**Impact case study (REF3b)**

**Institution:** Institution of Cancer Research  
**Unit of Assessment:** UoA1  
**Title of case study:** Discovery of a new class of cancer drugs: HSP90 inhibitors

### 1. Summary of the impact

HSP90 is a key molecular chaperone protein, and cancer cells are particularly dependent on its function. However, given its wide-ranging action, many doubted it would be possible to produce an effective and safe HSP90 inhibitor. Multidisciplinary research at the ICR has validated HSP90 as an oncology target and defined useful biomarkers leading to HSP90 currently being one of the most actively pursued targets in the drug industry. ICR’s own drug candidate, AUY922, was licensed to Novartis and is now in late stage clinical trials. It has shown promising therapeutic activity, especially in HER2-positive breast and non-small cell lung cancers, including drug resistant cases. HSP90 inhibitors could be used against a wide range of other cancers including breast, lung, prostate, ovarian and colon.

### 2. Underpinning research

Chaperones are proteins that assist the folding, stability and activity of “client” proteins and the assembly or disassembly of other macromolecular structures. HSP90 is a key chaperone protein, particularly important in cancer cells, and therefore a potential target for novel therapeutics. However, given its wide-ranging action, many doubted it would be possible to produce an effective and safe HSP90 inhibitor.

ICR’s first significant contribution to the HSP90 field was made by Dr Lloyd Kelland (ICR Faculty, 1990-2002) and Professor Paul Workman (ICR Faculty since 1997). They demonstrated that 17-AAG; a natural product-based HSP90 inhibitor developed by the National Cancer Institute (NCI), which was the first agent to enter the clinic, had a major metabolic toxicity and drug resistance liability and was unlikely to be a useful drug (Ref 1). 17-AAG is no longer being developed because of its limitations.

Professor Laurence Pearl (ICR Faculty, 1999-2010) and Dr Chris Prodromou (ICR Staff Scientist, 1999-2010) had published the first accurate crystal structure of HSP90 in 1997. At ICR, they began a collaboration with a drug discovery team led by Professor Workman with the objective of using the protein structure to help discover novel and effective HSP90 synthetic small-molecule inhibitors which were competitive at the critical ATP site.

HSP90 drug discovery at ICR began with a primary screen against the yeast enzyme and then the team developed an innovative counter screen for testing against the human enzyme; this secondary assay was based on ICR’s discovery and functional elucidation of the co-chaperone Aha1 (Ref 2). Using these screening assays in conjunction with; structure-based design, medicinal chemistry and tumour biology models, the ICR team discovered the pyrazole resorcinol series of HSP90 inhibitors (Ref 3). AUY922, the novel drug that is now undergoing clinical trials, is based on this resorcinol series.

In 2002, the ICR began a research collaboration with the UK company Vernalis. The two teams continued to optimize the ICR’s pyrazole resorcinol series using structure-based design and medicinal chemistry both at ICR and Vernalis. The majority of the biological research studies were undertaken by the research team led by Workman at ICR and these provided important validation of HSP90 as a useful oncology target (Ref 4).

From their optimisation of the pyrazole resorcinol series, the ICR/Vernalis team identified a potential clinical candidate. In 2004 Vernalis licensed the ICR/Vernalis HSP90 programme to Novartis, and Novartis adopted the clinical candidate identified by ICR and Vernalis (AUY922) (Ref 4). AUY922 is now in Phase II trials worldwide.

ICR has provided intellectual leadership for clinical trials of novel HSP90 inhibitors. Professor Ian
Judson, an ICR faculty member, led this clinical programme. ICR, together with its clinical partner the Royal Marsden NHS Foundation Trust (RM), began this work by conducting trials of 17-AAG. (ClinicalTrials.gov NCT00003969 and NCT00104897). These pioneering studies led to the first clinical demonstration of the detailed molecular signature of HSP90 inhibition and established that HSP90 inhibitors could be delivered safely.

ICR and RM have also played a central role in the clinical testing of ICR’s drug AUY922 (Ref 6). The first phase I trial at ICR and RM, led by Dr Uday Banerji (ICR Faculty), demonstrated proof-of-concept for target engagement and inhibition of tumour metabolism (FDG-PET). Two key phase II trials of AUY922 have been completed, showing promising activity in breast and non-small cell lung cancer.

3. References to the research

All ICR authors are in bold and ICR team leaders/Faculty are in bold and underlined.


