

Accelerating Cancer Drug Development



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**ALDERLEY PARK'S
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CAMPUS IS NOW
HOME TO 65
SMES AND 150
START-UPS, MANY
OF WHICH WORK
IN ONCOLOGY.**

Attrition rates in drug discovery and development have been a major bane to the pharmaceutical industry and contribute greatly to the high cost of research and development. These challenges are magnified in oncology. A multiplicity of disease types, genetic variations and drug targets, together with the complex demands of demonstrating drug safety, efficacy and tolerance in clinical studies, as well as meaningful value in carefully stratified trial populations, call for multidisciplinary R&D strategies.

How the rates can be improved was the focus of the recent *Accelerating Cancer Drug Development – From Target to Patients* conference organised by Bionow. It was hosted at Alderley Park in Cheshire where its Mereside life science campus is home to some 65 SMEs and 150 start-ups, many of which work in oncology.

“Oncology is different”, stressed Richard Knight, co-founder of ApconiX, which specialises in integrated toxicology and ion channel research. For example, clinical-trial subjects are typically the first to receive a new treatment; they generally have a poor prognosis; and their tolerance for adverse effects is higher than average. Yet treatment is also complicated by co-morbidities and existing medication.

Regulatory guidance on cancer drugs (e.g., ICH S9) talks of avoiding unnecessary animal work and expediting the entry of promising new compounds into patients, Knight pointed out. In the clinic, patients are given maximum tolerated doses, with a variety of potential dosing schedules and combinations. Moreover, dosing and duration are not limited by preclinical data.

Taking a multidisciplinary approach means involving all of the key stakeholders in successful cancer-treatment outcomes, from academic scientists and clinicians to biopharmaceutical companies and outsourced providers, healthcare professionals and patients.

The conference heard from a number of delegates who said that research and development hubs which draw on a broad ecosystem of ‘joined-up’ local expertise, resources and translational science, such as Alderley Park, can contribute substantially to widening the flow of treatment advances across the cancer spectrum.

Stumbling Blocks

Delegates were also told that analyses to identify the key stumbling blocks in R&D productivity has flagged up a number of opportunities for improvement. One key area was shifting the attrition to earlier phases – enabling companies to kill off projects before embarking on more expensive and time consuming clinical trials. A major component of this has been a greater focus on improving the predictive value and development of better preclinical models for desired disease settings.



**BEST CHANGES IN
CARE COME THROUGH
BEST RESEARCH
– ROB BRISTOW,
MCRC**

Keynote speeches highlighted the North of England’s successes and challenges in cancer drug discovery and development. Opening the event was Dr Susan Galbraith, Vice President of oncology at AstraZeneca, whose accelerated development strategies moved the cancer drug Tagrisso (osimertinib) through clinical trials in under three years.

A set piece presentation was also delivered by Professor Robert Bristow, a world authority on prostate cancer, who took over as Director of the University of Manchester’s Manchester Cancer Research Centre and Chief Academic Officer at The Christie NHS Foundation in 2017.

Most cancer therapeutic candidates fail in Phase II and Phase III efficacy assessments, pointed out Rob Bristow. This highlights just how difficult it is to translate promising preclinical observations into products that can help patients. Indeed, a popular lament in the general media is how good the pharma industry has been at curing many cancers in mice but not in people.

He addressed the opportunities to tackle these roadblocks by harnessing ‘team science’. The principal challenges begin with bringing together teams from academic medicine and the biopharmaceutical industry in meaningful ways that effected real change in clinical-care states. This entailed aligning researchers and their partners to end products used in the National Health Service, applying biomarkers to plan drug impact a priority, and hence reducing ‘translational purgatory’.

He also highlighted that driving prognostic factors into predictive factors using patient sub-groups. Here, genomic and immuno-oncology markers could help to separate out baseline characteristics from activated effects. A further, related issue was how the microenvironment affected these observations, and how it could be measured.

Similarly, priority needs to be given to addressing curative endpoints more rapidly in first-line cancer therapies.

Rob Bristow also stressed the importance of detecting early signals that changes in care were leading to changes in outcome, as well as knowing whether these signals actually mattered in real-world practice.

