Institution: Imperial College London

Unit of Assessment: 8 – Chemistry

Title of case study: B8-1 The Invention of Samuraciclib, a Highly Selective CDK-7 Inhibitor, the Formation of Carrick Therapeutics and Clinical Trials on Treating Patients with Resistant Cancers

Period when the underpinning research was undertaken: January 2000 to March 2016

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Prof Anthony G.M. Barrett, Prof Matthew J. Fuchter, Prof Simak Ali Prof Charles Coombes	Professors of Synthetic Chemistry Professors of Surgery and Cancer	January 1993 to present; July 2008 to present; August 1992 to present; October 1997 to present.

Period when the claimed impact occurred: March 2016 to 31 December 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

Hormone therapy-resistant and triple negative breast and prostate cancers cause considerable morbidity and mortality globally (2018: 3.4M new cases; 986K deaths). CDK7 is a critical enzyme regulator of gene expression and cell cycle progression, processes deregulated in cancers. The team reasoned that CDK7 inhibitors should provide new medicines for treating cancers. Over 11 years, they designed, synthesised, bio-assayed and optimised potent, selective inhibitors of CDK-7. These were licenced to Carrick Therapeutics, which thereby secured $95M in funding for the development of ICEC0942 (CT7001; Samuraciclib), and successfully completed Phase 1 clinical trials. Samuraciclib is now in Phase II trials to treat resistant cancers and has already rescued and improved the lives of critically ill patients with resistant breast and prostate cancers.

2. Underpinning research (indicative maximum 500 words)

Research was carried out from 2005-2016 by the Barrett and Fuchter (Chemistry, IC) and Coombes and Ali (Surgery and Cancer, IC) teams, in collaboration with Professor Dennis C. Liotta and James P. Snyder at Emory University in Atlanta, GA, USA on the design, synthesis, bioassay *in vitro* and *in vivo*, optimisation, de-risking and scale-up synthesis of highly selective inhibitors of the Cyclin Dependent Kinase-7 (CDK7).

In 2000, Ali and Coombes showed that recruitment of the transcription complex CDK-7-TFIIH to the estrogen receptor (ER), enables ER phosphorylation and activation by CDK-7. Subsequent studies demonstrated the importance of CDK-7-ER in resistance to breast cancer therapy, identifying CDK-7 as a novel important drug target for therapy-resistant breast cancer **[1, 2]**

In 2005 Barrett suggested six novel series of potential kinase inhibitors which differed in the bicyclic heterocyclic core and were functionalised with three peripheral ring substituents: an alkyl group, a substituted benzylamino group and an alkylamino residue functionalised by hydroxylation. Additionally, he proposed that these compounds should be selective modulators of the CDKs in particular CDK-7. These six classes were prioritised by CADD studies in Emory University as to their expected selectivity of inhibition of CDK-7 versus CDK-2 and of other kinases. Derivatives of the pyrazolo[1,5-a]pyrimidine core were selected and the CADD studies were used to refine the three peripheral ring substituents.

Subsequent medicinal chemistry design and parallel synthesis (led by Barrett and Fuchter) and bioassays developed at IC (led by Ali and Coombes), led to two major discoveries; BS-181 and

BS-194 **[3, 4]**. Although BS-181 had poor water solubility and oral bioavailability (2%), it possessed very high selectivity against CDK-7 but much lower activities against other CDKs and myriad other kinases in the National Cancer Institute's collection in the USA. In contrast, BS-194 had an oral bioavailability of 85% but was not as selective as a CDK-7 inhibitor.

Building on this knowledge, the IC chemists synthesised >1400 analogues, which were multiply bio-assayed by the Ali team in *in vitro* and *in vivo*. Iterative design, synthesis and bioassay, enabled the development of potent selective CDK-7 inhibitors, with minimised toxicity-related off-targets (hERG, CYPs), optimised physicochemical properties, ADME and PK, and efficacy in mouse xenograft studies. Ultimately, this led to the 3rd and most pharmaceutically important discovery, ICEC0942, a highly active, selective, safe, and orally bioavailable medicine for treating many cancers. In mouse xenograft studies of human cancer cell lines HCT116 (colon cancer) and MCF7 (breast cancer), ICEC0942 monotherapy showed significant reductions in tumour volume relative to controls and no significant weight loss or toxicities. Additionally, these studies showed enhanced tumour volume reductions with ICEC0942 and Tamoxifen or Fulvestrant combination therapies in a mouse xenograft model of ER+ MCF7 cells **[5, 6]**.

The IC chemists additionally developed a scalable highly stereoselective synthesis for the cost-effective manufacture of ICEC0942 using enantioselective catalytic hydrogenation and described methodology for the synthesis of diverse analogues including potential back-up candidates and their chemical and biomedical characterisations **[6]**.

