Research Assessment Exercise 2020
Impact Case Study

University: The Hong Kong Polytechnic University
Unit of Assessment (UoA): 1 Biological Sciences

Title of case study: New anti-cancer drug candidates create commercial and health benefits

(1) Summary of the impact

PolyU research has led to the development of four new anti-cancer drugs. Four international pharmaceutical companies have invested in developing these drugs since 1 October 2013 creating around 30 new jobs while supporting many more. One drug has been licensed for US$5 M. An estimated US$42.5 M has been invested in Phase I and Phase II clinical trials involving 160 participants during this RAE period. A trial with 15 liver cancer patients saw statistically significantly improved life expectancy. One melanoma patient entered remission and has been cancer-free for 30 months. Our first-in-class human arginase has prompted others to develop competitor drugs, with one in Phase III trials after an estimated US$78 M investment.

(2) Underpinning research

Despite huge improvements in cancer treatments there is still a need for better drugs for many common cancers, such as liver cancer that has no successful drug treatment. Interdisciplinary research at PolyU, including molecular biology, protein engineering, chemical biology and medicinal chemistry, has focused on designing new cancer drugs through increasing the efficacy of natural compounds and proteins.

Arginine depletion - Many cancers cannot create the amino acids that are essential for their survival. This provides a new cancer treatment approach, starving cancer cells to death (while leaving normal cells unharmed) by using enzymes to degrade the external supply of certain amino acids. In 2000, Professor Thomas Leung (PolyU staff 1996-present) and Dr. Thomas Lo (PolyU staff 1994-present) started collaborating with *Bio-Cancer Treatment International (BCT*), then a start-up, to investigate arginine depletion. Their research was at the forefront of this field, creating and reporting the world's first human arginine-depleting enzyme (*human arginase*) in a pioneering paper in 2007 that demonstrated inhibition of liver cancer cells both in vitro and in vivo [1].

Leung and Lo's innovation was to create a recombinant form of *human arginase* (covalently modified with polyethylene glycol), stabilizing the enzyme without affecting its activity so that it lasts long enough in the body to affect arginine levels. Subsequent research demonstrated their engineered arginase as having synergistic effects when used with other approved drugs, providing significant anticancer efficacy for a wide range of cancers (liver, breast, cervical, pancreatic, colorectal, lung, gastric, prostate cancer and melanoma) [e.g. 2]. *BCT* followed up on additional research and development, leading to the first-in-class clinical candidate (*BCT-100*) in 2008. Leung and Lo developed *2nd generation human arginase* through rational design in 2013, improving the 1st generation's efficacy [3].

Since 2014, Leung has applied his rational design expertise to *albumin-binding arginine deiminase (NEI-01)* – another biological route to starving cancer cells of arginine. In partnership with *New Beta Innovation*, he has designed and patented a modified *NEI-01* molecule [4].

Flavonoids - The membrane transporter permeability-glycoprotein (P-gp) has a key role in cancer drug efficacy. Cancer cells overexpress P-gp, pumping cancer drugs out and leading to patient

treatment failure. P-gp in intestinal cells can prevent drugs even being absorbed in the first place. Similarly, P-gp also reduces drug efficacy by preventing drugs penetrating the blood-brain-barrier. Interdisciplinary research between biologist Professor Larry Chow (PolyU staff 1997-present) and Professor Tak-Hang Chan (PolyU staff 2002-present) developed a new inhibitor for P-gp. This is as potent as any previously developed inhibitors, but crucially without the toxicity problems that have prevented the others from getting through the clinical trial phase.

As naturally occurring flavonoids can mildly inhibit P-gp, Chow and Chan's innovation was to create synthetic *flavonoid* dimers that recognise the two parts of the target transporter. Their 'two-handed' molecule, joined together by polyethylene glycol (PEG) chains of various lengths, greatly increases drug efficacy. These dimers also modulate drug chemosensitivity and retention in multi-drug resistant breast and leukemic cells, enhancing the cytotoxicity of common cancer drugs [5, 6]. They also demonstrated that the dimers can increase the oral bioavailability of *paclitaxel* (although this is one of the most effective anti-cancer drugs, it could not be administered orally) and *topotecan*. The use of Chow and Chan's flavonoid dimers can allow oral use of these drugs thereby avoiding painful intravenous administration with its attendant side-effects, risks and expense.