Delegates heard that the MCRC embodies the ‘team science’ principle by embracing multidisciplinary collaboration and strong integration of clinicians and academics, while reflecting the complexity and multiplicity of cancer through its large and diverse patient population.

Bristow gave a few practical tips on how cancer research could be driven on a team basis to achieve genuine improvements in patient care. They included defining clearly the clinical question and ambition for samples, then making sure that biomarker endpoints were suitably powered in addition to outcome endpoints.

These core principles should be buttressed with top-quality basic and discovery researchers, who should be kept “excited and

hungry”, Bristow added. Part of that job was hiding politics from juniors while sharing successes with other researchers, patients and industry. Inventiveness should be regarded as a commercial opportunity to transform patient-care pathways.

Bristow also called for a better definition of ‘bad’ R&D failures to optimise use of genetic tests in defining potentially responsive patient sub-groups.

Improving Preclinical Insights

Nicolas Floc’h, an associate principal scientist at AstraZeneca, described how getting predictive models right at the preclinical stage was fundamental to pushing more viable cancer drugs into the clinic and beyond.

Recognising seven years ago that it had fallen below industry R&D productivity norms, AstraZeneca embarked on a new



strategy which saw it transform rates for candidate drugs advancing from preclinical investigation to completion of Phase III trials from just 4% in 2005-2010 to 19% in 2012-2016.

Improving the predictive value of preclinical work in oncology drug discovery was a major catalyst for this dramatic shift in R&D productivity. “Understanding pre-clinical models is critical,” Floc’h commented. “Since joining the company in 2014, I have seen a strong commitment to develop the right models to address key questions.”

One example was AstraZeneca’s efforts to develop more relevant translational preclinical models during the development of Tagrisso. As Floc’h explained, the company generated a cell line resistant to Tagrisso using two different approaches: constant dosing and progressive dose escalation. “We saw that acquired resistance to Tagrisso is associated with increased dependence on MAPK signalling,” he noted.

However, while the *in vitro* approach involving a cell line-derived xenograft (CDX) model predicted some key pathways, it did not flag up the actual mutation observed in patients. The failure of CDX models to predict human efficacy for most drugs targeted to cancer-driving proteins has been linked to low approval rates (5-7%) at the US Food and Drug Administration (FDA) for precision therapies.

“We then tried to generate resistance *in vivo*, with the hope of recapitulating the clinical landscape and allowing us to test a combination of novel therapeutic approaches to overcome resistance,” Floc’h added.

AstraZeneca developed a patient-derived xenograft (PDX) model involving subcutaneous implantation of surgically derived human tumour material into immunodeficient mice. The advantage of PDXs is that they can stably retain molecular, genetic and histopathological features of the originating tumours, thus helping to predict therapy responses.

While AstraZeneca has made substantial advances in pre-clinical productivity – the success rate following candidate nomination was 88% for the company’s preclinical projects between 2012 and 2016, compared with 66% between 2005 and 2010 – Floc’h pointed to a number of challenges still confronting drug developers.

“Model systems or *in vivo* models that identify key toxicities will become increasingly important,” he predicted. “Modelling diversity of patient segments will improve success while



Aerial view of Alderley Park

building a framework of disease progression, modelling the likely patient evolution over time, will guide treatment.”

Service Ecosystem

The conference heard that pharma multinationals have the potential and resources to achieve many of their ambitions in-house. Smaller biopharmaceutical companies, which still face the same challenges of understanding targets and identifying the best molecules by reducing chemistry-related liabilities, have to reach out to third parties for these services.

It is in this sweet spot that Alderley Park is rapidly building an ecosystem of start-ups with specialist skills across drug discovery and development – especially in, but not restricted to, the oncology space.

“The ability to predict clinical toxicity from preclinical work is still poor,” Apconix’s Richard Knight told delegates. “A preclinical safety profile is crucial to rapid development. There are lots of ways to stack the deck by eliminating liabilities at the compound design stage, by aiming to safely and efficiently explore the true effect of compounds in patients.”

