OPINION

Managing drug resistance in cancer: lessons from HIV therapy

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Abstract | Drug resistance is a common cause of treatment failure for HIV infection and cancer. The high mutation rate of HIV leads to genetic heterogeneity among viral populations and provides the seed from which drug-resistant clones emerge in response to therapy. Similarly, most cancers are characterized by extensive genetic, epigenetic, transcriptional and cellular diversity, and drug-resistant cancer cells outgrow their non-resistant peers in a process of somatic evolution. Patient-specific combination of antiviral drugs has emerged as a powerful approach for treating drug-resistant HIV infection, using genotype-based predictions to identify the best matched combination therapy among several hundred possible combinations of HIV drugs. In this Opinion article, we argue that HIV therapy provides a 'blueprint' for designing and validating patient-specific combination therapies in cancer.

HIV infection and cancer are among the most common causes of death worldwide (see the World Health Report website). They are connected by the fundamental role of genetic control and evolution in the course of the disease. In HIV infection, the viral genome takes partial control over the host and pursues its own genetic agenda, which is centred on self-replication. In cancer, the human genome itself incurs damage and gives rise to autonomous cancer genomes, which are programmed for growth regardless of the body's checks and balances. Fuelled by cellular heterogeneity and high error rates in the molecular machinery of cancer cells, various genetically and epigenetically distinct disease clones emerge and compete in the host ecosystem. This evolutionary component has direct clinical relevance because it fosters drug resistance, which is an important cause of treatment failure in both HIV infection[1] and cancer[2].

This Opinion article explores the hypothesis that insights from HIV therapy can serve as a 'blueprint' for personalizing cancer treatment. We describe the arsenal of targeted therapies for HIV, which form the basis for tackling drug resistance; and we discuss the use of prediction algorithms for designing patient-specific combination therapies against HIV. By comparison, we summarize recent advances and limitations in the arsenal of targeted cancer drugs, and we outline how biomarkers and prediction methods are increasingly contributing to personalized therapies for cancer. We conclude by sketching an approach to cancer therapy that is modelled on the success story of treating drug resistance in HIV infection, and we also discuss relevant obstacles and limitations to the implementation of such an approach.

HIV therapy

Targeted drugs and mechanisms of resistance. Personalized medicine relies on access to multiple treatment options for the same disease. Ideally, several drugs should be available that target different disease-relevant mechanisms, allowing physicians to design personalized combination therapies that maximize efficacy at acceptable levels of toxicity and side effects. Over the past two decades, extensive biomedical research on HIV infection has resulted in more than two dozen approved antiviral drugs[3], which constitutes a sizable 'toolbox' for designing patient-specific combination therapies. Currently available HIV drugs target five different phases of the viral life cycle, including viral attachment (chemokine receptor antagonists), cell entry (entry inhibitors), reverse transcription of the RNA-encoded viral genome (reverse transcriptase inhibitors), integration into the host genome (integrase inhibitors) and viral maturation (protease inhibitors and maturation inhibitors).

Several factors have contributed to the quick and successful development of multiple targeted drugs against HIV infection. First, HIV biology is relatively straightforward compared with the complexity of human cancers, which has enabled researchers to quickly identify promising drug targets in the viral life cycle. Second, viral functions are carried out by proteins that clearly qualify as 'druggable', meaning that their activity can be inhibited by small molecules that can be identified through high-throughput chemical screening[4]. Third, viral load (as measured by plasma levels of viral RNA) provides an accurate biomarker and surrogate end point for evaluating new HIV drugs (see the US Center for Drug Evaluation and Research website), which initially led to faster drug approval compared with a focus on overall survival as the only measure of treatment success[5].

Antiviral drugs can reduce viral load to undetectable levels, but the infection persists in (almost) all patients and quickly relapses when treatment is stopped. Therefore, HIV drugs are given as chronic medication for the rest of the patients' lives, unless severe side effects mandate therapy interruption, or drug resistance renders all available therapies obsolete in a given patient. Drug resistance can emerge at any time during therapy, constituting a major cause of disease progression and death in patients with HIV[1]. Three sources of resistant viral clones are currently discussed as the most important causes of drug resistance. First, the viruses that are transferred during primary infection may already be resistant to certain drugs, typically owing to the treatment history of the infecting host. This type of drug resistance currently accounts for only a small proportion of HIV infections[6,7]. Second, drug-resistant clones can emerge as a result of random mutations in the acute phase following primary infection, which usually occurs before diagnosis and the initiation of drug treatment. Treatment with an antiviral drug immediately after exposure to HIV may effectively reduce the risk of chronic infection[8], which is facilitated by the small number of viruses that constitute a typical primary infection. However, simulation studies suggest that fairly soon after infection the viral population reaches a size and level of genetic heterogeneity that is sufficient for maintaining resistant clones against single-drug regimens[9–11], which explains the swift emergence of resistance against single-drug regimens. Third, new mutations continue to arise during viral replication even in patients who are treated with highly effective antiviral therapies, allowing viral clones to incrementally accumulate multiple resistance mutations[9]. This process is accelerated by suboptimal therapy adherence of the

