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Challenges in pharmacology of anti-cancer drugs – the search for addictions

Olivier Feron*

Institute of Experimental and Clinical Research, Pole of Pharmacology, Université Catholique de Louvain, Brussels, Belgium
**Correspondence: olivier.feron@uclouvain.be*

The goals of cancer therapy are easy to summarize: to identify patients at the earliest stage possible of the disease and to eradicate tumors without altering the overall health condition of the patients. The identification of cancer biomarkers and tumor-selective drugs therefore represent obvious challenges for the next decades. In the genomics and proteomics era, the temptation is thus enormous to claim that the detection of oncogenes or oncoproteins participating in the progression of a given cancer represents the main avenue to diagnose the disease at early stages and to subsequently target these genes or proteins in order to block tumor growth. However, although the last 30 years have been rich in grasping information about genetic features distinguishing cancer cells from normal cells through the identification of oncogenes and tumor suppressor genes (Hahn and Weinberg, 2002), the translation of this information in new drugs is limited to very few examples. Worse yet, old demons of conventional chemotherapy, namely toxicity and resistance, are now dampening the original enthusiasm (Force et al., 2007; Knight et al., 2010).

Imatinib/Gleevec, as an inhibitor of the bcr-abl fusion protein (Druker et al., 2001) and trastuzumab/Herceptin as inhibitor of the human epidermal growth factor receptor 2 (HER2) (Baselga et al., 1998) are two of the very first examples of the development of molecularly targeted therapies. These drugs have represented breakthroughs in the treatment of chronic myelogenous leukemia (CML) and breast cancers, respectively. The identification of patients who may benefit from these treatments was guided by the detection of corresponding genetic alterations: the Philadelphia chromosome consistently found in CML patients, formed by a reciprocal translocation of DNA leading to a fusion gene between cABL (chromosome 9) and BCR (chromosome 22) (Bartram et al., 1983), and the overexpression of HER-2/neu as observed in 20–25% invasive breast cancers (Slamon et al., 1987). No doubt that these drugs administered to the right population of patients have increased response rates and survival. Still, we know today that the disease can find a way to advance despite the treatments: patients with BCR-ABL or HER2-positive cancers can still progress after receiving the above targeting drugs (often despite encouraging first responses). Potential mechanisms of resistance to oncogene-targeting drugs include bypass mechanisms and mutations of the targets (Gorre et al., 2001; Jones and Buzdar, 2009). In addition, potentially fatal cardiac toxicity is reported with trastuzumab (Telli et al., 2007) and although better tolerated, hematological (neutropenia), and non-hematological (skin rashes, edema, muscle cramps) toxicities are reported with imatinib (Deininger et al., 2005).

The responses to these frustrating observations may be of two kinds. The obvious one is to understand the reasons for the heterogeneity in responses to a given drug, i.e., between patients but also for a given patient, between the early beneficial phases of a treatment and the late development of resistance. This should lead to rapid results with the apparition of second and third generations of drugs. Some are already making their way to the clinics. Drugs such as nilotinib and so-called ABL allosteric inhibitors may now for instance overcome resistance caused by some BCR-ABL mutations responsible for relapse after initial imatinib treatment (Weisberg et al., 2007; Zhang et al., 2010). This better understanding should also stimulate the search for new predictive biomarkers to tailor the treatment to a patient's individual genetic profile (for review, see Hanash et al., 2008; Sawyers, 2008). The need in this matter is so acute that there is an increasing consensus to integrate promising biomarkers, even if not clinically qualified, into early phase trials as exploratory and intermediary endpoints (Yap et al., 2010).

