Cell

How Much Longer Will We Put Up With $100,000 Cancer Drugs?

Paul Workman,[1] Giulio F. Draetta,[2] Jan H.M. Schellens,[3,4] and René Bernards[5,*]
[1]Cancer Research UK Cancer Therapeutics Unit, The Institute of Cancer Research, London, UK
[2]Department of Genomic Medicine and Institute for Applied Cancer Science, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[3]Division of Clinical Pharmacology, the Netherlands Cancer Institute, 1066 CX Amsterdam, the Netherlands
[4]Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, the Netherlands
[5]Division of Molecular Carcinogenesis and Cancer Genomics Centre Netherlands, the Netherlands Cancer Institute, 1066 CX Amsterdam, the Netherlands
*Correspondence: r.bernards@nki.nl
http://dx.doi.org/10.1016/j.cell.2017.01.034

The spiraling cost of new drugs mandates a fundamentally different approach to keep life-saving therapies affordable for cancer patients. We call here for the formation of new relationships between academic drug discovery centers and commercial partners, which can accelerate the development of truly transformative drugs at sustainable prices.

The Problem

The recently developed targeted drugs and immunotherapies deliver significant benefit to cancer patients. However, the spiraling prices of these new drugs threaten the financial sustainability of cancer treatment. Healthcare spending has risen sharply in the United States, reaching 17.1% of the gross domestic product in 2014. Cancer drugs are of particular concern, even if they only represent a fraction of the overall costs. As early as 2012, 12 of the 13 newly-approved cancer drugs were priced above $100,000 annually, and the situation has only gotten worse since (Light and Kantarjian, 2013; Mailankody and Prasad, 2015). Particularly worrisome is the notion that these drugs often need to be combined for optimal clinical results. For instance, the cost of the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA4) is priced around $252,000, exceeding the median cost of a US home ($240,000 in 2016). With a lifetime risk of developing cancer of close to 40%, the problem is clear.

The pharmaceutical industry has traditionally defended these high prices by pointing at the high attrition rate during clinical drug development and the cost of large registration studies. But are these arguments still as sturdy in the new era of personalized medicine? Targeted cancer drugs are often genotype-selective, which makes for a higher success rate due to better upfront patient selection. Consequently, approval of such drugs often no longer requires expensive phase III trials with thousands of patients. As one example, the registration study of the ALK inhibitor crizotinib required only 347 patients with ALK-positive lung cancer (Shaw et al., 2013). Furthermore, in 2016 FDA approved crizotinib for the treatment of lung cancer patients with mutations in *ROS1*, which the drug also inhibits, on the basis of a study of only 50 patients (Shaw et al., 2014). So why are drug prices going up instead of down? One clue can be gleaned from the pricing of the recent checkpoint blockade immunotherapeutics nivolumab and pembrolizumab. Both drugs received initial FDA approvals in 2014 for metastatic melanoma, but their indication was widened in 2015 to include certain lung cancers and renal cancer (nivolumab) and in 2016 to head and neck cancer (pembrolizumab) and Hodgkin lymphoma (nivolumab). If development cost would be a major factor in the pricing structure, a simple law of economics would have mandated a considerable reduction in price when the eligible patient population increases, but that has hardly happened. This is a recurring theme in pharma. For instance, trastuzumab was first approved for advanced breast cancer and later also for early disease (adjuvant) without a reduction in price. Healthcare payers should not accept this lack of price-volume relationship. Moreover, there is very little relationship between drug price and clinical benefit (Mailankody and Prasad, 2015). This has sparked widespread criticism, alleging that cancer drug pricing is primarily based on "what the market will bear." There is a clear and urgent necessity to lower cancer drug prices to keep lifesaving drugs available and affordable for patients. As one patient advocate recently put it: "Innovation is meaningless if nobody can afford it."

