Institution: University of Glasgow

Unit of Assessment: Unit 1; Clinical Medicine

Title of case study: Transforming the treatment of chronic myeloid leukaemia

1. Summary of the impact

Chronic myeloid leukaemia (CML) is a rare blood cancer, with around 560 new cases diagnosed in the UK each year. Research conducted by Professor Tessa Holyoake's team at the University of Glasgow has led drug development and stimulated clinical trials of therapies targeting CML stem cells at two major pharmaceutical companies (Novartis and Bristol-Myers Squibb). The researchers are listed as co-inventors of a novel compound (LDE225) and have promoted two further therapies targeting CML stem cells (BMS-833923 and hydroxychloroquine) into clinical trials as treatments for CML. Holyoake also had a key role in establishing the Paul O'Gorman Leukaemia Research Centre in May 2008, funded by more than 1,800 charitable donations totalling around £2.6 million and giving patients unprecedented access to the latest clinical trials.

2. Underpinning research

Since 1999, a team of University of Glasgow investigators led by experimental haematologist Professor Tessa Holyoake has conducted research into chronic myeloid leukaemia (CML). The hallmark of CML is a genetic rearrangement that produces BCR-ABL, a chimeric protein instrumental in cancer development. BCR-ABL is a tyrosine kinase that modulates the functions of other proteins and is permanently active in the cancer cells of patients with CML. These properties of BCR-ABL were exploited by the pharmaceutical industry to create the first targeted therapy for CML—the tyrosine-kinase inhibitor (TKI) imatinib.

Holyoake was the first scientist worldwide to demonstrate that all CML patients have a pool of cancer-forming stem cells ('CML stem cells') that lead to leukaemia in experimental animal models (1999; work conducted at the Terry Fox Laboratory, Canada). This discovery provided the cornerstone for her subsequent world-leading research at the University of Glasgow.

In 2001, Holyoake's group demonstrated that CML stem cells from newly diagnosed patients produced specific factors (cytokines) that switch on key signalling pathways to facilitate their survival and expansion,[1] thereby suggesting a mechanism for the growth advantage that CML stem cells have over normal cells (which do not produce these cytokines). In 2002, the University of Glasgow research group published the first study to show that CML stem cells are resistant to treatment with imatinib because they can survive in a dormant state.[2] This observation highlighted a major limitation of imatinib—patients with CML are unlikely to be cured by treatment with imatinib alone, despite the drug lengthening their lives, because of the persisting CML stem cell population. In response, pharmaceutical companies developed more-potent TKIs such as dasatinib, nilotinib and bosutinib. However, research conducted in the Holyoake laboratory demonstrated that CML stem cells were also resistant to these new compounds,[3] leading the team to focus on identifying novel methods of enhancing the effects of TKIs.

Holyoake's group discovered that intermittent exposure to granulocyte colony-stimulating factor forced CML stem cells out of their dormant state, thereby enhancing the ability of imatinib to kill them (published in 2006).[4] Furthermore, the University of Glasgow team showed that CML stem cells can be killed by compounds that target pathways other than that involving BCR-ABL, such as those active during cellular responses to environmental signals (e.g. stress) and mechanisms that prevent cell death. For example, Holyoake's team and their international research collaborators (see below) showed that treatment with imatinib induced metabolic stress and provoked an autophagy response in CML stem cells that, by promoting the degradation of damaged intracellular organelles and cytosolic proteins as an alternative source of energy, allowed them to survive the toxic effects of the drug.[5] By contrast, suppressing autophagy, either by knockdown of essential autophagy genes or by pharmacological agents such as chloroquine, allowed imatinib to more effectively kill CML stem cells. The validity of this approach was confirmed by the discovery in 2012 that CML stem cells do not depend on the activity of BCR-ABL to stay alive.[6] This study showed

that inhibiting BCR-ABL in a laboratory setting did not affect the ability of CML stem cells to survive in sub-optimal conditions. Taken together, this body of research demonstrates that treatment with a TKI alone cannot cure CML because of the residual population of TKI-resistant CML stem cells.

***Key University of Glasgow researchers*:** Tessa Holyoake (Professor of Experimental Haematology, 1992–present); Mhairi Copland (Clinical Research Fellow, 2003-2008; Clinical Senior Lecturer, 2008-2013; Professor of Translational Haematology, 2013–present); Heather Jørgensen (Research Fellow, 2006–present); Ashley Hamilton (Research Assistant, 2004-2010); David Irvine (Clinical Research Fellow, 2008-2012, Clinical Lecturer, 2008-present); G Vignir Helgason (Postdoctoral Fellow, 2007-present); Susan Graham (Research Assistant, 1999-2006; now at Novartis).
Key external research collaborators: Connie Eaves and Xiaoyan Jiang (Terry Fox Laboratory, Canada); Paolo Salomoni (University College London, UK); Bruno Calabretta (Thomas Jefferson University, USA).