The second and non-exclusive option to tackle the limited amounts of safe and efficient drugs issued from our genetic knowledge of cancers is to identify additional filter(s) which should be implemented to select for better anticancer drugs. It is now clear that *in vitro* activity is not the bottleneck to the development of such drugs considering the huge amounts of cytotoxic compounds which have been identified along the years. Experimental and preclinical *in vivo* activity should however not either be considered as the ultimate filter before clinical evaluation. Indeed, many studies using animal models of cancer do report the identification of a critical pathway exquisitely responding to a therapeutic modality based on tumor growth delay measurements or Kaplan–Meier survival curves. These read-outs clearly underestimate the complexity of signaling networks that *in fine* determine the clinical response to a treatment. Instead, the bottleneck to the development of better anticancer drugs lies in their therapeutic window, i.e., the range between the dosage that gives an anti-tumor effect and the amounts that give more adverse effects than desired effects. The new therapeutic strategies based on targeting antibodies or small molecules are certainly a first step in this direction. However, although examples as such described above are the proof that "intelligent" drugs may be designed, the next step is probably to identify the best target for this new generation of molecularly targeted drugs. In other words, we need to understand more about the molecular networks that control cancer cell biology and behavior in order to identify the nodes in the signaling circuitry of tumor cells, which are the most critical in driving cancer progression.

If one considers that a genetic defect related to the loss of a tumor suppressor gene is pharmacologically difficult to correct, the Holy Grail would consist in the identification of activated oncogenes acting as "vital" nodes in the signaling network of cancer cells. The

blockade or the silencing of the expression of protein encoded by such an *oncogene to which cancer cells are addicted* (Weinstein, 2002; Weinstein and Joe, 2008; Luo et al., 2009), should logically lead to tumor cell death. Addiction mostly arises from the loss of collateral signaling pathways that renders survival of the tumor cell strictly dependent on the activity of a given oncogene (Kamb, 2003). Such dependence largely explains the success of imatinib for CML or gastrointestinal stromal tumor (GIST) wherein driving oncogenes are BCR-ABL and cKIT, respectively. It is noteworthy that the identification of addicting oncogenes may require a careful dissection of the signaling circuitry in tumor cells. Such oncogene may indeed result from a mutation which was neutral for the mutations that preceded them but is absolutely required for mutations occurring later. Also, it may correspond to one of the numerous low-frequency mutations occurring during malignancy progression and probably largely underestimated so far (Greenman et al., 2007).

The above considerations support the concept of *synthetic lethality* initially used in yeast and fly genetic studies and more recently introduced in the field of anticancer treatments (Kaelin, 2005). Two genes are said synthetic lethal if mutation of either gene alone is compatible with viability but mutation of both leads to death. Inhibiting the products of genes that are synthetic lethal should by definition kill cells that harbor such mutations, while sparing normal cells. This concept may inspire different thoughts or scenarios. First, a combination of two molecularly targeted agents fulfilling the task of inhibiting synthetically lethal genes or the corresponding proteins has more chance to lead to a safe cancer cure than any other combination of drugs, even if active on apparently distinct targets. This is particularly attractive for pathways that are activated early during carcinogenesis since more likely to be synthetically lethal with one of the consecutive mutation in the malignant cell transformation process. Second, pharmacological inhibition of one gene synthetically lethal with another gene mutated in tumor cells should also selectively kill cancer cells (the wild-type form of the later gene protecting normal cells). Third, and probably most interestingly, the concept may be extended to tumor suppressor genes which although generally described as undruggable, may indirectly participate in promoting the efficacy of specific drugs. A good example is the efficacy of poly-ADP-ribose polymerase (PARP) inhibitors in BRCA-deficient tumors (Bryant et al., 2005; Farmer et al., 2005; Fong et al., 2009). BRCA genes are classical tumor suppressor genes: a defect in homologous recombination and associated defect in DNA repair are observed in cancer patients carrying germline BRCA gene mutations. While in healthy tissues, BRCA proteins may compensate for the PARP-driven inhibition of single stranded DNA break repair, such buffering is lost in BRCA-mutated tumors. Other examples of addiction dependent on tumor suppressor genes are the loss of PTEN and pRB, which lead to the stimulation of PI3K/mTOR (Neshat et al., 2001) and E2F (Sellers and Kaelin, 1997), respectively. Those defects consequently render tumor cells particularly sensitive to mTOR inhibitors and etoposide (which inhibits E2F-activated topoisomerase II).