Lack of Effective Solutions

Much has been written about the reasons behind the exorbitant drug prices and what to do about it. One recurring theme is the notion that the US federal government is prohibited by law from negotiating drug prices as a result of the 2003 Medicare Prescription Drug, Improvement and Modernization Act. Considering that Medicare and Medicaid spend $ 140 billion on medicines annually, this represents a serious impediment in driving down drug prices. Lack of competition and a general absence of a connection between drug price, sales volume, and clinical performance are other arguments in the drug pricing discussion (Jaffe, 2015). Indeed, lack of competition and bargaining power made US prices of cancer drugs among the highest in the world, increasing by 10% annually between 1995 and 2013, far above the average inflation rate (Howard et al., 2015).

While negotiations may bring prices down, a recent cost comparison in EU countries shows that the ability of individual nations to negotiate discounts is limited, most likely due to the modest market sizes of the EU countries (van Harten et al., 2016). In the longer term, it is unlikely that the European Union will be able to collectively negotiate with the pharmaceutical industry, given that some nations in the EU with a large pharma sector are likely to protect their national interests. The UK's pioneering National Institute for Health and Care Excellence (NICE) has been able to restrain prices to £30,000 per "quality-adjusted life year" (QUALY) added or £50,000 per QUALY for "end of life" treatments that include many cancer drugs—but this has also resulted in many oncology agents being turned down or delayed, leading to complaints from patient groups and manufacturers. There is also increasing evidence of pressure on pricing in the US. Researchers at the Memorial Sloan Kettering Cancer Center have developed an online tool called Drug Abacus to help healthcare providers assess the value of cancer drugs (www.drugabacus.org/). What is urgently needed however are mechanisms to encourage scientific and therapeutic innovations that will allow cancer patients to access new treatments at affordable and sustainable prices.

Inefficiency in Drug Development

One element that contributes significantly to the high cost of cancer drugs is the inefficiency of the overall commercial enterprise. As one recent example, there are currently 803 clinical trials testing checkpoint immune-therapeutics (at least 12 antibodies from a dozen different pharma companies), which together plan to enroll over 166,000 patients (Brawley, 2016). There is enormous redundancy in these studies, as many pharmaceutical companies perform similar trials with comparable drugs, but fail to share the data generated. This herd mentality is caused in part by the notion that immune checkpoint therapies can indeed lead to long-lasting remissions (potentially even to cures) and that significant numbers of patients in each clinical indication benefit from these treatments. While it is in the short-term good that so many patients get access to potentially lifesaving drugs, in the longer term, patients will have to pay the price for this inefficiency and duplication.

Another factor is the frequent absence of a rigorous biomarker program to identify patients who may benefit from a given drug. The primary incentive of the pharma industry is to increase sales, which are restricted by identifying drug-responsive subpopulations. Biomarkers are critical, as they represent a handle to control drugs costs to society. Regulatory bodies should set standards for drug approval employing validated and clinically useful biomarkers for patient selection. This will prevent patients being treated with toxic drugs that do not improve survival and/or quality of life and will save costs to society.

Historically, some 90% of all drugs entering the clinic have failed at some stage and most biotech start-ups have a similar fate. This severe attrition rate in drug discovery and development has been attributed to various factors, including failure to validate drug targets with sufficient rigor; limited predictive value of animal models; inability to firmly identify tumor subtypes that might benefit from treatment; poorly defined clinical endpoints; organizational pressure to continue clinical development, such as stock market considerations for small one-product biotech firms; and senior management fear of admiting defeat in larger pharma. The Tufts Center for the Study of Drug Development has estimated that the development of a drug on average costs $2.558 billion, but it is difficult to determine how this was calculated—and includes costs of failed projects and controversially incorporates selected examples of successful drugs and the cost of capital (Avorn, 2015). Some consideration should be given to the fact that large pharmaceutical companies encounter significant challenges due to the large size of their operations, redundant activities at multiple sites, huge infrastructure costs, heavily matrixed organizations with multiple levels of decision makers, and endless rounds of restructuring, mergers, acquisitions and down-sizing—which all ultimately contribute to time delays (time is money!), reduced productivity, and increased expenses. Smaller biotech start-ups have significant challenges as well, with tremendous recent increases in space and infrastructure build-up costs and competition for talent (with consequent increased employee salaries), particularly in the Boston and San Francisco communities. Furthermore, all commercial entities, large and small, spend very significant sums on hefty salaries for senior management. We therefore assume that both organizational and scientific inefficiencies contribute to escalating drug development costs.