patient and explains why initially effective combination therapies can fail after months or years of successful treatment.

Devising patient-specific combination therapies. Combination therapies against HIV infection were introduced more than 15 years ago[1], and have been refined substantially over the years. FIGURE 1a shows a typical course of disease and therapy for patients with HIV, illustrating how the adaptive selection of drug combinations enables the long-term control of viral replication and defers progression to AIDS. Combination therapies against HIV infection usually comprise two or more drugs from at least two distinct drug classes, with each targeting a different protein or having a different mechanism of action. For example, a typical first-line treatment for HIV infection consists of two distinct drugs from the largest class of HIV drugs (nucleoside reverse transcriptase inhibitors) and a third drug from a different class (such as protease inhibitors)[12]. Successful combination therapies minimize the residual viral population from which resistant clones can emerge, and they raise the number of resistance mutations a viral clone needs to acquire before it gains a substantial selective advantage and emerges as a driver of drug-resistant disease. The introduction of combination therapies against HIV has had a tremendous clinical impact, transforming HIV infection from a uniformly fatal disease to a chronic condition with a moderate reduction in quality of life[3].

Nevertheless, drug resistance continues to be a major challenge for HIV therapy[1,13], as most or all drug combinations can be overcome by drug-resistant viral clones. When antiviral therapy begins to fail in a given patient, physicians try to identify an alternative combination therapy to which the viral population harboured by the patient is still susceptible, in order to prevent disease progression and death. In contrast to first-line combination therapies (which can be relatively standardized because the majority of primary infections currently involve wild-type viruses), the treatment of drug-resistant HIV needs to account for patient-specific resistance profiles at the point of treatment failure[12]. In principle, such resistance profiles can be obtained by measuring the resistance of the patient's viral population against various drugs in a cell-based assay. The 'cellular phenotype' (BOX 1) of *in vitro* resistance strongly correlates with clinically observed drug resistance and is thus highly informative when making treatment decisions. However, these cell-based assays are time-consuming and costly to carry out, which has hindered their integration into routine clinical practice. Instead, routine profiling of patient-specific resistance against HIV drugs is almost always based on viral genotyping, an assay that is sufficiently fast, cost-efficient and accurate for clinical use[14].

The interpretation of viral genotype data was initially carried out using expert-curated tables that listed known resistance mutations and susceptibility mutations for each available drug[15], but computer-assisted resistance prediction has emerged as a well-validated alternative[16]. Current computer-assisted methods for predicting HIV drug resistance from viral genotypes can be divided into two classes. Expert systems provide a computational interface to a handcrafted set of rules, thus constituting a user-friendly alternative to printed mutation tables. By contrast, statistical learning methods can directly infer genotype-based models for resistance predictions from virological and clinical training data ('virtual phenotypes' (BOX 1)), without the need for an expert committee to manually analyse the relationship between viral genotype and drug-resistance phenotype[17]. Viral genotyping

