TALKING UP TRANSLATION

Alan Ashworth took a cancer drug from Petri dish to patients in near record speed. **Daniel Cressey** meets a biologist who is evangelical about translational research.

A short, laminated article has fallen off the wall of press cuttings outside Alan Ashworth's London office. It is an editorial published in 2000 by Britain's widely read and notoriously opinionated tabloid newspaper, *The Sun* — and it is praising geneticists who study cancer. "They are, without doubt, the most important people alive," it crows. "People like Professor Alan Ashworth and his team at the Institute of Cancer Research are dedicated to the cause."

Last year, Ashworth's work was lauded, somewhat more quietly, in an editorial in the *New England Journal of Medicine (NEJM)*¹. "Readers may be surprised by the editors' decision to publish a small early-stage trial," the journal wrote of a study largely based on Ashworth's discoveries, "but this trial not only reports important results — it also points to a new direction in the development of anticancer drugs".

That Ashworth has won praise from these diverse camps is a testament to his record in 'translational' medicine — moving developments in basic science into the doctor's surgery. In just under 15 years, he has gone from early work on the major cancer-risk gene *BRCA2*, to involvement in the development of a promising cancer drug based on knowledge about the gene's biology. His work "is really the shining example of successful translation of a basic biology idea into successful clinical application", says Julian Downward, from Cancer Research UK's London Research Institute. Ashworth — who prefers the term 'integration' to translation — plans to make his approach a central tenet of the Centre for Molecular Pathology, the London facility he will lead, which is scheduled to break ground early this year and should be completed in 2012 at a cost of £20 million (US\$33 million). He has even become something of an integration evangelist, chastising those who do basic cancer research without considering the work's future application. "This integrated approach

is something I demand of everybody," he says.

Yet what Ashworth makes look easy, others find extraordinarily hard. He says that the key to his success has been a thorough understanding of basic biology and a commitment to seeing it through to application, plus a sprinkle of serendipity. But others say that Ashworth is also set apart by his drive, his charm and his ability to win over others to build the networks of expertise needed for integration. "One of his big achievements," Downward says, "has been to actually hold together this grouping of people who aren't usually very good at talking to each other."

In the 1980s, when Ashworth started a PhD in biochemistry at University College London, molecular biology was in the "really early phase of gene cloning", he says. It was his flair in this field that led him in the 1990s to Mike Stratton,

then at the Institute for Cancer Research in Sutton, UK, who had recently shown² that *BRCA2* — which, along with *BRCA1*, was known to be important for determining breast cancer risk — was

localized to a small region of chromosome 13.

Ashworth says that he was brought in "as kind of a hired gun" to help clone the gene. And he was confident that he would. Over a bawdy meal in April 1995, Ashworth predicted that the gene would be in hand within a year and scrawled his prediction on a napkin, witnessed by several colleagues. The group didn't need the whole year. In December 1995, *Nature* reported³ the cloning of *BRCA2*.

Ashworth recalls when the first woman was tested for *BRCA2* mutations; she had been scheduled for prophylactic mastectomy because of her family's cancer history. The tests were negative, and the surgery was called off. "It was only then that I realized I could apply what I was good at to patient benefits," he says.

By the end of the 1990s, Ashworth was directing a team at the Institute of Cancer Research in London and had developed a mouse with a

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mutated *Brca2* gene that was highly susceptible to cancer⁴. Work by several groups showed that the gene is involved in repairing DNA damage by a process called homologous recombination (see graphic). When it is mutated, DNA breaks start to accumulate, increasing the risk that a cell will turn cancerous. "We had to retool essentially and start to understand DNA repair," says Ashworth. In 1999, he was chosen to lead the Breakthrough Breast Cancer Research Centre at the Institute of Cancer Research, where he came into close contact with patients and physicians.

Double jeopardy

Ashworth became interested in the idea that a mutated *BRCA* gene could not only render cells susceptible to cancer — it could also be exploited to target them. The team turned to a concept in genetics called 'synthetic lethality', in which mutations are harmless on their own but together will kill a cell. They theorized that cancer cells bearing a mutated *BRCA2* were now reliant on another leg of their DNA repair machinery. Taking out a second repair pathway should bring them to the floor.