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

[1] Cheng PN, Lam TL, Lam WM, Tsui SM, Cheng AW, **Lo WH**, **Leung YC**. Pegylated recombinant human arginase (rhArg-peg5,000mw) inhibits the in vitro and in vivo proliferation of human hepatocellular carcinoma through arginine depletion. *Cancer Research*, 2007. **67**(1): p. 309-17.
[2] Lam TL, Wong GK, Chow HY, Chong HC, Chow TL, Kwok SY, Cheng PN, Wheatley DN, **Lo WH**, **Leung YC**. Recombinant human arginase inhibits the in vitro and in vivo proliferation of human melanoma by inducing cell cycle arrest and apoptosis. *Pigment Cell & Melanoma Research*, 2011. **24**(2): p. 366-76.
[3] **Leung YC**, **Lo WH**. Site-directed pegylation of arginases and the use thereof as anti-cancer and anti-viral agents. United States Patent No. 8507245 B2. 13 Aug 2013.
[4] Wong BL, Wai NFM, Kwok SY, **Leung YC**. Albumin-binding arginine deiminase and the use thereof. United States Patent No. 9255262 B2. 9 Feb 2016.
[5] Chan K-F, Zhao Y, Burkett BA, Wong ILK, **Chow LMC** and **Chan TH.** Flavonoid Dimers as Bivalent Modulators for P-Glycoproteins Based Multidrug Resistance (MDR): Synthetic Apigenin Homodimers Linked with Defined-length Polyethylene Glycol Spacers Increase Drug Retention and Enhance Chemosensitivity in Resistant Cancer Cells. *Journal of Medicinal Chemistry*, 2006. **49**(23): p. 6742-59.
[6] Yan SW, Wong IL, Chan KF, Kan JW, Chong TC, Law MC, Zhao Y, Chan SW, **Chan TH**, **Chow LMC**. A new class of safe, potent and specific P-gp modulator: flavonoid dimer FD18 reverses P-gp-mediated multidrug resistance in human breast xenograft in vivo. *Molecular Pharmaceutics*, 2015. **12**(10): p. 3507-3517.

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(4) Details of the impact

Cancer is the second leading cause of death globally, responsible for around 1 in 6 deaths. The anti-cancer drugs market is growing, with revenues expected to increase by 50% globally in the next five years. PolyU drug candidates (*first*- and *second-generation arginase, NEI-01*, and *flavonoid dimers*) are being directly exploited by four companies. Work on arginase has led another company to invest heavily in development and clinical trials.

First-generation arginase (BCT-100) is currently in Phase I and II trials and has already benefited a small number of late stage cancer patients. *BCT* and PolyU's relationship continued into this RAE period with *BCT's* co-founder holding an Adjunct Associate Professor position until 2016.

Submitted by *BCT* as its sole owner, *BCT-100* was Hong Kong's first ever drug to receive investigational new drug (IND) approval from the U.S. Food and Drug Administration (FDA), allowing *BCT* to initiate US based clinical trials as well as Hong Kong trials [C1]. During the RAE period *BCT* have completed three clinical trials including two Phase II trials, and have another three trials on-going [C2]. The trials, covering cancers such as leukemia, melanoma, prostate cancer and hepatocellular carcinoma (HCC), have involved around 140 participants. In 2016, the average cost of Phase I and Phase II oncology trials was reported as US$4.5 M and 11.2 M respectively. Therefore, an estimated US$38 M has been invested in clinical trials during this RAE [C3].

In 2014, early stage trials of *BCT-100* on 15 late-stage HCC patients resulted in statistically significant survival increase by 4.7 months for patients surviving long enough to reach adequate arginine depletion [C4]. HCC is the most common type of primary liver cancer with 500,000 new cases annually. In almost all cases it is deadly within 3 to 6 months. Currently the only drug on the market extends life for just 3 months. In this trial, for patients reaching arginine depletion, results meant averaging another 6.4 months of life rather than 1.7 months. This time could make an enormous difference to patients and their families to deal with practical and emotional consequences of bereavement.

In a 2017 US clinical trial, *BCT-100* showed a breakthrough result: one late-stage melanoma patient, for whom two immunotherapy treatments had failed, achieved complete remission. The patient experienced no toxicity from the treatment and had been clear of cancer for 30 months by May 2018 [C5]. This is a significant result not just for this individual, but as an indication that arginase is living up to its promise to be a revolutionary treatment, succeeding even where immunotherapy (itself heralded as a sea-change in adult cancer management) has not.

Beyond treating cancers, *BCT-100* research results show that it is also effective in treating autoimmune diseases such as rheumatoid arthritis [C1], further boosting *BCT's* commercial prospects.