3. References to the research

1. Holyoake, T.L. *et al.* Primitive quiescent leukemic cells from patients with chronic myeloid leukemia spontaneously initiate factor-independent growth in vitro in association with up-regulation of expression of interleukin-3. *Blood* 97**,** 720–728 (2001) doi:10.1182/blood.V97.3.720.
2. Graham, S.M. *et al*. Primitive, quiescent Philadelphia-positive stem cells from patients with chronic myeloid leukemia are insensitive to STI571 in vitro. *Blood* 99, 319–325 (2002) doi:10.1182/blood.V99.1.319.
3. Copland, M. *et al*. Dasatinib (BMS-354825) targets an earlier progenitor population than imatinib in primary CML but does not eliminate the quiescent fraction. *Blood* 107, 4532–4539 (2006) doi:10.1182/blood-2005-07-2947.
4. Jørgensen, H.G. *et al.* Intermittent exposure of primitive quiescent chronic myeloid leukemia cells to granulocyte-colony stimulating factor in vitro promotes their elimination by imatinib mesylate. *Clin. Cancer. Res.* 12, 626–633 (2006) doi:10.1158/1078-0432.CCR-05-0429.
5. Bellodi, C. *et al*. Targeting autophagy potentiates tyrosine kinase inhibitor-induced cell death in Philadelphia chromosome-positive cells, including primary CML stem cells. *J. Clin. Invest.* 119, 1109–1123 (2009) doi:10.1172/JCI35660. [A Hamilton, joint first author]
6. Hamilton, A. *et al.* Chronic myeloid leukemia stem cells are not dependent on Bcr-Abl kinase activity for their survival. *Blood* 119**,** 1501–1510 (2012) doi:10.1182/blood-2010-12-326843.

Grant funding

Medical Research Council. *Is the induction of autophagy by tyrosine kinase inhibitors a key survival mechanism for chronic myeloid leukaemia stem cells?* (Feb 2010–Jan 2013, £1,041,000; T Holyoake, principal investigator).

4. Details of the impact

CML is classified as an orphan disease—one so rare that it only affects a very small number of people and might, therefore, be a low priority for pharmaceutical company pipelines. However, if left untreated, late-stage CML can be fatal within 3–6 months and its prevalence is increasing. CML is anticipated to become the commonest leukaemia in the future, highlighting the urgent need for new therapies.

Bone marrow transplantation was long considered the only realistic treatment for CML, but it is a toxic procedure that requires suitable donor tissue and is associated with serious side effects and high death rates. Crucially, bone marrow transplants cannot be performed in older patients and the average age of CML onset is 55–60 years. Directed therapy with imatinib changed the landscape of CML care forever: what was once a deadly disease became a persistent but manageable condition—many patients now live essentially normal lives after diagnosis. Consequently, although the incidence of CML remains stable, its prevalence has dramatically increased since TKIs became widely available.

University of Glasgow researchers have taken a mechanistic approach to understanding the factors influencing CML stem cells with a view to identifying new therapeutic targets. Holyoake's

team was the first to demonstrate that TKIs are only the initial step towards curing CML. A leading expert on CML[a] and former winner of the highly prestigious Lasker prize for the development of imatinib states the importance of this finding: "*Holyoake was the first to alert the clinical research community to the fact that cancer stem cells could not be killed by imatinib. Her work on the concept of cancer stem cells has since been confirmed in other blood and solid cancers.*"

Impact on industry

Holyoake has worked closely with key industrial partners, such as Novartis and Bristol-Myers Squibb (BMS), acting as consultant, opinion leader and international advisor, as well as Principal Investigator for numerous international clinical trials.[b] Her research has led to a paradigm shift in the research and development (R&D) strategy of the pharmaceutical industry, refocusing the efforts of major companies towards a cure by pursuing the TKI-resistant CML stem cell population, which in turn has translated into clinical trials of innovative compounds.[b,c]

Novartis, the third largest pharmaceutical company worldwide in 2012, has developed a10-year strategy to achieve, *"successful TKI discontinuation and potentially provide an operational cure for CML patients.*" This strategy was developed at a Novartis Advisory Board meeting at which Holyoake was the sole UK expert.[c] The pathogenesis-driven pathways identified by Holyoake's research were incorporated as key targets for the development of novel therapies to be given in combination with first-generation or second-generation TKIs. According to Novartis,[c] "*Professor Holyoake is one of very few clinician–scientists with a long-standing interest and expertise in LSC [CML stem cell] biology … her work has led to the current understanding of LSC kinetics in CML and the development of possible treatment approaches for the management of minimal residual disease.*" He continues: "*Novartis Oncology has regularly chosen Professor Holyoake to participate as an expert advisor on stem cell biology for our global Advisory Boards. Professor Holyoake has participated in several Novartis-sponsored global clinical trials in CML as Principal Investigator. Only a limited number of global experts with expertise in the conduct of CML trials are chosen for this role.*"

