Interview

Professor Alan Ashworth took his BSc in Chemistry/Biochemistry at Imperial College, London, and subsequently completed his PhD in Biochemistry at University College, London. Since 1986, he has worked at the Chester Beatty Laboratories (The Institute of Cancer Research; ICR) in London and was a member of the team that discovered the BRCA2 gene in 1995.

In 1997, Alan was appointed Professor of Molecular Biology and became Head of Section of Gene Function and Regulation at the ICR. He was appointed Director of the Breakthrough Breast Cancer Research Centre on 1 August 1999. He is an elected member of EMBO and a Fellow of the Academy of Medical Sciences (taken from Breakthrough Breast Cancer webpage).

Interview with Alan Ashworth

One of the first important pieces of work you were involved in was the cloning of the BRCA2 gene in 1995. How did you get involved in breast cancer research?

I was a molecular biologist and involved in cloning genes from a wide variety of areas, although I was especially interested in sex chromosome biology and X-inactivation. I became involved in BRCA2 by accident as an interesting cloning project, and through this I became involved in breast cancer research. I saw that by identifying this gene, in a project led by Mike Stratton, we could make a real difference in a relatively short time. Women could be told whether they were at a high risk of developing breast cancer, or if they were a non-carrier in a BRCA2 family.

Since your involvement in gene cloning, have you seen a change in the public perception of genetics; for example, are people now more aware of screening and how their genes can affect their health?

Yes, to a certain extent, although screening has not advanced as rapidly as I would have hoped. In fact, over the last ten years there are not that many more genes that can be screened for, and certainly in breast cancer there are no other genes that have so far emerged as candidates. In fact, there may not be any other major susceptibility genes for breast cancer other than BRCA1 and BRCA2. People are aware of genetics with regard to the inheritance of "bad" genes, but there is less understanding about genetics and genes underpinning all of life as well as diseases. We need to be more proactive in teaching people about this area given that it will be very important in the future and they will be making critical life decisions based on this information.

Often medical health professionals can be confused about screening and what the public should be told about recent genetic developments, which doesn't help.

Exactly. It comes back to this issue of risk. People generally don't understand what risk means, and equally scientists are not very good at explaining risk. For example, a 10% increase of risk and a 10% risk can be confused in the public perception, and they are clearly different. That's why you often see on the front page of newspapers hugely exaggerated stories about the risk of, underwired bras or deodorants in causing breast cancer, for example, when really there is no real evidence to support these claims. In fact, people seem to find those things pose a greater risk than crossing the road, smoking or drinking, when really they are the more obvious routine risks. So for example, people may stop flying on aeroplanes as they are perceived as a higher risk. After 9/11 fewer people flew in the US, but there was a perceptible increase in the net incidence of road accidents, and actually more people died as a result. Another example is the huge reduction in the risk of developing ovarian cancer that comes from taking the contraceptive pill for five years, although associated with this is a very small increase in the risk of breast cancer. So being clear about the facts and balancing risks involving life matters is something that people need to understand much more clearly.

That leads us on to talking about the Breakthrough Generations study (a massive project to collect epidemiological data from 100,000 women over the next 40 years), which is trying to discover what the life risks for breast cancer might be in combination with other genetic events. How is the recruitment for this study coming along?

We are about half way there as of this week (01.06.06), and we expect to get the other 50,000 blood samples and questionnaires within the next 12-18 months. The level of response we have had is a testament to how much women want to drive research, in particular breast cancer research. So we're well on the way to recruiting 100,000 women, which is ambitious, but it is one of the few ways we can tackle the interaction between genes and environment. One way to think of these factors is as a fruit machine, where bringing up three lemons would result in breast cancer. One lemon would represent family history, another lifestyle and another environment, and so small things add up to a major consequence. What we are very bad at understanding is how genetic risk is affected by lifestyle factors, and the whole scale of the study will allow us to concentrate on this issue.

Scientifically speaking, when are you going to be ready to start to analyse the data, and have you targeted any specific genes to examine?

Because it's a prospective study, it's going to be five to ten years before we have enough breast cancers that have occurred during the study, but an unexpected consequence of setting up the study is that there are a number of women who have had breast cancer who wanted to be involved, so we have embedded in the 100,000 prospective study a case control study. This will provide us with an extremely good resource to analyse existing risk factors before we get on to the main group. We will also start to analyse genes that have already been implicated, but of course one needs to look at thousands of samples to validate any particular interaction. Due to the number of samples, it's going to be a very expensive exercise.

How much manpower are you going to need to analyse the huge amounts of information generated over the next 40 years?

We haven't started recruiting for the genetic analysis phase yet, but we already have 20 people working on the epidemiological aspects. But even to extract the DNA from 100,000 samples will require an enormous amount of work.

Your 2005 paper in Nature described how PARP-inhibitors can be used to selectively kill cells with defects in BRCA1 or BRCA2. Are these drugs now in clinical trial?