In 2016, PolyU research graduates founded a new company**,** *Avalon PolyTom***,** to develop and exploit the *second-generation human arginase*. *Avalon PolyTom* licensed the arginase in 2016, attracting a US $3.4 M investment from global pharmaceutical company *Athenex* to fund the start-up and initial drug development. *PolyTom* have created two R&D scientist jobs in Hong Kong [C6]. Their ongoing PolyU relationship provides the company with access to state-of-the-art equipment and research consultancy from Leung and Lo. In June 2018, *Athenex* obtained worldwide rights for *PolyTom'*s novel therapy. Completing the licensing deal, *Athenex* paid US $3 M in cash and US $2 M in stock to *PolyTom* [C7]. *PolyTom* have already successfully completed preclinical investigations and in June 2019 they received *U.S. FDA* allowance of *Investigational New Drug (IND) Application* for the *second-generation human arginase* (PT01 – Pegtomarginase).

Since the 2007 publication of the initial *human arginase* results, biopharmaceutical company *Aeglea* has heavily invested in human arginase development. They have completed three clinical trials (Phase I & II) with three more underway, including one Phase III trial [C8]. Therefore, an estimated US$78 M has been invested during this RAE [C3]. Based on evidence that their arginase is a substantial improvement on available rare arginine-deficiency disorder therapy, *Aeglea* have received *FDA Breakthrough Therapy Designation* to expedite its development.

In 2014, *New Beta Innovation*, a Hong Kong based biopharmaceutical company, approached Leung to help them create a new molecule to deprive cancer cells of arginine, based on an existing bacterial enzyme. *New Beta Innovation* have now created around 27 Hong Kong based jobs developing Leung's re-designed *NEI-01* [C9]. These staff support production process development, quality tests development, preclinical studies, animal efficacy and toxicity studies and quality assurance. This represents a significant investment by HK investors.

Research into synthetic *flavonoid dimers* has already had economic and commercial impact via PolyU's industrial partner, US-based global clinical stage biopharmaceutical company *Athenex*. Since 2015, they have licensed three flavonoid patents from PolyU and are developing a new oral cancer drug ('*Oratopo*') using the flavonoids' ability to increase existing drugs' oral bioavailability. Explaining how they benefit**,** *Athenex's* Chief Executive states:

"The compounds licensed from PolyU have been pivotal in understanding the science in a key area of research at Athenex. The science of oral absorption of drugs and the role of transport proteins is quite complicated. The pharmacological profile of the PolyU compounds were instrumental in deconvoluting and understanding the role of transport proteins in this process and directing Athenex research towards compounds with the greatest chance of success in human clinical trials. This research continues at Athenex" [C10].

In March 2017, *Athenex* received US FDA "IND" approval to proceed to human trials for *Oratopo*. Being only Athenex's seventh IND allowance, this represented a significant proportion of their current assets in the clinic. Three months later, *Athenex* listed on the NASDAQ stock market, raising US$64 M in net proceeds. Descriptions of the PolyU research areas supported their IPO by forming part of the case filed with the Securities and Exchange Commission [C10]. *Athenex* now has a market capitalisation of around US$800 M. In July 2018, a 24 patient Phase I trial was launched, with an estimated US$4.5 M investment [C3].

In 2018 *Athenex* also created a new permanent position in Hong Kong specifically to work on this drug development. A further 10 employees work on the oral absorption research program in both the United States and Hong Kong. *Athenex* say that the insights gained from the research on the licensed PolyU compounds "*have certainly helped secure funding for these employees to continue the research program*" [C10].

(5) Sources to corroborate the impact

[C1] *BCT* website: https://www.bio-cancer.com
[C2] Clinical Trials database for *BCT-100* (archived November 2019)
[C3] Estimate of average clinical trial costs in US, *page 121, figure 1*
[C4] Phase II study report by *BCT* and the *University of Hong Kong*
[C5] Sustained complete remission in immunotherapy-resistant melanoma article
[C6] Testimonial from Director of Biologics Development, *PolyTom*, September 2019
[C7] US Securities and Exchange Commission report, June 2018: details of *Athenex* / *PolyTom* licensing deal, page 3 (archived November 2019)
[C8] Clinical Trials database for *Aeglea* drug (*AEB1102*) (archived November 2019)
[C9] Testimonial from *New Beta Innovation*, October 2019
[C10] Testimonial from Chief Executive Officer and Board Chairman, *Athenex*, July 2019