Quality Indicators

Selected research grant support


2. Pearl – “The mechanism of client protein activation by the HSP90 molecular chaperone”, 2001-
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| 2006, total £865k | 3. Pearl – “Hsp90 molecular chaperone”, Wellcome Trust, 2006-2011, total £1.5m |

**Prizes**


2. American Association of Cancer Research Team Science Award 2012 for the team’s tremendous impact in preclinical and clinical studies relating to cancer therapeutics which included the highly innovative inhibitors of the molecular chaperone HSP90. ([http://www.aacr.org/home/scientists/scientific-achievement-awards/scientific-award-winners/team-science-award-.aspx](http://www.aacr.org/home/scientists/scientific-achievement-awards/scientific-award-winners/team-science-award-.aspx)).

3. The Royal Society of Chemistry named Professor Workman World Entrepreneur of the Year in 2012 “for his work as a scientific pioneer and serial entrepreneur whose numerous commercialized discoveries and academic research led to his founding two successful chemical companies” ([http://www.rsc.org/ScienceAndTechnology/Awards/EntrepreneuroftheYear/2012-Winner.asp](http://www.rsc.org/ScienceAndTechnology/Awards/EntrepreneuroftheYear/2012-Winner.asp))


4. Details of the impact

The ICR’s HSP90 research programme has had significant impacts on health and on commerce.

ICR research has validated HSP90 as a drug target and identified biomarkers to be used in clinical trials. This work was published, so that pharmaceutical companies worldwide could use the public domain information to develop their own in-house drug discovery programmes and more than 20 novel HSP90 inhibitors are now in clinical trials.

The ICR independently discovered the pyrazole resorcinol series of HSP90 ATP competitive inhibitors and then entered into a research collaboration with the UK biotechnology company Vernalis to optimize this chemical series further in order to identify a clinical candidate. Later Vernalis licensed the programme to Novartis, who adopted the ICR/Vernalis clinical candidate, named it AUY922 and took it into clinical trials worldwide.

**Impacts on Health**

- AUY922, a novel HSP90 inhibitor discovered by the ICR, is now progressing through clinical trials in the UK and internationally, and some of the Phase II trials have now been completed. Since 2008, many patients have participated in these trials (4 trials with 89 patients have been completed and 18 trials with estimated enrolment of 845 patients are ongoing); the drug has a good safety profile and there is preliminary evidence of efficacy (20-30% response rate in breast and non-small cell lung cancer with positive Phase II data by objective RECIST criteria in both diseases). The most promising, advanced trials so far include phase II clinical studies in patients with HER2-positive breast cancers which have become resistant to the commonly used antibody drug trastuzumab (Herceptin), and also in patients with non-small cell lung cancer who have become resistant to the widely used drugs erlotinib and crizotinib, which target two tumour pathways driven by EGFR and ALK, the protein products of which require HSP90 [1, 2, 3, 4, 5 and Research Ref 6 above].
- The ICR validated HSP90 as a potential cancer target and provided intellectual leadership (in parallel with Memorial Sloan-Kettering and NCI). This encouraged other pharmaceutical
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companies to develop novel drugs and recruit patients into clinical trials. Over 20 novel HSP90 inhibitors are now in clinical trials [6]. Over 15 international pharmaceutical or biotechnology companies have cited the ICR’s published research in this field (Web of Science data).

- The ICR developed novel pharmacodynamic biomarkers that are being used internationally in clinical trials of HSP90 inhibitors. Use of these biomarkers demonstrates target engagement and increases the rational basis for proceeding with treatment and reduces the risk of later attrition. Research Ref 5 above has been cited 280 times and by more than 7 international companies (Web of Science data).

Impacts on Commerce

- Vernalis has received substantial licence fee and milestone payments from Novartis as a result of the HSP90 deal. This has helped Vernalis to continue to employ UK staff at its facilities in Cambridge and Reading. Vernalis’ Interim Results report 29th July 2013 states that AUY922 is one of the operational highlights and that the company’s collaboration income has been growing [7].
- Vernalis has added shareholder value by having AUY922 in its pipeline [7, 8].
- Novartis has added shareholder value by having AUY922 in its pipeline. A Novartis investor report listed AUY922 as one of its potential blockbusters (Novartis 2nd quarter 2011 results and a Novartis R&D Investor Day presentation lists accelerating AUY922 development as a planned key activity in 2013-14 [9].
- Industry has invested in HSP90 research. Novartis and other pharmaceutical companies are conducting clinical trials of HSP90 inhibitors. There are 90 clinical trials of HSP90 inhibitors listed on the National Institute of Health Database, ClinicalTrials.gov, with a conservative estimate of an excessive of 5,000 patients treated with these inhibitors worldwide.

5. Sources to corroborate the impact


[2] Schroder CP et al. 2011, Use of biomarkers and imaging to evaluate the treatment effect of AUY922, an HSP90 inhibitor, in patients with HER2+ or ER+ metastatic breast cancer, J Clin Oncol ASCO Annual Meeting Abstracts. 29 (No 15_suppl), e11024