3. References to the research (indicative maximum of six references)

[1] Chen, D., Riedl, T., Washbrook, E., Pace, P. E., Coombes, R. C., Egly, J. M. and Ali, S. Activation of Estrogen Receptor by S118 Phosphorylation Involves a Ligand-Dependent Interaction with TFIIH and Participation of CDK7. *Molecular Cell* **2000**, 6, 127-137. https://www.ncbi.nlm.nih.gov/pubmed/10949034

[2] Sarwar N, Kim JS, Jiang J, Peston D, Sinnett HD, Madden P, Gee JM, Nicholson RI, Lykkesfeldt AE, Shousha S, Coombes RC, Ali S. Phosphorylation of ERalpha at serine 118 in primary breast cancer and in tamoxifen-resistant tumours is indicative of a complex role for ERalpha phosphorylation in breast cancer progression. *Endocrine Related Cancer* **2006**, 13, 851-861. https://www.ncbi.nlm.nih.gov/pubmed/16954434

[3] Ali, S.; Heathcote, D. A.; Kroll, S. H. B.; Jogalekar, A. S.; Scheiper, B.; Patel, H.; Brackow, J.; Siwicka, A.; Fuchter, M. J.; Periyasamy, M.; tolhurst, R. S.; Kanneganti, S. K.; Snyder, J. P.; Liotta, D. C.; Aboagye, E. O.; Barrett, A. G. M.; Coombes, R. C., The Development of a Selective Cyclin-Dependent Kinase Inhibitor that Shows Antitumor Activity, *Cancer Research* **2009,** *69*, 6208-6215. http://cancerres.aacrjournals.org/content/69/15/6208

[4] Heathcote, D. A.; Patel, H.; Kroll, S. H. B.; Hazel, P.; Periyasamy, M.; Alikian, M.; Kanneganti, S. K.; Jogalekar, A. S.; Scheiper, B.; Barbazanges, M.; Blum, A.; Brackow, J.; Siwicka, A.; Pace, R. D. M.; Fuchter, M. J.; Snyder, J. P.; Liotta, D. C.; Freemont, P. S.; Aboagye, E. O.; Coombes, R. C.; Barrett, A. G. M.; Ali, S., a Novel Pyrazolo[1,5-a]pyrimidine is a Potent Inhibitor of Cyclin-Dependent Protein Kinases 1, 2, and 9, which Demonstrates Antitumor Effects, in Human Tumor Xenografts Following Oral Administration, *Journal of Medicinal Chemistry* **2010,** *53*, 8508-8522. http://dx.doi.org/10.1021/jm100732t

[5] Patel, H.; Periyasamy, M.; Bondke, A.; Slafer, B.W.; Kroll, S.H.B.; Barbazanges, M.; Starkey, R.; Ottavianl, S.; Harrod, A.; Aboagye, E.; Buluwela, L.; Fuchter, M.J.; Barrett, A.G.M.; Coombes, R.C.; Ali, S., ICEC0942, an Orally Bioavailable Selective Inhibitor of CDK7 for Cancer Treatment, Molecular Cancer Therapeutics, **2018**, *17*, 1156-1166. https://mct.aacrjournals.org/content/17/6/1156

[6] Bondke, A.; Kroll, S.; Barrett, A.; Fuchter, M.; Slafer, B; Ali, S.; Coombes, C.; Snyder, J. P., Pyrazolo[1,5-a]Pyrimidine-5,7-Diamine Compounds as CDK Inhibitors and their Therapeutic Use, US Patent 9,932,344 B2 https://worldwide.espacenet.com/?locale=en_EP search US 9932344

4. Details of the impact (indicative maximum 750 words)

Cancer is the second leading cause of death, with 9.6M deaths in 2018 globally and 178K in the UK. Novel therapeutics to better treat resistant cancers have a major impact on the quality of lives and significantly mitigate the high economic costs of these terrible diseases.

Following drug discovery and the identification of ICEC0942 as the most preferred pre-clinical candidate, Drs Theo Balasas and Tommy Rennison from Cancer Research Technologies (CRT) in collaboration with Imperial Innovations and the Office of Technology Transfer in Emory University marketed the IC CDK inhibitor portfolio which led to a successful mutually beneficial licensing deal with Carrick Therapeutics [http://www.carricktherapeutics.com/], a newly formed Biotechnology company. Access to the IC IP, was instrumental to the company, which raised $95M to develop ICEC0942 (renamed by Carrick as CT7001 and subsequently Samuraciclib) further and to take it into clinical trials and full commercialisation. The funders for Carrick Therapeutics were a consortium of ARCH Venture Partners, Woodford Investment Management, Cambridge Enterprise Seed Funds, Cambridge Innovation Capital, Evotec AG, Google Ventures and Lightstone Ventures. The licensing deal with Carrick Therapeutics was significant for IC, Emory and Cancer Research UK. [redacted] The $95M funding raised was to take CT7001 into the clinic as well as to develop other new cancer medicines **[A, B]**.

