Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Multi-million pound investment through discovery and development of a first-in-class inhibitor of CDK7

Period when the underpinning research was undertaken: 2000 - 2019

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:
Coombes, R Charles	Professor of Medical Oncology	1990 – present
Ali, Simak	Professor of Molecular Endocrine Oncology	1992 – present
Fuchter, Matthew	Professor of Chemistry	2008 – present
Barrett, Tony	Sir Derek Barton Professor of Synthesis	1993 – present

Period when the claimed impact occurred: 2016 - present

Is this case study continued from a case study submitted in 2014? No

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

Access to Imperial College biological data and intellectual property allowed Carrick Therapeutics to secure US $95,000,000 in funding for research, development and clinical trials.

CDK7 promotes growth and resistance to therapy in a wide variety of cancers, including breast and prostate, the two commonest malignancies in the UK. Imperial College researchers validated CDK7 as a cancer drug target, and synthesised and characterised the first-in-class CDK7 inhibitor ICEC0942. Following successful patent application, ICEC0942 and related compound families were licensed by Cancer Research UK (CRUK) and Imperial College London to Carrick Therapeutics Ltd in 2017.

2. Underpinning research (indicative maximum 500 words)

Normal cellular function requires the appropriate transcription of information encoded in the genome, generating the protein effectors that drive and regulate all cellular functions, including cell growth and division. Failure to limit expression of key genes is an important impetus for uncontrolled cell growth, one of the hallmarks of cancer.

The production of proteins from the genetic blueprint is a two-step process. First, an enzyme called RNA polymerase II *transcribes* information encoded in DNA into messenger RNA (mRNA), the key intermediary. mRNA is then *translated* into the proteins that execute all cellular functions. CDK7 is a critical orchestrator of all gene transcription. It activates RNA polymerase II by a process called phosphorylation.

Studies from Imperial College Professors Coombes and Ali from 2000-2006 showed that, in addition to activating RNA polymerase II, CDK7 also phosphorylates the oestrogen receptor (ER) (1), the key driver of breast cancer growth, itself a protein that controls expression of genes required for cell proliferation. Their findings showed that ER phosphorylation by CDK7 induces ER activity. Importantly, Ali's team identified in the lab that the action of CDK7 on ER was a potential mechanism by which ER-positive breast cancers could become resistant to hormone therapies. 80% of all breast cancers are ER positive, and hormone therapy is the mainstay of breast cancer treatment worldwide. Using tumour samples from patients, Ali's team then went on to show that CDK7 levels are increased in ER-positive breast cancer and that ER phosphorylation

was elevated in breast cancers that are resistant to hormone therapy, confirming their original hypothesis (2).

These studies prompted a collaboration with Professors Barrett and Fuchter from the Department of Chemistry to develop selective CDK7 inhibitors for treatment of hormone therapy resistant breast cancer, with BS-181 as the very first inhibitor of CDK7 (3).

Subsequent analogue design, synthesis, testing and optimisation was undertaken between 2008-2013 through CRUK funding, all work being carried out by the Imperial College investigators (3, 4). The work yielded ICEC0942, an orally administrable, selective small molecule inhibitor of CDK7 (5).

Between 2015-2017, the Imperial teams showed the potential of ICEC0942 to treat ER-positive breast cancer, its efficacy in combination with hormone therapies in ER-positive breast cancer and the inhibitory activity of ICEC0942 against breast cancer cells expressing mutant forms of ER, which is another important mechanism of hormone therapy resistance in patients with breast cancer (5, 6). Furthermore, screening of independent panels of almost 1,000 cancer cell lines established the likely benefit of ICEC0942-mediated CDK7 inhibition for the treatment of other cancer types, a finding that was confirmed in models of colorectal cancer (5).

Importantly, the early phase trials of ICEC0942 have shown encouraging activity with acceptable toxicity in patients with recurrent and metastatic ER positive breast cancer as well as recurrent prostate cancer.

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., Ali, S. (2008). Activation of estrogen receptor alpha by S118 phosphorylation involves a ligand-dependent interaction with TFIIH and participation of CDK7. *Molecular Cell*, 6(1): 127-137. DOI.

(2) Patel, H., Abduljabbar, R., Lai, C.F., Periyasamy, M., Harrod, A., Gemma, C., Steel, J.H., Patel, N., Busonero, C., Jerjees, D., Remenyi, J., Smith, S., Gomm, J.J., Magnani, L., Győrffy, B., Jones, L.J., Fuller-Pace, F., Shousha, S., Buluwela, L., Rakha, E.A., Ellis, I.O., Coombes, R.C., Ali, S. (2016). Expression of CDK7, Cyclin H, and MAT1 Is Elevated in Breast Cancer and Is Prognostic in Estrogen Receptor-Positive Breast Cancer. *Clinical Cancer Research*, 22(23):5929-5938. DOI.

(3) Ali, S., Heathcote, D.A., Kroll, S.H., 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., Coombes, R.C. (2009). The development of a selective cyclin-dependent kinase inhibitor that shows antitumor activity. *Cancer Research*, 69(15):6208-15. DOI.