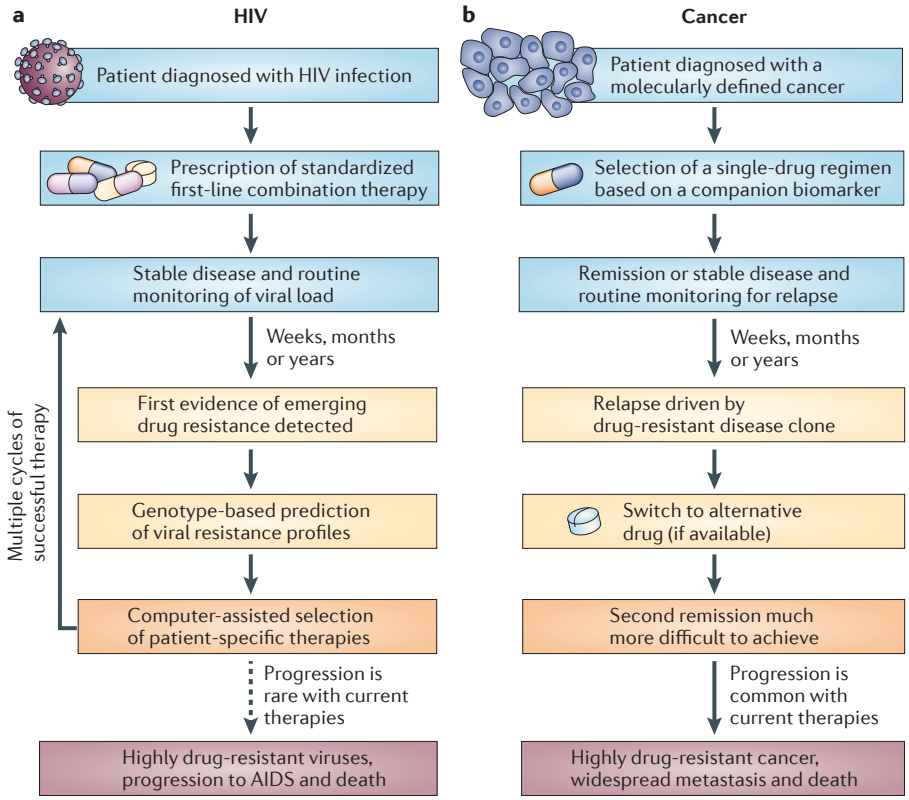

Figure 1 | **Molecularly targeted therapy for HIV infection and cancer.** This figure shows a typical course of disease and therapy for HIV infection (part **a**) and for a metastatic cancer that is treated with molecularly targeted drugs (part **b**). Rather than describing the full clinical complexity of either disease, this schematic drawing illustrates characteristic similarities and differences in the ways that these diseases are currently treated. For HIV infection, antiretroviral therapy always uses a combination of drugs with different target proteins and/or different mechanisms of action; and the first-line therapy can be relatively standardized because new infections rarely involve the transmission of drug-resistant viruses. By contrast, targeted cancer drugs are often selected on the basis of companion biomarkers that confirm the presence of the targeted protein; and they are most commonly given as single-drug regimens. For both HIV infection and cancer, initially successful treatments frequently fail after some time owing to the emergence of drug-resistant clones. At that point, a diagnostic test can be carried out to identify the molecular cause of the observed drug resistance. In the treatment of HIV infection, computer-assisted prediction of drug-resistance profiles (based on viral genotyping data) provides the basis for selecting combination therapies in a patient-specific way. This cycle of therapy selection, therapy failure, resistance profiling and therapy reassessment can go on for multiple rounds, allowing patients to live with stable disease for decades. In metastatic cancers, the options are more limited because drug resistance quickly accumulates when using targeted drugs in sequential order. The wider use of combination therapies is likely to attenuate this problem.

in combination with the computational prediction of drug resistance phenotypes has emerged as a clinically accepted and widely used biomarker for guiding patient-specific combination therapy in HIV infection[12,18,19]. Furthermore, researchers are exploring algorithms for predicting the clinical effectiveness of drug combinations in addition to the resistance towards individual drugs[20,21]; and ongoing research is directed towards integrating increasingly sophisticated prediction methods into routine clinical practice[22]. Such software-based systems are likely to broaden access to patient-specific combination therapies against drug-resistant HIV, which currently remains the domain of expert teams.

In summary, over the past three decades since its discovery, HIV has emerged as a 'poster child' of personalized medicine. The rapid expansion of knowledge on HIV biology has facilitated the development of multiple drugs that target different stages of the viral life cycle. The establishment of viral load as a surrogate end point of drug efficacy contributed to fast clinical validation and time-to-market for early HIV drugs. Furthermore, viral genotyping evolved into a highly informative biomarker that helps physicians to tackle drug resistance by devising patient-specific combination therapies. Finally, computer-assisted methods have become accepted clinical practice for predicting drug resistance phenotypes from the viral genotype, which has contributed to patient-specific combination therapies becoming widely available as the preferred treatment for drug-resistant HIV infection.

Cancer therapy

Targeted drugs and mechanisms of resistance. Personalized cancer therapy has not yet reached the level of sophistication that we observe in HIV therapy, suggesting that it may be worthwhile to explore which therapeutic concepts are transferable between infectious diseases and cancer[23]. In this article, we argue that patient-specific combination therapies for drug-resistant cancer could be designed and validated in similar ways to those in HIV therapy.