The opportunity to test the theory presented itself when, as Ashworth puts it: "I met a bloke in

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Alan Ashworth wrote his prediction that *BRCA2* would be cloned by 1996 on a napkin; it was done in 1995.

a pub and he offered me some drugs." That bloke was Steve Jackson, a DNA-repair researcher from the University of Cambridge, UK. The company he had started, KuDOS Pharmaceuticals, had developed the drug olaparib, which inhibits an enzyme vital for the repair of DNA breaks: poly(ADP-ribose) polymerase, or PARP. Over a drink, Jackson and Ashworth hit on the idea of testing whether Jackson's 'PARP inhibitor' would take out the second leg in *BRCA2* mutant cells (see graphic).

"It wasn't months; it was days or weeks after the compounds went down to his lab that they told us about these absolutely stonking results," says Jackson. The team showed in 2005 that *BRCA2* mutant cells died when they were hit by Jackson's drug⁵, and a back-to-back report from Thomas Helleday, then at the University of Sheffield, UK, echoed the finding⁶.

When it came to testing the drug in people, Ashworth had a head start: olaparib had already passed many of the early safety and regulatory hurdles required for a new drug. But human trials bring other challenges: intellectual property, financing and mountains

of regulatory bureaucracy can be enough to smother anyone's translational ambitions.

Ashworth, who had access to clinical expertise via the cancer centre and nearby hospital, is sanguine, and says that the key has been to listen to those from different disciplines "so I can understand what they do". Part of Ashworth's success may lie in his air of being a regular, amiable scientist who can seem slightly uncomfortable in a suit. "It may be because he was slightly outside the normal operation of all those things," says Downward. "He's not a clinician, he's not a pharma person."

Killer instinct

Of the 60 participants recruited into the eventual phase I clinical trial, 23 had mutations in one of the *BRCA* genes; and after treatment, 12 of these people showed a 'clinical benefit'⁷, such as no progression of their disease for 4 months or longer. The synthetic lethality approach — the new direction in anticancer drugs referred to in the *NEJM* editorial — looked highly promising, and the cancer community was abuzz. AstraZeneca, which acquired KuDOS in 2006, is now developing the drug and the results of a phase II trial, presented at the American Society of Clinical Oncology meeting in 2009, showed that more than a third of patients taking the maximum dose showed some improvement in their tumours⁸. "I've no doubt this approach will work," says Ashworth. The drug might also work against cancers with other DNA-repair defects. Last year, his team showed that PARP inhibitors were also lethal in cancer cells with mutations in *PTEN*, one of the genes most com-

monly disrupted in cancers⁹.

Ashworth cites another example of the integration he seeks between basic and applied research. His team knew that *BRCA*-mutant tumours develop resistance to the platinum-based drugs such as cisplatin that are a mainstay of treatment; the group went back to the lab to work out whether the PARP inhibitors would run up against the same problem. The resulting paper in *Nature*¹⁰, along with one from another group¹¹, showed that drug resistance arises when the mutant *BRCA2* undergoes a deletion, restoring DNA repair. This means that PARP inhibitors might sometimes need to be used with other therapies.

Ashworth's evangelism is persuasive. "It is a fantastic feeling to think that the work you've done in the lab can actually have an output in patients," he says, "and I think many other people want to feel like that." He imagines a future in which all tumours are targeted according

to their precise genetic characteristics, a vision that many researchers are now working towards. At the new Centre for Molecular Pathology, he plans to collect genetic and molecular profiles of patients as they enter trials to

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— Julian Downward

work out which people are most likely to benefit from the therapies being tested.

He is also heavily involved in running Breakthrough Generations, a study into the genetic and environmental causes of breast cancer that has recruited 100,000 British women and has received £12-million in start-up funding from the Institute of Cancer Research and the Breakthrough Breast Cancer charity. The plan is to collect detailed health information over the next 40 years to improve understanding of the causes and prevention of cancer.

Today, he finds some escape in the basic biology. "It's a relief to look at data rather than at higher-level political things," he says. "What really drives me is looking at experiments. I still get very, very excited — some would say too excited — when there's a hint of a good result."

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SYNTHETIC LETHALITY

In normal cells, base-excision repair removes damaged bases from DNA; homologous recombination replaces broken DNA with an intact copy. Cancer cells can lose one of these mechanisms when one of the *BRCA* genes is mutated, and die when a PARP1 inhibitor takes out the second.

ADAPTED FROM REF. 1

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