A New Approach

Many of the fundamental discoveries that formed the basis for new categories of cancer drugs were made by academia. Examples of truly disruptive contributions from academic research that enabled radically different treatment strategies include the identification of recurrent mutations in cancers from the large-sale sequencing efforts (enabling targeted therapeutics) and the decades-long investments in unraveling the basic biology underlying recognition of cancer cells by the immune system (enabling recent immuno-oncology drugs). The National Cancer Institute budget of over 5 billion dollars annually virtually guarantees that this stream of innovations in oncology drug targets from academia will not dry up any time soon. It should also be recognized that academic drug discovery has already been very successful as several drugs that are part of the therapeutic armamentarium have been developed by academic researchers, e.g., the brain tumor DNA alkylating drug temozolomide and the prostate cancer CYP17 inhibitor agent abiraterone, as well as the biomarker strategy for the PARP inhibitor olaparib in *BRCA* mutant ovarian cancer patients.

To further develop these academic discoveries, the traditional model of self-supporting research investigators who drive their independent research programs needs to be complemented by concerted multidisciplinary team efforts that are adequately financed and staffed with scientists having all the required expertise to enable drug discovery (Frye et al., 2011; Schultz Kirkegaard and Valentin, 2014). Indeed, in recent years there has already been a steady increase in the number of

academic centers involved in drug discovery. The Cancer Research UK Cancer Therapeutics Unit at The Institute of Cancer Research, London (www.icr.ac.uk/our-research/our-research-centres/cancer-research-uk-cancer-therapeutics-unit) and the Institute for Applied Cancer Science at MDAnderson cancer center (www.mdanderson.org/cancermoonshots/research_platforms/Institute_for_applied_cancer_science.html) are just two examples of relatively large-scale academic cancer drug discovery units that have been established to date. The Academic Drug Discovery consortium currently lists 146 drug discovery centers in 15 countries, 80% of which have programs in oncology drug development (www.addconsortium.org/).

A key advantage of academic drug discovery is the freedom and indeed incentivization to tackle major challenges that would be viewed as too risky by big pharma and even by many biotech companies. Currently only a fraction of the cancer genes listed in the Cancer Gene Census have drugs or chemical leads that act on the cognate protein. This means that there are very large numbers of cancer genes that remain to be drugged. For example, we have no drugs that work directly on mutant KRAS, mutant p53 or MYC. Hence there is a huge amount of work to be done to complete the job of drugging of the cancer genome. Moreover, there are gene classes that do not fall into the conventional categories of oncogene addiction and synthetic lethality targets, including non-oncogene addiction, microenvironmental, drug resistance and immuno-oncology targets.

Tackling any one of these new targets carries very high risk—either biological risk because there is relatively little knowledge of the role of the gene in cancer, or technical risk because the protein is not readily druggable by current technology. These are the targets for which academic drug discovery can make an enormous impact in a number of ways. For example: (1) conducting very rigorous target validation to ensure robustness of the effects; (2) linkage of the sensitivity to a robust biomarker that can be potentially used for patient selection as well as pharmacodynamic biomarkers to demonstrate target engagement as part of a Pharmacologic Audit Trail (Banerji and Workman, 2016); (3) demonstration of druggability by a small molecule approach; (4) production of chemical probe or biological reagent that demonstrates proof of concept in a disease-relevant animal model; (5) progression of a candidate drug through preclinical development; and (6) conduct of an early stage clinical trial to show tolerability and proof of concept in cancer patients (Hoelder et al., 2012).