Combination therapies are not a new concept in cancer therapy[24]. Starting in the 1960s, researchers have successfully combined various cytotoxic drugs and developed combination therapies that have become the standard of care for several cancers, including paediatric leukaemias, Hodgkin's lymphoma and testicular cancer. However, the cytotoxic drugs that are widely used in classical chemotherapy regimens do not constitute ideal building blocks for patient-specific combination therapies. First, their broad toxicity to proliferating cells often comes with strong side effects, which limits the number and dose of drugs that can be safely combined. Second, these drugs tend to have a small therapeutic window, making it relatively easy for cancer cells to become resistant to therapeutic doses (for example, by upregulating drug efflux pumps that reduce the drug concentration in cancer cells). Third, the mechanisms of action of most cytotoxic drugs converge on a small number of pathways, which is why resistance mutations in apoptosis control genes and DNA repair pathways can confer resistance to a broad range of cytotoxic drugs[25]. Most or all of these limitations could be overcome by using molecularly targeted drugs as the building blocks for patient-specific combination therapies, instead of classical cytotoxic drugs[26,27].

Targeted drugs modulate proteins or pathways that are specific to a molecularly defined subset of cancers[28,29]. Analogous to HIV drugs, targeted cancer drugs modulate disease-specific mechanisms that are absent in healthy cells, which makes them better tolerated and thus more suitable for chronic treatment than classical cytotoxic drugs. Furthermore, combining targeted drugs against alternative or complementary disease pathways is likely to increase efficacy and limit the options for cancer cells to become resistant, in much the same way as in HIV therapy[30,31]. Researchers are currently pursuing multiple strategies for developing new classes of targeted cancer drugs, including the inhibition of oncoprotein activity (which has so far been the most prominent and successful approach), the targeted delivery of toxic molecules and the activation of a specific immune response against cancer cells[32–34]. A sizable number of targeted cancer drugs have already gained regulatory approval (see the National Cancer Institute Fact Sheet website), and these drugs are starting to have a substantial positive impact on patient survival in cancers such as breast cancer, chronic myelogenous leukaemia (CML), non-small-cell lung cancer (NSCLC) and metastatic melanoma[28,29]. The oestrogen receptor (ER) antagonist tamoxifen improves survival in ER-positive breast cancer and constitutes the earliest example of a molecularly targeted drug[35]. More recently, a chemical inhibitor (lapatinib) and a

Box 1 | **Cellular phenotypes and their prediction from genotype data**

Most cancer biomarkers that have been developed to date aim to predict clinical parameters directly from genomic characteristics. For example, they predict drug response or patient survival on the basis of resistance mutations or gene expression signatures. These efforts have often met with limited success[66], which is hardly surprising given the complexity of cellular and organismal processes that mediate the relationship between measured genotype and observed clinical phenotype. A potential solution for bridging the gap between genotype and phenotype comes from the field of neurogenetics. Faced with the problem of identifying genetic risk factors for neuropsychiatric diseases, researchers have developed the concept of 'endophenotypes' (REF. 68). These intermediate traits are associated with the disease of interest but are more closely related to the genotype than the clinical phenotype itself, which facilitates the search for robust statistical associations between genotype and endophenotypes. Examples of endophenotypes in neurogenetics research include psychological measures of neuroticism (high values are predictive of depression), test scores quantifying working memory function (low values are predictive of schizophrenia) and electroencephalography signals (specific patters are predictive of alcoholism)[69]. Analogously, drug resistance that is observed in a cellular model of HIV infection or cancer can be interpreted as an endophenotype, suggesting that the cellular resistance phenotype may facilitate the development of genotype-based biomarkers for these diseases. Several proof-of-concept studies suggest that cellular phenotypes can often be predicted with high accuracy from a combination of genome, epigenome and transcriptome data. For example, drug resistance of HIV can be predicted from the viral genome using statistical learning methods[70]; drug resistance of cancer cell lines can be predicted from the expression levels of drug transporter genes using correlation coefficients and bootstrapping[71]; immune tolerance of human lymphocytes can be predicted from the DNA sequence of human leukocyte antigen (HLA) genes using expert-curated rules[72]; differentiation propensities of human pluripotent cell lines can be predicted from gene expression profiles using gene-set enrichment analysis[60]; and growth rates of yeast cells can be predicted from gene expression profiles using linear regression models[73]. In all these cases, a similar approach is taken towards predicting a cellular phenotype. First, a database with genotype data and matched cellular phenotype data is established. Second, an algorithm is developed for predicting the cellular phenotype from the genotype data, giving rise to a 'virtual phenotype' that emulates the cellular phenotype. With adequate clinical validation, such virtual phenotypes can contribute to the design of patient-specific combination therapies.