Getting it wrong and carrying safety risks into the clinic may mean lower starting doses, slower clinical-trial recruitment with increased exclusions and drop-outs, and extended pro-

gramme times with tougher patient monitoring requirements and concomitantly higher costs.

Moreover, if risks are not addressed properly, companies can suffer regulatory delays and dilution of partner or investigator interest, ultimately leading to reduced competitiveness and asset value, Knight observed.

Value In Getting It Right

Getting it right, on the other hand, can add a huge amount of value. Although AstraZeneca’s Tagrisso was much later into the clinic than competing candidates, the tight focus on designing the best possible molecule to inhibit selectively mutant forms of EGFR in non-small cell lung cancer has paid dividends.

The company advanced from first-in-human trials to approval in only 2.6 years, against an industry average of just under 9 years.

“There were already several competitors with molecules in clinical phase,” Knight pointed out. However, AstraZeneca delayed nominating its candidate until it had a molecule with selectivity over wild-type EGFR (avoiding skin rash in the clinic), minimal hERG inhibition (avoiding the need for ECG monitoring) and minimal insulin-receptor kinase inhibition (avoiding the need for glucose management).



Among other examples, Knight illustrated how understanding the toxicity, relevant biomarkers, dose response, time course, and reversibility associated with a potential first-in-class kinase inhibitor was key to having a productive conversation with regulators at the FDA.

Visualising Biomarkers

As Juliana Maynard, Head of Imaging Services at Alderley Park, pointed out, robust and sensitive biomarkers are vital to preclinical studies, particularly in an environment where the traditional 'bench to bedside' model is becoming more complex and iterative, with demand for more information on drug efficacy, safety and mechanism of action.

Biomarkers can provide information critical to understanding biological effects. And imaging technologies "help visualise biological functions and accelerate disease understanding and drug development", Maynard noted.

With imaging, she explained, researchers can better understand the impact of a candidate compound across a number of key areas, such as organ accumulation, target expression and engagement, biological activity, toxicities and drug interactions. Imaging technologies are also a way of quantifying surrogate clinical endpoints.

Progress Being Made

Survival rates in the UK have doubled over the past 40 years and for a number of cancers, including breast and skin cancer, more than eight out of 10 people will beat the disease, reflected Dr Chris Doherty, Managing Director of Alderley

Park. Research has led to better treatments, new drugs, more accurate tests, earlier diagnosis and screening programmes. He said that a number of life-saving cancer drugs have been developed at Alderley Park over the years and the focus is now on growing the number of new generation companies and organisations, allowing the Park to continue this trend. The site is a focal point for oncology development adjacent to Manchester, a city that has, in the past decade or more, become an important global centre for cancer research.

Manchester is home to The Christie Hospital, the largest single site cancer centre in Europe treating more than 44,000 patients a year. With valuable breakthroughs also being made in Newcastle, Sheffield, Liverpool and elsewhere across the North, he said Alderley Park was a catalyst for the cancer research and development community in the North. They were working to draw together important strands such as drug development, clinical trials, personalised medicine new target identification and chemistry and link this to the needs of patients.

The conference heard that helping UK small to medium-sized enterprises access technologies and expertise in oncology drug discovery is a key role for the Alderley Park-based Medicines Discovery Catapult (MDC). Established by the UK government through Innovate UK, its innovation agency, the catapult program is designed to promote success of key industries. "It is an opportunity to reinvigorate the UK's drug discovery industry by growing drug discovery and technology businesses and addressing systemic problems and bottlenecks," Peter Simpson, CSO at MDC, told delegates.

MDC is creating an inventory of national consulting expertise and experimental capabilities to facilitate deep collaborative research partnerships, establishing an informatics resource for companies, real-world relationships with key contacts, CROs and consultants as well as making it easier for start-ups to access assays and techniques, disease expertise, technologies and drug discovery know how.

With Redx Pharma, Quay Pharma, NewGene and Concept Life Sciences presenting at the Alderley Park meeting, as well academics from the Universities of Newcastle and Sheffield, it was clear the UK offers a wealth of talent, expertise and opportunities beyond the golden triangle of Oxford, Cambridge and London. One confirmation of that potential is the succession of non-British companies now relocating to, or co-locating in Alderley Park, and taking advantage of the site's many strands of life-science knowledge, experience and expertise.