Factors that have improved the success of cancer drug discovery efforts in academia include embedding experienced drug discovery scientists within a comprehensive cancer center that provides expertise in basic cancer research, clinical trials and treatment. The recruitment of experienced medicinal chemists and drug discovery biologists has been critical. Adequate funding and resources to support a portfolio of projects as well the range of expertise and technologies is important as is experienced leadership and decision-making.

Once new chemical entities have been developed and tested in experimental animals, the (mostly academic) hospitals become involved in the three major phases of clinical testing of compounds. Selected Good Laboratory Practice and Good Manufacturing Practice-certified academic pharmacies can develop and manufacture oral and/or parenteral drug formulations fit for clinical use. Academic clinicians clearly have the skills to execute large clinical trials, especially given that some of the recent large clinical trials were ''investigator initiated,'' meaning that an academic investigator was leading the study. Based on the arguments above, it is evident that academia in principle has all the tools and skill sets to discover drug targets, to convert these targets into clinical candidates and to test these compounds rigorously in clinical trials.

Bringing Drugs to Patients under New Assumptions

There are three main reasons why academic drug development typically stalls at the stage of clinical testing. First, the stringent quality control over the large-scale manufacturing of clinical grade drugs and their formulation is not a routine skill of academic groups. Second, the funds to support the high cost of performing non-clinical regulatory toxicology studies and clinical trials are hard to raise by non-profit organizations. Third, even when these first two steps could be executed, academic drug discovery and development units are not equipped to handle marketing and sales of approved drugs. Yet, it is at the level of commercialization that the interests of large pharma to maximize return on investment are diagonally disparate from the typically idealistic motivation that drives most academics to spend countless hours at modest compensation to solve important problems in oncology. Nevertheless, academics are driven into the arms of big pharma after initial proof of concept clinical trials for the reasons listed above. While it is gratifying for most academic investigators to see their discoveries reach the clinic, it leaves them unable to influence the pricing of ''their'' drugs when they reach the market. There are examples of charities funding later stage trials, but these are exceptions and academic drug discovery cannot rely on charity funding only to bring their candidates to patients.

How can we break free of this catch 22 situation in academic drug development? A possible solution may reside in what happens to cancer drugs when their patents expire. At this point so-called ''generic'' drug makers bring generic versions (biosimilars in the case of biological agents) to the market at greatly reduced prices. These lower prices are possible because the companies do not bear the cost of research and development. Given that generic drug makers are used to working with lower profit margins, they may be one potential partner to develop highly innovative, but de-risked, drugs from academic drug discovery and development (Figure 1). Especially when the drugs have a strong mechanistic rationale and an associated biomarker of response (key aspects of academic drug development), the registration trials can be small and the success rate much higher than in traditional pharma trials. As a result, the prices of such drugs can be far lower than we have witnessed recently. Regulatory bodies are also open to novel ways for drug approval. The European Medicines Agency (EMA) has launched an adaptive licensing program enabling