monoclonal antibody (trastuzumab) against the ERBB2 (also known as HER2) oncoprotein have been shown to be effective against ERBB2-positive breast cancer[36]. In CML, the inactivation of the oncogenic fusion protein BCR–ABL using the tyrosine kinase inhibitors imatinib, dasatinib or nilotinib prevents disease progression and may even cure a subset of patients[37]. Specific oncoprotein inhibition has also been achieved for EGFR-overexpressing NSCLC using the tyrosine kinase inhibitors gefitinib or erlotinib[38,39]. Finally, vemurafenib (PLX4032) — an inhibitor of the BRAF-V600E oncoprotein — has recently been approved for the treatment of metastatic melanoma[40].

Targeted cancer drugs tend to have a fairly large therapeutic window and as a group tackle a diverse set of disease pathways, which may render combinations of targeted drugs less susceptible to mechanisms that confer resistance against a broad range of cytotoxic drugs (for example, the upregulation of drug efflux pumps and the deactivation of apoptosis control genes). Nevertheless, drug resistance remains a major problem for targeted cancer drugs[41–45], especially when single drugs are used in isolation. Resistance to targeted cancer drugs can occur in similar ways to those in HIV therapy but is generally more diverse in its causes. First, the specific oncoprotein that is targeted by the drug may be absent or irrelevant in a given tumour, making it highly unlikely that the patient responds to the drug. To avoid this type of drug resistance, it has become common practice to develop targeted cancer drugs together with molecular biomarkers ('companion diagnostics') that identify carriers of the targeted molecular aberration[46]. Second, cancers that express the targeted oncoprotein can become resistant through mutations that alter the target in such a way that it can no longer be bound and inhibited by the drug. As in the case of HIV, these resistance mutations may already be present in untreated tumours and selected for in response to drug treatment, or they may be acquired during low-level cell replication in the presence of the drug. Third, a subset of cancer stem cells may be constitutively protected from the effect of drugs that have been developed against the bulk of more differentiated cancer cells[47]. Fourth, acquired changes in the regulatory networks and signalling pathways can confer drug resistance by overcoming the dependence of the cancer on the targeted protein. Recent observations using vemurafenib (PLX4032) against metastatic melanoma illustrate the diversity of molecular mechanisms by which a tumour can become resistant to a molecularly targeted drug (BOX 2).

Devising patient-specific combination therapies. Targeted cancer drugs are currently prescribed either as monotherapy or as a combination with non-targeted cytotoxic chemotherapy[30,31], and most clinical trials exploring the combinations of targeted drugs are still at an early stage[26,27]. In the absence of reliable criteria for selecting drug combinations in patient-specific ways, targeted drugs can only be used sequentially in order to tackle drug-resistant disease (FIG. 1b). Because resistance to a targeted drug tends to be maintained by minority clones even after switching to another drug, sequential treatment quickly exhausts the arsenal of applicable drugs.

The speed with which most cancers become drug-resistant to monotherapy with targeted drugs suggests that patient-specific combination therapies might lead to equally profound improvements for cancer therapy as they do in HIV therapy. For example, if a combination therapy targets three independent but essential pathways, it will typically require at least three resistance mutations to accumulate in a single disease clone before the clone can become a driver of drug-resistant cancer. Similar to HIV therapy, this combinatorial effect creates an increased genetic barrier that is more likely to exceed the capacity of the cancer to maintain resistant minority clones for most drug therapies before treatment begins. The cancer will thus no longer be able to become resistant simply by selecting for minority clones that already harbour the relevant resistance mutations. Instead, it must go through an arguably more time-consuming stepwise procedure, in which individual disease clones incrementally accumulate a sufficient number of partial resistance mutations. In either case, the example of HIV therapy suggests that drug resistance is likely to emerge in a subset of patients even when the most powerful combinations of targeted drugs are being used. For this reason, methods are needed for designing combination therapies against drug-resistant cancer in patient-specific ways.