Dr Chris Doherty
Managing Director, Alderley Park

How SMEs Are Delivering Oncology Breakthroughs

In the last decade big pharma has overhauled its approach to R&D. Total spending has remained at around \$70 billion a year, but where that resource gets deployed continues to evolve. One of the reasons it's happening is because attitudes have changed to the 'in-house only' R&D orthodoxy. Outsourcing and partnering are seen as key to innovation.

Accessing a wider pool of ideas through partnering can certainly improve the chances of coming up with something truly novel. It's about having diversity in chemistry and targets.

There's also an argument that says smaller companies have less tolerance for pet projects. They are quicker to call out programs by asking the critical questions earlier in the process – generally before the investment of resource on a whole battery of other tests.

We have 65 SMEs at Alderley Park, and another 150 in start-up or virtual mode. Many of them are oncology-focused or operate in the supply chain. In terms of therapeutics, these include Redx Pharma, which last year sold one of its cancer assets. This BTK inhibitor program went for USD40 million to the American company, Loxo Oncology. Redx also has an immuno-oncology asset, RXC004 Porcupine, that's expected to progress to clinical trials this year.

Our oncology start-ups include BiV-ictriX, which is developing ADC drugs



Dr Chris Doherty

that tackle antigens on the surface of cancer cells – it's a more targeted form of chemotherapy. One of the challenges with ADCs is that many of them target antigens that are also present on the surface of healthy cells. Toxicity is a huge issue. BiVictriX is working to progress an ADC that target two types of antigens that are only present on cancer cells, specifically cancer cells found in Acute Myeloid Leukaemia (AML).

Alderley Park's translational ecosystem includes CROs specialising in pre-clinical, clinical, safety/tox, CMC/formulation, regulatory, chemistry and proteins. This community features the likes of Concept Life Science, Gentronix, and Hematogenix, which all have an oncology focus.

Our oncology cluster reflects the reality that the North West of the UK and Manchester in particular has become a significant centre of cancer research. Alderley Park is currently home to The Cancer Research UK Manchester Institute

(CRUKMI). Our neighbours at The Christie Hospital, meanwhile, operate the largest single site cancer centre in Europe, treating more than 44,000 patients a year. Other significant participants include The University of Manchester's Manchester Cancer Research Centre (MCRC).

The UK government's Life Science strategy sets out plainly the goal of creating four biotech companies worth more than £20bn in the next 10 years. There's no doubt that SMEs based at our site will be key contributors towards achieving this objective. Having the right infrastructure is part of the equation. In terms of capability, few sites in Europe can match Alderley Park's physical assets, the scale of the investment that has been made and the access Alderley Park provides to a scientific workforce. Crucially, these resources are available at a significantly reduced cost, circa 25- 30%, to other locations in the South and East of the UK.

**MERESIDE
ALDERLEY PARK**

The UK's Largest Single Site Bioscience Campus

Alderley Park is home to the internationally-recognised Mereside bioscience campus which offers more than 1m sq ft of high specification ready to go chemistry and biology laboratories, a range of shared scientific services and a dedicated incubator.

Facilities on the Mereside campus also include:

- 2 x High field NMRs – 700MHz and 500MHz
- Biobanking
- Tissue culture suites
- Open access laboratories
- High density fume cupboard chemistry laboratories
- Biology laboratories with Class 2 cabinets
- Biotech pilot plant (10x40L)
- Pre-clinical imaging suite (MRI, PET, CT, SPECT)
- Vivarium
- Media preparation
- Analytical suites
- Archiving facility
- Equipment validation services

- Mass spectrometry
- Waste and logistics management

Alderley Park's on-site incubator specialises in the start-up and scale up of biotech and life science businesses by providing the facilities, services and support they need for success. The incubator is supported by an extensive network of entrepreneurs, key industry figures and senior executives who can provide expert training and business support. Their valuable assistance and coaching includes:

- Raising investment
- Developing an accelerated path to market
- The latest tools for entrepreneurial excellence

Two on-site venture funds are available to qualifying businesses, each offering access to all-important funding and investment.

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