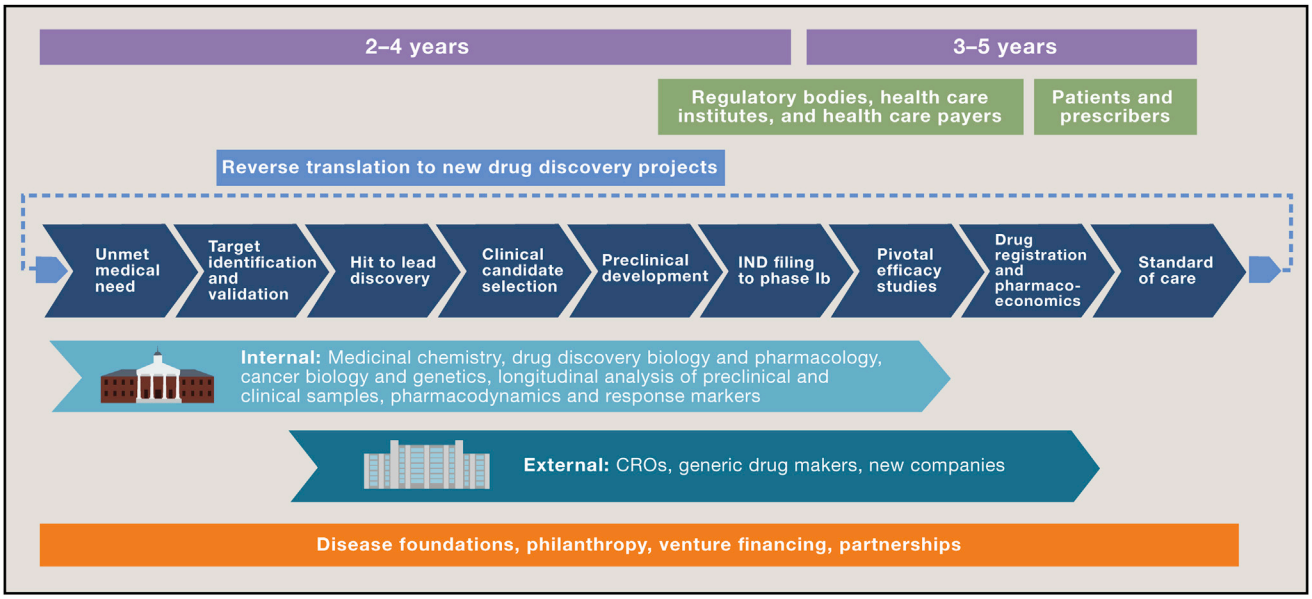

Figure 1. The Academic Drug Discovery and Development Continuum and Its Relationships with Stakeholders

Critical components of the cancer drug discovery and development process through commercialization are described. Through comprehensive integration of expertise, cancer biologists and geneticists, drug discovery scientists and pharmacologists are able to precisely formulate a Clinical Candidate Profile based on tumor subtype(s) and patient population that might best benefit from treatment. Project financing leverages philanthropic donations and partnerships with CROs and generic drug makers, allowing not-for profit entities to retain control from the start through commercialization.

CRO, contract research organization, a provider of services to the biopharmaceutical industry; PD, pharmacodynamics, determines a drug mechanism of action and safety profile; generic drug maker, a high-volume, low profit margin organization devoted to the manufacturing and commercialization of drugs past their patent expiry; pharmaco-economics, a comprehensive evaluation of the impact of a given program on the health of a population, often leads to decisions on policies; response biomarker, a biological indicator predicting response to a given treatment.

companies to obtain marketing authorization approval on the basis of a small well designed, biomarker supported trial. Post-marketing commitments of the company forcing them and the community to deliver extended proof of benefit at acceptable risk is a safeguard to them and the community that the early market launch was justified. If such commitments are not met, the drug will be withdrawn.

Two elements will be mission critical for this model to succeed. First, academic organizations will need to abide by their societal responsibility and resist the temptation to sell their drug candidate to the highest bidder. Second, it will be imperative that agreements on price caps are part of the negotiations with potential investors or with companies that take forward drugs arising from academic drug development. Ideally, this approach would also be accompanied by pricing strategy leading to affordable drug cost in middle- and low-income countries, thereby reducing inequality in global cancer therapy. Given the substantial de-risking achieved prior to commercialization, our model should be attractive to these parties and their investors. The academic drug discovery and development units could be sustained in this model by receiving royalties on sales of the drugs they originated.

We need to recognize that building up a collection of academic centers with required scale and expertise that would produce significant numbers of drug candidates will take time and money and will not be an overnight solution to the global pricing problem. It is, however, a move in the right direction. Moreover, the creation of such groups alongside generics partners or newly created commercial entities will create competition and drive down prices in conventional pharma and biotech.

Where to Start with Academic Drug Discovery and Development?

