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Personalized Cancer Medicine: Are We There Yet?

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It is now more than 15 years since Daniel von Hoff delivered the *21st Richard and Hinda Rosenthal Foundation Award Lecture* with the provocative title "There Are No Bad Anticancer Agents, Only Bad Clinical Trial Designs" [1], in which he postulated that the main reason why 90% of new cancer drugs failed in the clinic (at that time) was because these novel agents were not being tested in appropriate clinical trials, leading to a process of programmed drug death, which he referred to as "pharmacoptosis". He highlighted the imperative for a closer collaboration between the bench scientist and the clinical investigator, emphasizing the need to take into account the mechanism of action of a potential drug candidate when deciding which group of patients should be treated with the experimental protocol. His call for collaboration between the bench scientist and the clinician was really a forerunner of the science of translational medicine.

von Hoff's hypothesis appears to have come back into vogue with the presentation by National Cancer Institute Director Harold Varmus at the recent American Association for Cancer Research Conference in Washington, D.C., where he discussed how precise molecular evaluation of samples from a minority of patients (1%–2%) who showed exceptional therapeutic responses in "failed" cancer clinical trials (von Hoff's "pharmacoptosis" trials), may harbour distinct genetic stratification clues that allow these previously rejected agents to be tested for beneficial effects, repurposing previously discarded clinical entities for therapeutic benefit in the most appropriate subpopulation of patients. This phenotype to genotype (P2G) approach is among the strategies that are discussed in this month's edition of *European Perspectives*, where cancer clinical trial leaders from Europe and the U.S. respond to the pertinent question "Cancer Clinical Trials—Do We Need a New Algorithm in the Age of Stratified Medicine?" both in an expert opinion article [2] and in an accompanying online roundtable that took place during the EORTC-NCI-AACR Conference on Molecular Targets [3].

The translation of discovery science to clinical application is also at the heart of the second article in this month's *European Perspectives*, in which Edison Liu, Director of the Jackson Laboratory, and Patrick Johnston, Co-editor of ***The Oncologist*** **European Edition**, respond to the intriguing title, "Personalized Medicine: Does the Molecular Suit Fit?", both in print [3] and in an online roundtable that took place at the time of Dr. Liu's delivery of The Annual George Mitchell Lecture at Queen's University Belfast, Northern Ireland.

Personalized cancer medicine is at the most crucial phase in its development. There has been intensive debate recently on the availability (and cost) of new innovative drugs such as vemurafenib, the novel drug that targets mutant B-RAF, and ipilimumab, the CLA4 inhibitor, in malignant melanoma [4]. A more precise understanding of the biology of malignancy has heralded this new wave of drugs that are designed to "hit" a particular abnormal gene or pathway in a cancer cell. The most successful of these drugs, as highlighted in the Liu and Johnston article [3], has undoubtedly been imatinib mesylate, the tyrosine kinase inhibitor (TKI) that is directed against BCR-ABL, the mutant protein that leads to aberrant signalling and resistance to chemotherapy in chronic myeloid leukemia (CML). Imatinib was introduced as a therapy in 2001, following a highly fruitful collaboration between academia and the pharmaceutical industry, and has become the gold standard for the treatment of CML [5]. Ten-year survival has increased from 20% to 80%, and CML is now less like a cancer and more like a chronic disease such as diabetes, for which continuing therapy can ensure prolonged survival. Imatinib and its associated second and third generation TKIs represent a sine non quon of how personalized medicine can significantly influence disease outcome [6].

But are the increasing costs associated with these new drugs acceptable, particularly in the current economic climate? Last month, 100 international experts in CML, including Brian Druker, the originator of the TKI approach, published a revealing article in *Blood*, the journal of the American Society for Hematology [7]. In this article, they argue that the current pricing of cancer drugs is becoming unsustainable, particularly in the U.S. In 2001, when imatinib was introduced, its costs were high, approximately $30,000 (~€22,900) per patient per year. One of the reasons for this high price was to pay for the costs of development of a new drug, which are estimated at approximately $1 billion (~€763 million). However, by 2012, the cost had risen over threefold to $92,000 (~€70,000) per patient per year, despite the fact that the annual sales in the U.S. were initially over $900 million (~€685 million), meaning that developmental costs would have been recouped within the second year of sales. Fortunately in Europe, due to governments pressing for bulk-buying deals from pharmaceutical companies, the cost is lower than in the U.S.,

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but it is still a significant burden on our individual and collective health budgets.

There have been many advances in the 15 years since Dr. von Hoff's lecture and accompanying article advocated a stratified approach in patient selection for clinical trials. The ability (and appetite) of the oncology community to empower collaborative personalized medicine approaches has the potential to deliver transformational benefits for the European cancer patient. However, while innovation must be rewarded and the development of personalized medicine holds significant promise for cancer patients, there needs to be a balance between a just price and excessive profiteering for these new innovative agents. As the recent article in *Blood* highlights, "Grateful patients may have become the 'financial victims' of the treatment success, having to pay the high price annually to stay alive." Bringing discovery science from the bench to the bedside can certainly improve the health of our citizens, but we must engage in an open dialogue, ensuring that the principles of equality are embedded in this translational process, so that the patient, the scientist, the doctor, the industry, the economy, and the health care system all benefit in an equitable fashion.

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