(4) Heathcote, D.A., Patel, H., Kroll, S.H., 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., Fuchter, M.J., Snyder, J.P., Liotta, D.C., Freemont, P.S., Aboagye, E.O., Coombes, R.C., Barrett, A.G., Ali, S. (2010). 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. *J Med Chem.* 53(24):8508-8522. DOI.

(5) Patel, H., Periyasamy, M., Sava, G.P., Bondke, A., Slafer, B.W., Kroll, S.H.B., Barbazanges, M., Starkey, R., Ottaviani, S., Harrod, A., Aboagye, E.O., Buluwela, L., Fuchter, M.J., Barrett, A.G.M., Coombes, R.C., Ali, S. (2018). ICEC0942, an Orally Bioavailable Selective Inhibitor of CDK7 for Cancer Treatment. *Molecular Cancer Therapeutics*, 17(6):1156-1166. DOI.

(6) Harrod, A., Fulton, J., Nguyen, V.T.M., Periyasamy, M., Ramos-Garcia, L., Lai, C.F., Metodieva, G., de Giorgio, A., Williams, R.L., Santos, D.B., Gomez, P.J., Lin, M.L., Metodiev, M.V., Stebbing, J., Castellano, L., Magnani, L., Coombes, R.C., Buluwela, L., Ali, S. (2018).

Genomic modelling of the ESR1 Y537S mutation for evaluating function and new therapeutic approaches for metastatic breast cancer. *Oncogene* 2017 Apr 20;36(16):2286-2296. DOI.

Key Research Grants:

Co-PIs AGM Barrett & R.C. Coombes, Mining the Interface of Chemistry & Medicine: the Discovery of Novel Compounds for the Detection and Treatment of Cancers, EPSRC, 01 August 2005 to 31 July 2009, £505,903.

Co-PIs AGM Barrett & R.C. Coombes, The Development of Inhibitors of Cdk Activating Kinase (CAK), EPSRC, 18 December 2007 to 17 December 2008, £96,613.

Co-PIs AGM Barrett & R.C. Coombes, Transatlantic Training in Cancer Medicinal Chemistry and Drug Discovery, Cancer Research UK (CRUK): C21484/A6944, 1 October 2006 to 30 September 2015, £1,000,000.

Co-PIs AGM Barrett & R.C. Coombes, Imperial College Small Molecule Cancer Drug Discovery Programme Grant, CRUK: C37/A9335, 1 April 2008 to 31 March 2013, £2,500,000.

Co-PIs RC Coombes & S Ali, Transcriptional mechanisms regulating endocrine resistance in breast cancer Program Grant, CRUK: C37/A18784, 1 October 2015 to 28 February 2021, £2,940,000.

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

Studies at Imperial identified CDK7 as a potential therapeutic target in ER-positive breast cancer as well as other cancers, including prostate and colorectal. Imperial researchers subsequently developed ICEC0942 as the first-in-class selective inhibitor of CDK7. This work has moved from basic cancer biology through drug discovery and development to commercial partnership and clinical trials evaluation. Patents concerning the pharmaceutical composition of these compounds and their use to treat disorders associated with CDK7 activity were filed in 2014 [**A**].

The research undertaken at Imperial College London has had significant economic and commercial impact with benefit to the pharmaceutical industry in the UK and EU. ICEC0942 and related compound families were licensed by Cancer Research UK and Imperial College London to Carrick Therapeutics Ltd in 2017.

[redacted]

As a result of this funding, Carrick was able to develop an on-going clinical development programme for ICEC0942. This included full toxicology and re-confirmation of Imperial College data in additional *in vivo* cancer models. Phase 1 studies of ICEC0942, which began in 2017 (ClinicalTrials.gov Identifier: NCT03363893) [**C**] under the drug name CT7001 [**D, E**] (now also known as sumaraciclib), have been completed in Manchester, Oxford and Imperial College, and four parallel phase 2 studies (hormone therapy-resistant and triple-negative breast cancers, non-small cell lung cancer and acute myelois leukaemia) have been started in US and UK.

Although the full clinical impact of ICEC0942 is still emerging, the drug has already had a positive impact in cancer care: during the phase-1 trial, several patients with advanced breast and prostate cancers achieved either durable remissions or stabilisation of disease with minimal toxicity. These patients were enrolled in the study because they had no other treatment options and thus ICEC0942 has offered these patients the potential for additional length and quality of life that they would not otherwise had. [redacted]

[redacted]

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

[**A**] Patent of compound structures protecting ICEC0942: https://patents.google.com/patent/CA2939786A1/en?oq=CA2939786A1. Archived here.

[redacted]

[**C**] Clinical trial registration: Archived here
ClinicalTrials.gov Identifier: NCT03363893:
https://www.clinicaltrials.gov/ct2/results?cond=&term=ct7001&cntry=&state=&city=&dist=

[**D**] Carrick Therapeutics Press announces first patient on CT7001: 30th Nov 2017: https://www.carricktherapeutics.com/carrick-therapeutics-announces-first-patient-dosed-phase-1-clinical-trial-oral-cdk7-inhibitor-ct7001/. Archived here.

[**E**] CRUK Website for CT7001 clinical trial in triple-negative breast cancer: (https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-ct7001-for-triple-negative-breast-cancer-module-1-part-b). Archived here.