Given the complexity and diversity of mechanisms by which cancer cells can become drug resistant (BOX 2), devising patient-specific combination therapies is far from straightforward. Companion biomarkers, which detect the presence or absence of targeted proteins, provide a first indication of applicable drugs but fail to account for the upregulation of alternative pathways and other complex forms of drug resistance. Experience from HIV therapy suggests that assays measuring cellular resistance phenotypes (BOX 1) may provide a powerful approach for predicting clinical drug resistance, although the complexity and cost of such assays pose considerable challenges in a clinical setting. Various assays have

Box 2 | **Mechanisms of resistance to targeted therapy in metastatic melanoma**

Patients with metastatic melanoma who are positive for the BRAF-V600E oncoprotein exhibit a strong initial response when treated with the selective BRAF inhibitor vemurafenib (PLX4032). However, after less than 1 year the vast majority of patients have undergone relapse, which is caused by the emergence of drug-resistant disease clones[74,75]. Various mechanisms have been identified that give rise to resistance against vemurafenib in these tumours[43,76]. First, melanoma cells can overcome drug-induced inhibition of MAPK–ERK signalling by acquiring an activating mutation in MEK1, which operates downstream of BRAF in the signalling pathway. Second, increased CRAF activity regulated by post-transcriptional mechanisms may substitute for BRAF-V600E activity. Third, activating mutations in NRAS seem to trigger MAPK–ERK signalling via MEK1 phosphorylation by RAF proteins other than BRAF. Fourth, upregulation of the *MAP3K8* gene, which encodes the COT kinase, leads to phosphorylation of MEK1 independently of any RAF proteins. Fifth, increased activity of one of two specific receptor tyrosine kinases, namely platelet-derived growth factor receptor-β (PDGFRB) or insulin-like growth factor 1 receptor (IGF1R), triggers various cancer-related signalling cascades and may constitute a resistance mechanism that does not depend on reactivation of MAPK–ERK signalling. Sixth, resistance mutations or genomic amplification of BRAF-V600E itself may confer vemurafenib resistance to melanoma cells, although clinical evidence for this plausible resistance mechanism is currently lacking. Last, a broad range of epigenetic and gene-regulatory mechanisms contributes to the transcription of key proteins involved in MAPK–ERK signalling, which is likely to give rise to additional mechanisms of vemurafenib resistance. In conclusion, this overview of the various resistance mechanisms against vemurafenib underlines the complexity of predicting patient-specific drug resistance; but it also supports the conceptual feasibility of this task because all of these resistance mechanisms are readily detectable by an integrative analysis of genomic data and cellular resistance phenotypes in a moderate number of patients.

been developed for predicting sensitivity or resistance to single drugs and drug combinations[48]. For example, patient-derived cancer cells can be cultured *in vitro* and treated with individual drugs or drug combinations, using cell survival as a phenotypic measure of drug resistance. Such *in vitro* assays of chemosensitivity and chemoresistance have been extensively evaluated, but it remains unclear under which circumstances they give accurate and clinically useful results[49]. A major limitation of cell culture is the lack of tissue structure, which may lead to results that do not generalize well to the primary tumour from which the cell line was derived. Xenograft transplantation and drug treatment in mice could provide a more faithful model for measuring phenotypic resistance, and early studies suggest that this assay might accurately reflect the resistance patterns that are observed in patients[50,51]. Although further research is clearly required, it seems plausible that a carefully designed cell transplantation assay can indeed provide patient-specific predictions of clinical drug resistance[26]. However, the practical effect of such phenotypic assays is limited by their high cost and labour intensity.

Complementary to single-gene companion biomarkers and labour-intensive phenotypic assays, high-throughput genomic profiling is emerging as a promising alternative for diagnosing drug resistance. On the basis of recent advances in high-throughput sequencing and microarray technologies, it is now feasible to establish genome-wide maps of the genome, epigenome and transcriptome of individual cancer samples at a reasonable cost[52]. Such data provide a comprehensive 'snapshot' of the cell state, which is likely to contain sufficient information for diagnosing most types of drug resistance — not only those that arise from mutations in the immediate drug target, but also those that are caused by the deregulation of alternative pathways. Importantly, with sensitive sample preparation methods[53], deep sequencing[54] and suitable computational algorithms[55], it is probably feasible to account for extensive heterogeneity within a tumour, which can arise from minority clones or cancer stem cells with a distinct drug-resistance profile. Supporting the feasibility of a genomic approach to drug-resistance profiling, in a handful of cases, it has already been shown that computational methods can be used to predict disease-specific drug sensitivities[56–58]. Applying such methods to comprehensive profiles of drug-resistant cancers could eventually give rise to a 'fingerprint' (REF. 59) or a 'scorecard' (REF. 60) of drug resistance that is informative for designing patient-specific combination therapies.