Initially, Carrick and their UK CRO, Sygnature Discovery Ltd (Nottingham) were advised by Barrett and Dr Alex Bondke (a former Barrett PhD student) and carried out the design, synthesis and bioassay of further analogues of CT7001 to encompass additional chemical space and further patents were filed with Barrett and Bondke as co-inventors. Following further late-stage preclinical studies by Carrick, the efficacy of CT7001 in further cancers including triple negative breast cancer and adult myeloid leukemia was demonstrated. Finally, with WuXi AppTec and STA (Shanghai), Carrick completed the manufacture of sufficient CT7001 on a multikilogram scale for both Phase I and Phase II trials using the method invented by the Barrett team **[A, C]**.

The first-in-human phase-1 trial was started in November 2017, with dose-escalation, investigating the safety and tolerability of CT7001 in monotherapy in [redacted] patients with advanced solid malignancies, to identify the minimum biologically active dose (MBAD) and maximum tolerated dose (MTD), towards establishing the optimal monotherapy dose of CT7001. This multi-centre study, in which patients were recruited into the study at the Christie NHS Foundation Trust/University of Manchester, Department of Oncology, University of Oxford and at Imperial College London, is now complete. The maximal dose level of 360 mg per day was established, CT7001 plasma exposure increased dose proportionally and pharmacologically active concentrations were achieved throughout the entire dosing period [redacted] and target engagement in normal cells was assessed by two PD markers of CDK7 inhibition. Across dose levels, a significant and sustained reduction was observed in phosphorylated RNA polymerase II in peripheral blood mononuclear cells ($p<0.01$) and in the number of circulating reticulocytes. Although anti-cancer efficacy of the drug is the not the endpoint of a Phase I cancer trial, data also demonstrated anti-tumour effects [redacted] with late-stage prostate cancer who showed a sustained reduction in Prostate Specific Antigen and symptomatic remission. [redacted] MBAD was identified as 120 mg once daily and MTD as 360 mg once daily. The recommended dose for Phase II has been established as 360 mg **[A, B, D, E, F, G, H, I]**.

Phase-2 clinical trials of Samuraciclib are now underway in over 30 hospitals in the UK and USA including Manchester, Oxford, IC, Glasgow, Cambridge, Southampton and the Dana Farber Cancer Institute, Boston, USA. Recruitment for these trials include [redacted] patients with late-stage triple-negative breast cancer; [redacted] patients with castration-resistant prostate cancer as well as patients with hormone receptor positive (HR+ve) and human epidermal growth factor-2 negative (HER2-ve) breast cancers.

Patients are being treated with monotherapy using Samuraciclib or combination therapies with Fulvestrant. Based on these studies, beneficiaries are patients with advanced breast, prostate and lung cancers, responsible for >30% of all recorded cancers, comprising, respectively, 165K and 5.5M new cases each year in the UK and globally as well as other resistant cancers. [redacted]

5. Sources to corroborate the impact (indicative maximum of 10 references)

Factual statements provided to Imperial by key users/beneficiaries, that corroborate specific claims made in the case study.

[A] Confidential Letter from Senior Partnership Manager, Commercial Partnerships, Cancer Research UK, 2 Redman Place, London E20 1JQ.

[B] Confidential Letter from Chief Scientific Officer, Carrick Therapeutics, Magdalen Centre, Robert Robinson Avenue, The Oxford Science Park, Oxford OX4 4GA

[C] Confidential Letter from Executive Director Emory Institute for Drug Development, Emerson Hall 305, Emory University, 1515 Dickey Dr, Atlanta, GA 30322, USA.

[D] Confidential Letter from The NHS Christie Trust, Wilmslow Rd, Manchester M20 4BX.

Representative Reports, reviews and web links

[E] http://www.carricktherapeutics.com/carrick-therapeutics-announces-first-patient-dosed-phase-1-clinical-trial-oral-cdk7-inhibitor-ct7001/ (Archived here)

[F] https://b-s-h.org.uk/about-us/news/new-cancer-drug-class-unveiled-at-imperial/ (Archived here)

[G] https://ashpublications.org/blood/article/130/Supplement%201/2645/80067/CT7001-a-Novel-Orally-Bio-Available-CDK7-Inhibitor (Archived here)

[H] http://www.englemed.co.uk/18/18apr111_tumour_new_drug_class.php (Archived here)

[I] Slide 19 on Evotec Publicity: https://www.evotec.com/f/6cc79a2f88eca089a23ad288333f2e86.pdf (Archived here)