitions and collaborations; do you see that as being the future of your business, that growth will come through acquisition and collaboration rather than organic growth?

Well, not necessarily, as we do invest significant internal resources in this area. For example I've got 70 scientists here in Cardiff who are focused on providing new products, new tools, new technologies in this area. I also work with one of our R&D teams in Piscataway, New Jersey and invest in their R&D development. We have access to an amazing research capability within GE, and we're investing in the Global Research Centre not just in the US but in the research centre in Bangalore, India, as well, on providing basic research around quite a lot of the tools that we're developing in this area. So there is a lot of organic activity going on. But also, there are opportunities out there and there will continue to be opportunities to add to our portfolio through licensing and acquisitions and we also have a very active programme in business development and being part of GE really does add quite a lot of capabilities in those areas. GE as an organization has a lot of experience and expertise in licensing and acquisitions.

'...the most basic tool... is the cell that you're doing the experiments on'

Since becoming part of GE Healthcare have you had a change of emphasis in the sort and targets and projects you set up, and if so what?

Since becoming part of GE Healthcare we have been given greater scope. What is interesting actually is that we've been part of the GE Healthcare organization for only about a year now, and quite quickly we've realized that within GE there are amazing, tremendous resources. I mentioned the Global Research Centre resource, we quickly identified and realized that there are people within that global research team that had skills that we could access that we would find very difficult to find within the old Amersham organization. In fact, shortly after the acquisition we announced the transfer of the discovery systems research activities to the GE Global Research Centre in Niskayuna, New York. By transferring Discovery Systems' Research activities to GE Global Research, we benefit from unparalleled scientific and technological resources. So, for example, where GE has material scientists, they have people working on nano-technology and one of the projects that we're working on at the moment is really trying to address R&D challenges by applying different disciplines. So we can now take a completely different view to a problem, utilising expertise that is very deep and very broad in material science, for example, and be able to come up with novel solutions to biological problems. I think

interview

that's really exciting and what's been great is the response from the scientists within GE. Material scientists, for example, love the idea of working with biologists, because they may have been working in the lighting business for the last 10 or 15 years, but then when they start talking to a biologist they very quickly switch on, if you'll pardon the pun, to other ideas and other ways of exploiting their knowledge in a completely different application, in a completely different market. You might wonder how you can access these people when you've got over 300 000 employees, but GE is an amazing resource and its been remarkably easy to find people who are willing to talk to you, very willing to work with you, on some of these far-out projects which could result in some amazing technologies in the future.

'Work with better tools to be able to make better quality decisions'

Could you give me some idea of the so-to-speak jewels of the crown of your current development pipeline?

It's going to be quite tough for me to talk about things that are still in the pipeline because a lot of that it is confidential. What I can say is that within the cellular analysis area we're focusing on two things that we think are going to change in the future, and two things that I think we will impact. I can say, short term, I believe there will be a greater reliance on the use of transiently expressing cell lines rather than stable cell lines used in cell based assays and potentially, cell based screening. We have an active programme at the moment to look at the exploitation of viral delivery to develop assays in cells very quickly, so that the researchers in Pharma or Biotech or in academia can get access to transient cell assays much more easily and much more quickly than they currently can do. That's where we're focusing on the biology side short term. Longer term, I think that a really exciting opportunity exists to and move away from the traditional use of cell lines that are in the industry at the moment and to start thinking about the provision and use of cells that are much more phenotypically relevant than a particular experiment. What I mean are cells that are more closely related to (in fact in the ideal world they will be exactly) the kind of cell that you would find in the body of a human in a particular organ or tissue. Just to give you an example of what I'm talking about is that one of the challenges today in pre-clinical toxicology is to get enough relevant liver cells to do large-scale cell based toxicology. If we had a way of providing large amounts of phenotypically-relevant human hepatocytes, then a lot of the toxicology studies in cells could be seen to be a lot more relevant to the final outcome in humans. The key focus in pre-clinical toxicology is to make sure you weed out drugs that are potentially going to be a problem later on. There is a basic premise in the industry, at the moment, which is fail early, fail cheap. One of the ways of doing that is to work with better tools to be able to make better quality decisions earlier in the process. People often overlook some of the very basic tools and the most basic tool, if you're doing cellular toxicology, is the cell that you're doing the experiments on.

John Anson
Head of Product Development, Lead Discovery, Discovery Systems,
GE Healthcare BioSciences,
The Maynard Centre Forest Farm ,
Whitchurch, Cardiff ,
UK CF14 7YT