A route towards patient-specific combination therapies guided by genotype–phenotype predictions. Similar to HIV infection, many advanced cancers have proved difficult or impossible to eradicate from the patient's body. As a result, a growing number of researchers and clinicians are shifting their goals from finding cures to developing therapies that can convert a deadly disease into a chronic condition with long-term survival and an acceptable quality of life[61]. Targeted cancer drugs have a major role in these efforts, but their use as single-drug regimens is limited by the speed with which drug resistance emerges in most cancers (CML potentially being an exception with its relatively low rates of drug-resistant relapse[23]). It is thus becoming widely accepted that combination therapies involving several drugs with different mechanisms of action will be required to subdue drug resistance over longer periods of time[27]. In many cases, these combination therapies will need to be tailored to a patient-specific drug resistance profile and reassessed in response to emerging drug resistance, as is already common practice for HIV therapy (FIG. 1a).

What will it take to follow the example of HIV therapy and enable physicians to routinely design patient-specific combination therapies against drug-resistant cancer? On the one hand, a larger range of new drugs that target alternative cancer pathways is needed, so that physicians can select from a comprehensive toolbox of applicable drugs. Fortunately, our knowledge of the genes and pathways that contribute to cancer development and drug resistance is growing at an unprecedented rate[62], and the use of high-throughput methods in drug development is accelerating the time from target discovery to clinical proof-of-concept[63,64]. Over the coming decade, these developments are probably going to result in several approved drugs for each of the most relevant cancer-related pathways. On the other hand, accurate biomarkers for predicting drug resistance and the toxicity of combination therapies are needed to guide the rational design of patient-specific therapies. The technical obstacles to developing such biomarkers are vanishing, partly owing to the increasing availability of high-throughput sequencing in clinical diagnostics[65]. However, the statistical problem of establishing a robust correlation between the wealth of patient-specific molecular data (such as genomes, epigenomes and transcriptomes) and observed disease phenotypes remains exceptionally difficult to address, owing to the complexity of the molecular and cellular processes that contribute to drug resistance in patients[66].

Experiences from HIV therapy suggest that molecular phenotypes provide a powerful intermediate step for bridging the gap between genomic data and clinical outcomes. FIGURE 2 elaborates on this concept and outlines a two-phase approach for establishing the rational selection of patient-specific combination therapies for cancer. Like viruses, cancer cells exhibit several treatment-relevant molecular phenotypes that can be tested with cellular phenotype assays (BOX 1). For example, measuring the growth kinetics in a xenograft model treated with clinically relevant drug concentrations may provide a suitable method for establishing patient-specific drug-resistance profiles. In the first phase of the proposed approach (FIG. 2) resource-intensive cellular phenotype assays are applied to a well-defined and fairly small patient cohort; for example, patients with acute promyelocytic leukaemia or BRAF-V600E-positive but vemurafenib-resistant metastatic melanoma. The resulting, experimentally derived resistance profiles can be used to guide the design of patient-specific combination therapies in the study cohort. In fact, some cancer centres already use *in vitro*-derived drug-resistance profiles for selecting between alternative drug regimens (see the NCCN Clinical Practice Guidelines in Oncology), suggesting that the regulatory and ethical aspects of such clinical trials can be convincingly addressed in the current clinical environment. However, this experimental approach cannot be scaled to a large number of patients owing to the high cost and labour intensity of the cellular resistance assays.

In the second phase of the proposed approach (FIG. 2), the data gathered in the first phase are used to create computational models that can predict drug resistance from genomic data. This step is important because genomic assays are more feasible to carry out as part of routine clinical practice compared with cellular drug-resistance assays. Statistical models are developed to predict the results of cellular phenotype assays (such as drug resistance in patient cell lines or in a xenograft model), based on the comprehensive maps of patient-specific genomes, epigenomes and transcriptomes that have been collected for the initial patient cohort. Importantly, all data