Characterization of addictions other than those directly driven by oncogenes certainly represents alternative avenues for molecularly targeted compounds. Proteasome and heat shock protein inhibitors are examples of drugs which exploit synthetically lethal interactions although acting on targets which are themselves not oncogenic. Indeed, the imbalance in the stoichiometry of protein complex subunits resulting from dysregulated gene and protein synthesis is known to lead to protein misfolding and associated proteotoxic stress in tumor cells. Upregulation of chaperone proteins such as hsp90 is one kind of response to cope with the exacerbated need for correct folding (Whitesell and Lindquist, 2005) while elimination of excess unfolded or misfolded proteins by the proteasome is another one (Richardson et al., 2006). Interfering with either adaptation will thus lead to stress overload which will be more easily reached in tumor cells than in normal cells, thereby making strategies targeting *folding addiction* particularly safe and efficient.

One other exciting area of investigation is nowadays related to what could be coined as *metabolism addiction*. This concept is derived from the initial observation by Otto Warburg more than 50 years ago according to which proliferating tumor cells do not exploit the full capacity of oxidative metabolism of glucose to produce avidly needed ATP (Warburg, 1956). This observation further led to the conclusion that glycolysis is the main source of energy in tumors, even in the presence of oxygen, a phenomenon called the Warburg effect (Feron, 2009). Today, although we know that lactate and glutamine are also critical substrates for tumor cell metabolism (De Bereradinis et al, 2008; Sonveaux et al, 2008; Feron, 2009), glycolysis or more exactly glucose to lactate oxidation remains a hallmark of many cancers. Interestingly, this upregulation of glycolysis is thought to find its origin in an adaptation to environmental constraints during carcinogenesis, in particular the advantage to favor local acidosis to harm adjacent cell populations and thereby promote tumor cell survival (Gillies and Gatenby, 2007; Gatenby and Gillies, 2008). Another consequence is also a higher capacity to degrade extracellular matrix and thereby to stimulate invasiveness. The Warburg observation can today be interpreted as follows: the glycolytic preference provides such surviving advantages that clonal selection of tumor cells with mutations or epigenetic changes will always privilege this metabolic pathway even though supporting oncogenes and tumor suppressor genes may differ (Gillies et al., 2008). Although one view is that it continues to confer a proliferative advantage even to fully transformed cells, another possibility, yet non-exclusive, is to consider that tumors cells actually became addicted to this metabolic preference at the time of pre-malignant lesions or at least at early stages of the disease. Various drugs aiming to block key metabolic pathways in tumors are under development (see Tennant et al., 2010 for review) and offer the theoretical advantage to target early lesions as well as more aggressive cancers.

As a conclusion, I want to stress that the choice was deliberate to not use words such as angiogenesis or immunity in this Grand Challenge and to stay focus on the tumor cells themselves. This is by no means a denegation of the relevance of the strategies targeting these pathways, neither of other conventional treatments such as radiotherapy. These modalities represent perfect complementary approaches to block or reduce the tumor burden. The therapeutic effects resulting from these other approaches are however also a question of addiction. For instance, the extent of the dependency on angiogenic vessels or the influence of immunosuppressive tumor-associated macrophages will determine whether drugs targeting these pathways lead

either to a time- and tumor area-limited effect, a shift from a progressive to a stable disease, or a clinical response really impacting the overall survival of cancer patients. The message is thus that whatever the field of interest of scientists working on tumor biology or anticancer drug discovery, the focus should be placed on any forms of tumor addictions if one wishes to propose therapies with a higher potential to cure more cancer patients in the next decades. To that end, Frontiers in *Pharmacology of Anti-Cancer Drugs* welcomes a broad range of contributions that may help the field going forward.

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