Rare cancers: the greatest inequality in cancer research and oncology treatment

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Molecular biology has transformed the treatment of solid tumours over the last decade. By improving through better biomarkers for traditional standard of care (Mulligan et al., 2014), delivering the promise of targeted therapeutics (Tan and Lynch, 2012) or opening the avenue of immune checkpoint therapeutics (Sharma and Allison, 2015), the landscape of oncology treatment has changed substantially, and numerous new targeted therapies and predictive diagnostics have been added to the known ER/Tamoxifen and Her2/Trastuzumab examples. Genomic medicine, imperfect as it may be (Tannock and Hickman, 2016), is providing some patients with longer, better lives. And yet, 1 in 4 patients with cancer will have these new therapeutics denied in the near future because of the way national grant agencies and research-focused charities are prioritising the administration of scientific resources. The work by Alvi et al. (2017), published in this issue of the BJC, supported by a generous donation from a cancer patient, is an example of the difficulty of aligning competitive funds to a neglected area of cancer research.

Although some of the issues regarding rare cancers are shared by many other diseases, there are specific questions in relation to funding that are probably specific to rare cancers in adults. Indeed, rare cancers comprise a staggering 198 varieties (a complete list can be obtained at http://www.rarecarenet.eu/rarecarenet/index.php/cancerlist) and are primarily grouped according to the site of origin. (Rare Cancers Europe, 2017; RARECARE, 2017). Some rare cancers are clear-cut independent disease entities of low frequency (e.g., small bowel adenocarcinoma with only ~3000 cases diagnosed yearly in the US) whereas others are unusual subtypes of mainstream cancers (e.g., colorectal signet ring cell carcinoma comprises ~1% of all colorectal carcinomas; Nitsche et al., 2013). The latter is important because of the way we typically undertake research – such unusual subtypes are subsumed in large cohorts of common cancers, with no statistical power to discern their potential genetic uniqueness and very often they simply remain undetected, hidden amongst the common subtypes. Although there is no agreement on a precise definition, rare cancers are defined as those with an incidence rate of <6 per 100 000 persons per year, whereas in the US it is <15 per 100 000 (Greenlee et al., 2010; Cancer Research UK, 2016; RARECARE, 2017). Collectively, rare cancers represent ~22% of all cancer cases diagnosed in the EU and 27% of these in the USA (National Cancer Institute Epidemiology and Genetics Research, 2017; Rare Cancers Europe, 2017). The development of clinical trials in rare cancers in both early and advanced disease settings has been a major challenge, but the International Rare Cancers Initiative has recently catalysed clinical trials across the UK, Europe, N. America, Japan and Australasia in a variety of rare tumours (Bogaerts et al., 2015 and see http://www.irci.info/).

Grant funding agencies and grant reviewers (most of whom may not have had any experience in rare cancer research) face a major problem in judging the quality of rare cancer research proposals. Indeed, it is expected that such applications should contain all the components that make a successful application in the common cancer paradigm: adequate sample calculations for biomarker discovery and validation, preliminary in vitro evidence of the research question, cell lines and animal models to test the research hypothesis, adequately designed and powered clinical trials and so on. While some of these shortcomings can be tackled with international consortia, others are very difficult if not possible to address in the space of rare cancer research. As a result, when looking at the main expenditure in cancer research by leading research funding agencies, the amount of funding is generally related to the single most prevalent forms, and does not include significant funding for rare cancer research (https://www.everydayhealth.com/cancer/cancer-research-where-funding-goes.aspx).

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Figure 1. Schematic paths for research design in the context of translational research in cancer. In either model, we have highlighted in blue the activities that may need to be revisited (i.e. how we power a study in rare diseases) or avoided altogether (for instance, the use of animal models or cell lines that are usually not available for individual rare cancers) when designing discovery work in this field.

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