There is quite a bit of low hanging fruit to be harvested by academic consortia. In addition to their main task of discovering mechanistically innovative drugs, a near term focus should be on the repurposing of existing patent-expired drugs by finding new indications for these drugs, linked to effective biomarkers that are predictive of response. Academic groups are well equipped to carry out this research, and it would help if specific funding mechanisms would be made available for such projects. We emphasize that such funds should not be allocated at the expense of investments in fundamental cancer research. Second, academic consortia should also focus on finding effective combinations for drugs that were abandoned for lack of single agent activity, which appears in one out of three cases to be the primary reason new chemical entities are dropped from early phase clinical trials (Dimasi, 2001). Lack of single agent activity is often caused by redundancy or feedback in signaling pathways, which makes the inhibition of a single pathway ineffective without concomitant inhibition of the redundant or feedback pathway. As one example, had the BRAF inhibitor vemurafenib been tested initially in *BRAF* mutant colon cancer, it would have been discarded as ineffective, whereas it turned out to be very effective in *BRAF* mutant melanoma. We argue that far too many

potentially useful drugs are discarded early for the wrong reasons.

Besides tackling these initial lower risk projects, which can serve as a proof of concept (and cash flow) for the model proposed here, the academic drug discovery centers should have as a major emphasis the challenging task of discovering and developing drugs against highly innovative drug targets emerging from academic research. Such efforts must have a sharp focus on mechanism-based therapies with strong associated biomarkers of response to reduce attrition rates while allowing small clinical trials to show efficacy.

By partnering with generic drug makers or new companies specifically formed to enable this new model, academic drug discovery units and interested drug makers can lead by example and deliver innovative drugs at sustainable prices.

ACKNOWLEDGMENTS

R.B. is the founder of Qameleon Therapeutics (www.qamelonrx.com) that seeks to build a new model of partnership between generic drug makers and academia as described in this commentary. The authors are involved in multiple drug discovery and development projects with actual or potential commercial revenues and act as advisers to several companies. We welcome interaction with any drug maker interested in considering academic partnerships as described herein.

REFERENCES

Avorn, J. (2015). N. Engl. J. Med. *372*, 1877–1879.

Banerji, U., and Workman, P. (2016). Semin. Oncol. *43*, 436–445.

Brawley, L. (2016). Cancer Lett. *42*, 2–18.

Dimasi, J.A. (2001). Clin. Pharmacol. Ther. *69*, 297–307.

Frye, S., Crosby, M., Edwards, T., and Juliano, R. (2011). Nat. Rev. Drug Discov. *10*, 409–410.

Hoelder, S., Clarke, P.A., and Workman, P. (2012). Mol. Oncol. *6*, 155–176.

Howard, D.H., Bach, P.B., Berndt, E.R., and Conti, R.M. (2015). J. Econ. Perspect. *29*, 139–162.

Jaffe, S. (2015). Lancet *386*, 2127–2128.

Light, D.W., and Kantarjian, H. (2013). Cancer *119*, 3900–3902.

Mailankody, S., and Prasad, V. (2015). JAMA Oncol. *1*, 539–540.

Schultz Kirkegaard, H., and Valentin, F. (2014). Drug Discov. Today *19*, 1699–1710.

Shaw, A.T., Kim, D.-W., Nakagawa, K., Seto, T., Crinó, L., Ahn, M.-J., De Pas, T., Besse, B., Solomon, B.J., Blackhall, F., et al. (2013). N. Engl. J. Med. *368*, 2385–2394.

Shaw, A.T., Ou, S.H., Bang, Y.J., Camidge, D.R., Solomon, B.J., Salgia, R., Riely, G.J., Varella-Garcia, M., Shapiro, G.I., Costa, D.B., et al. (2014). N. Engl. J. Med. *371*, 1963–1971.

van Harten, W.H., Wind, A., de Paoli, P., Saghatchian, M., and Oberst, S. (2016). Lancet Oncol. *17*, 18–20.