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In memory of Tessa Holyoake and Her Work on Chronic Myeloid Leukemia Stem Cells

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The development of imatinib and other ABL1 kinase inhibitors has significantly improved the outcome and the quality of life of patients with chronic myeloid leukemia (CML), caused by the *BCR-ABL1* fusion gene. Long-term follow-up of imatinib-treated CML patients has confirmed the efficacy of imatinib over long periods and the lack of major cumulative or late toxic effects.¹ However, despite these impressive results and the achievement of major molecular responses in about 90% of patients,¹ complete eradication of the leukemic cells seems more difficult to achieve. Indeed, imatinib stopping trials show that in about 60% of CML patients with undetectable minimal residual disease, *BCR-ABL1*-positive cells re-emerge in the first 2 years after imatinib discontinuation.²

These data clearly demonstrate that CML stem cells are difficult to target with imatinib alone. Tessa Holyoake was among the first to realize and demonstrate this problem when she illustrated that CML stem cells were not very sensitive to imatinib.³ She initially used short-term cultures of CD34⁺ progenitor cells obtained from CML patients and demonstrated that in these purified populations, imatinib treatment had little effect on the viability of quiescent cells.³ In subsequent studies, Tessa demonstrated that in a mouse model of CML, leukemia stem cells were able to persist upon inactivation of *BCR-ABL1* expression, and that in 12-day cultures of human CML cells, *BCR-ABL1* inhibition with dasatinib alone led to a mild and reversible reduction in the number of stem cells.⁴

With this knowledge, Tessa started to explore the mechanisms underlying this insensitivity of CML stem cells to ABL1 kinase inhibitor treatment, aiming to develop new strategies to target these cells more effectively. Based on the knowledge that the JAK/STAT pathway is implicated in cytokine receptor signaling, which is important in the stem cell niche, she identified the JAK/STAT pathway as a target for therapy. Her research demonstrated that treatment with the JAK kinase inhibitor ruxolitinib led to a reduction in the numbers of quiescent CML stem/progenitor cells.⁵ Next, using proteomics, transcriptomics, and network analyses, she elegantly demonstrated that perturbation of both TP53 and MYC in leukemia stem cells resulted in apoptosis and differentiation, leading to significant reductions in CML stem cell numbers, while sparing normal stem cells.⁶ In yet another study published in 2016, she demonstrated together with David Vetriche that epigenetic reprogramming can sensitize CML stem cells to combined EZH2 and tyrosine kinase inhibition.⁷

In a recent issue of *Nature Medicine*, the laboratories of Tessa Holyoake, Vignir Helgason, and Eyal Gottlieb combined forces to study metabolism as a possible target in CML stem cells. They found that CML stem cells rely on upregulated mitochondrial oxidative metabolism for production of energy and anabolic precursors and, as a consequence, for their survival.⁸ Interestingly, there is an FDA-approved antibiotic available (tigecycline) that inhibits bacterial and mitochondrial protein synthesis, and treatment of human cells with high doses of tigecycline should thus effectively inhibit the synthesis of proteins required for oxidative phosphorylation. Indeed, tigecycline treatment caused decreased levels of mitochondrial encoded proteins, demonstrating on-target effect of such treatment. Moreover, tigecycline treatment led to decreased numbers of colonies from CML CD34⁺ cells, and a combination with imatinib completely abolished colony formation. At similar doses, there was almost no effect on colony formation of normal CD34⁺ cells. Also in vivo, tigecycline combined with imatinib treatment of immunodeficient mice transplanted with CML CD34⁺ cells resulted in a dramatic reduction of the CD34⁺CD38[−] fraction in the bone marrow. Taken together, these data reveal mitochondrial oxidative phosphorylation as another vulnerability of CML stem cells and provide a new avenue to target CML stem cells.

For her groundbreaking work and dedication toward CML research, Tessa Holyoake was awarded the 2017 iCMLf Rowley Prize. The Rowley Prize is awarded each year by the International CML Foundation to celebrate investigators who have made outstanding lifetime contributions to the understanding of the biology of CML.

Tessa Holyoake, Professor of Experimental Haematology at the Glasgow Paul O’Gorman Leukaemia Research Centre, sadly passed away in August 2017, after a fight against metastatic breast cancer. She will be missed by all of us as a great colleague, outstanding scientist and enthusiastic EHA member who contributed to the EHA activities on many occasions. Tessa will be remembered in particular for her important contributions to our understanding of the behavior of CML stem cells, especially related to resistance of these cells to ABL1 kinase inhibitor therapy. All CML patients who have benefitted so much from Tessa’s seminal contributions to the field must hope that other investigators will similarly transform outcome for patients with metastatic breast cancer.

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