Novel compounds enter clinical trials for CML

Access to the R&D pipelines of pharmaceutical companies has enabled Holyoake and her group to identify compounds that kill CML stem cells in the laboratory, providing the basis for their progression into pioneering clinical trials. For example, a pathway called hedgehog, which is known to regulate stem cell functions such as growth, death and development, was shown to be highly active in the CML stem cell population. Pharmacological inhibition of this pathway is being investigated by both BMS and Novartis.[b,c]

University of Glasgow researchers Drs Mhairi Copland and David Irvine are listed as co-inventors (with three Novartis employees) of the hedgehog blocker LDE225 in a patent application filed by Novartis in the USA (12/539855) and more than 15 other countries (PCT/US2010/045133).[d] A phase I trial of LDE225 plus the TKI nilotinib (NCT01456676) was initiated by Novartis in January 2012 to assess toxicity and maximum tolerated dose. This trial is currently recruiting 36 CML patients from 17 centres in 9 countries in North America, Europe and Asia.

Copland also led the correlative stem cell assays for patients recruited from all participating centres worldwide for a phase I trial of the hedgehog blocker BMS-833923 plus the TKI dasatinib (NCT01218477).[e] This dose-assessment study was initiated by BMS in January 2011 and recruited 27 CML patients from 12 centres in 7 countries in North America and Europe (analysis is currently underway). The University of Glasgow was the sole UK centre for this trial.

Established drugs offer a fresh approach to treating CML

Hydroxychloroquine—an antimalarial drug also used to treat inflammatory diseases—was shown by Holyoake's team to kill CML stem cells by blocking autophagy. Holyoake is leading the phase II CHOICES study (NCT01227135), the first clinical trial to investigate treatment responses to the combination of hydroxychloroquine and imatinib. CHOICES began in March 2010 with the target to recruit 66 CML patients from ten centres in the UK, Germany and France. As of July 31st 2013, 36 CML patients have been recruited, 18 of whom have received this combination therapy.

Public engagement

Holyoake instigated and led the establishment of the Paul O'Gorman Leukaemia Research Centre (POGLRC), an enterprise funded by more than 1,800 charitable donations totalling in excess of £2.6 million, many of which were made by CML patients, their families and friends. POGLRC benefits patients with CML throughout the UK by giving them unprecedented access to the latest clinical trials. The centre was officially opened on 22nd May 2008 by Dr Richard Rockefeller,[f,g] a practicing clinician who himself has CML. Rockefeller donated $200,000 (approximately £124,000) to help launch POGLRC and at the opening ceremony said "*I have chosen to support POGLRC because among all the world's researchers, Dr Tessa Holyoake and her extraordinary staff stand out as offering the greatest promise of a medical cure for the leukaemia from which I have suffered*."

Established in 2009, the "Friends of POGLRC" is a committee of patients, volunteers and donors, chaired by Holyoake and administered by University of Glasgow, who raise awareness of, and conduct fundraising and educational activities for, the centre via social media.[h] The importance of cancer stem cells in driving drug resistance of leukaemia is the key message conferred through laboratory open days and regular newsletters. Over the past 5 years, more than 2,000 people have taken part in Cycle Glasgow, raising approximately £160,000 for POGLRC.[i] The event is supported by local and national companies (including Tunnock's, Costco, Grease Monkey Bicycles and Overton Farm Shop) who supply food and water for the participants. In addition, Tunnock's fields a team of fundraisers who to date have raised around £10,000.[i] In August 2008, the profile of this event was raised by the participation of record-breaking cyclist and broadcaster Mark Beaumont. Further events promoted by the Friends of POGLRC have included international treks (Vietnam, China and Africa, 2010), a zip slide across the river Clyde (2012), gala lunches (2012) and a fashion show (2013).[i]

In November 2009, Holyoake received a Scottish Health Award for her work in clinical cancer care at a ceremony hosted by the Scottish Government and the *Daily Record* newspaper.[j] She later received an award from the Lord Provost of Glasgow for services to health (May 2011). These awards honour people who have dedicated their professional lives to public service or worked selflessly for their communities. In 2013, Holyoake was one of 44 new Fellows elected to the Academy of Medical Sciences, which "*promotes the best of medical science for the benefit of society.*"

5. Sources to corroborate the impact

a. Statement from Director, Knight Cancer Institute (available on request).
b. [Text removed for publication]
c. Statement from Head of Hematology, Novartis Oncology (available on request)
d. LDE225 US (12/539855) and international (PCT/US2010/045133) patent application (available on request)
e. BMS-833923 clinical trial contract (available on request)
f. Statement from Dr Richard Rockefeller (available on request)
g. Opening of POGLRC media coverage, May 2008 in the Herald and University of Glasgow press release
h. Friends of Paul O'Gorman Facebook page
i. Fundraising for POGLRC, 2008–2013 (available on request)
j. Awards media coverage:
- Scottish Health Awards, Cancer Care Team award presented to Prof Holyoake, November 2009
- Lord Provost's Awards – Health Award presented to Prof Holyoake, May 2011
- Fellowship of the Academy of Medical Sciences awarded to Prof Holyoake, May 2013