The development of these compounds has gone extremely fast, the reason being that we were able to do a key piece of research and progress that in parallel with the clinical development of the PARP inhibitors for another purpose. So we were able to move them to a single agent usage in the BRCA mutation carriers very quickly. This was in collaboration with KuDOS Pharmaceuticals who have now been bought by AstraZeneca, and the Phase 1 trial, which is a stand alone treatment of PARP inhibitors (which was presented at ASCO in June 2006) shows that there is a very low toxicity associated with this treatment. What is needed now is to set up a Phase 2 trial in BRCA1 and BRCA2 mutation carriers to see if the spectacular sensitivity we see in the lab is replicated in people.

Would the Phase 2 trial be in combination with chemotherapy?

Initially we would do it as a stand-alone because we hope that there will be such a large therapeutic window in the BRCA mutation carriers that it will work alone. However, we are trying to work out at the moment what chemotherapeutic agents will synergise with PARP inhibitors, which will be very important in clinical development. Beyond that, we would also like to know if we can use this synthetic lethal approach in non-hereditary cases of breast cancer that we characterise as having "BRCA-ness", for example basal breast cancers. We're working very hard on this – it's an exciting time.

Do you think that in time PARP inhibitors will be given to BRCA mutation carriers before they develop breast cancer?

It's a possibility, but the problem is that at the moment we don't know anything about long term toxicity. One can imagine in the long term that women with a high risk of developing BRCA-related breast cancer could be given a prophylactic treatment every five years - PARP inhibitors or something else - to kill any pre-cancerous cells.

How diverse are breast tumours with respect to BRCA1 and BRCA2 defects, and to what extent does this affect the use of PARP-inhibitors on individual tumour types? Does the clinical trial randomise or select on such basis?

All the BRCA1 and BRCA2 mutant cell lines that we have tested so far have been sensitive to PARP inhibitors, although there may be certain mutants that aren't sensitive, we don't know very much about that at the moment. However, as long as a mutation disrupts the DNA repair ability of the cell it should be sensitive to PARP inhibitors, and we've shown that cells with disruptions in genes involved in other parts of the homologous recombination (HR) pathway, such as ATM and Fanconi, are sensitive. Other cancers that involve mutations in the BRCA genes, such as ovarian cancer, should also be treatable with these drugs.

Is there any association of breast cancer in women with other particular types of cancer?

Hereditary breast cancer in women is associated with ovarian and pancreatic cancer, and in men is associated with prostate and pancreatic cancer. As far as sporadic breast cancer goes, it is associated with another cancer and that is – breast cancer. So women who have had primary breast cancer have a much elevated risk of a second primary occurring in the contralateral breast. This is interesting from a genetic point of view, in that the women who get breast cancer are those that had at an intrinsically higher risk of getting breast cancer. It may be that many women do not have a predisposition towards developing breast cancer, but there is an enriched subgroup of women, say 30%, who are at an elevated risk of getting breast cancer. This is what we are trying to unravel with the Breakthrough Generations study. It will be important in the future to generate each

individual's risk of getting breast cancer, so that we can concentrate on those with a high risk and offer either prophylactic measures or screening.

Could any of this research lead to the development of a specific anticancer vaccine?

There is ongoing work into the possibility of developing anti-cancer vaccines, but in breast cancer they haven't been particularly successful and it is not something that we concentrate on in our laboratories.

Has the survival time increased significantly in the last 5-10 years in women suffering from a primary malignant lesion on their breast?

Yes, substantially. This is mainly due to adjuvant treatment such as Tamoxifen, improved chemotherapy regimes and increased screening. The onset of new generations of oestrogen suppressors such as Arimidex may improve matters even further, although for many women Tamoxifen may still be the best choice as the trial data is not completely clear. As the disease is heterogeneous, the treatment regime for each woman is taken on merit. The advent of Herceptin has greatly improved the survival time for women with HER2 positive breast cancer, who previously had a much poorer prognosis.

Will we see a rise on the number of cases of breast cancer as our population becomes skewed very much towards a preponderance of older people (> 50 years of age)?

From a worldwide perspective, there will definitely be an increase in breast cancer incidence. This will be partly due to the skew to an older population, and also may be due to developing countries (who currently have a low incidence of hormonal cancer) becoming more developed and taking up a Western-style diet. ■

References

1. Lancaster JM, Wooster R, Mangion J, Phelan CM, Cochran C, Gumbs C, Seal S, Barfoot R, Collins N, Bignell G, Patel S, Hamoudi R, Larsson C, Wiseman RW, Berchuck A, Iglehart JD, Marks JR, Ashworth A, Stratton MR and Futreal PA. *BRCA2 mutations in primary breast and ovarian cancers.* Nat Genet. 1996Jun;13(2):238-40.
2. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC and Ashworth A. *Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy.* Nature. 2005Apr14;434(7035):917-21.

For more information about the Generations study and other ongoing research, see the new Centre website http://www.breakthroughcentre.org.uk

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