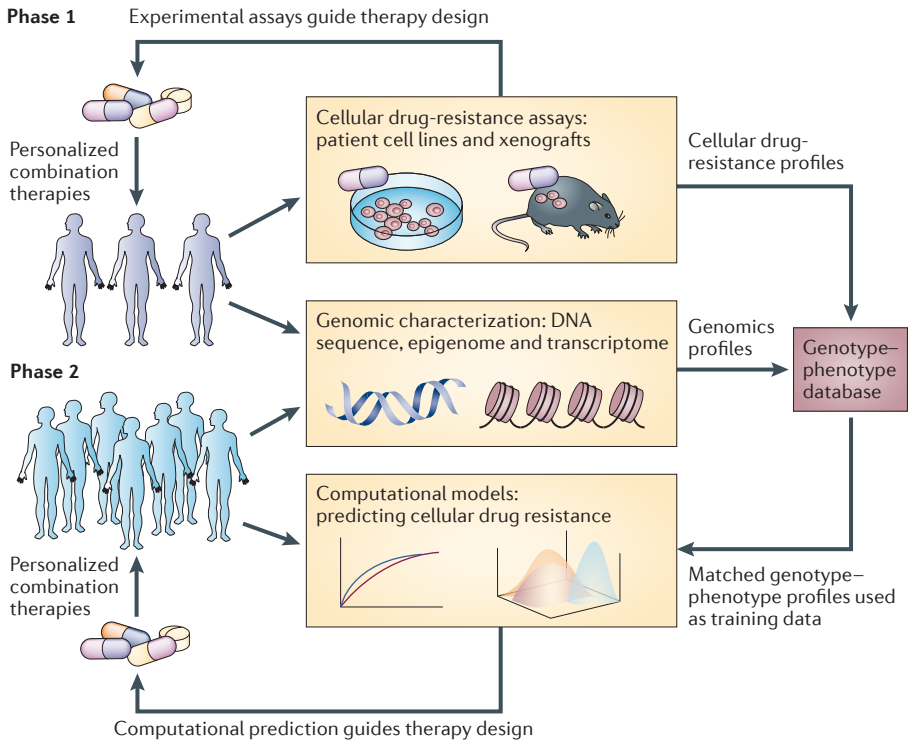

Figure 2 | **Towards patient-specific combination therapies for tackling drug resistance in cancer.** This figure illustrates a route towards patient-specific design of combination therapies in cancer. In the first phase, cellular drug-resistance assays are carried out for a moderately sized patient cohort, and the resulting measurements of resistance phenotypes are used to devise patient-specific combination therapies that tackle drug resistance in these patients. In the second phase, the cellular resistance assays are replaced by resistance predictions that are based on genomic patient profiles, which are substantially faster, cheaper and more practical under clinical conditions. To develop accurate computational prediction models, primary patient material from the first phase is subjected to comprehensive genomic characterization, giving rise to a database of patient genotypes (including genome, epigenome and transcriptome data) and matched cellular drug-resistance phenotypes. Computational resistance predictions are validated in terms of their ability to replace the cellular resistance assays (which is more feasible than a direct assessment of their effect on clinical outcome). This approach is likely to result in accurate, cost-efficient and informative biomarkers that can guide the design and validation of patient-specific combination therapies against drug-resistant cancer.

(primary tumour, cellular drug-resistance profiles and clinical outcome) must pertain to the same set of patients in order to allow for integrative statistical analysis and the construction of predictive models. This requirement distinguishes the proposed data collection efforts from ongoing work that aims to establish comprehensive catalogues of cancer cell lines[78,79], which are focused on cell lines that lack normal tissue controls and clinical data of the patients from which they were derived. The resulting prediction models are anticipated to be relatively accurate, as they link genotypes and pathway activities to observed cellular phenotypes, rather than trying to bridge a much wider gap and directly predict clinical disease phenotypes. These prediction models are also fairly cost-efficient and straightforward to validate because it is sufficient to show that they strongly correlate with the cellular resistance assay that they emulate. Furthermore, their conceptual similarity to cellular phenotype assays (with which physicians are already familiar) makes them easier to understand and interpret than biomarkers that predict clinical outcome based solely on statistical evidence. In summary, genotype-based predictions of cellular drug-resistance phenotypes could provide a relatively straightforward path towards personalized medicine, because biomarkers that predict cellular phenotypes are easier to develop, validate and integrate into clinical practice than biomarkers that aim to directly predict disease outcome.

Conclusion

A broad range of targeted cancer drugs is currently under development, and the first drugs of this new generation are already having substantial effects on clinical practice. The use of targeted drugs is often guided by companion biomarkers, which help to avoid treating patients who are unlikely to respond. Unfortunately, even among those patients that do respond to targeted therapy, drug-resistant clones frequently evolve by a variety of mechanisms, resulting in treatment failure and death (BOX 2). This situation is somewhat reminiscent of the state of HIV therapy 20 years ago, when new drugs gave rise to stunning initial responses but quickly lost their efficacy when drug resistance emerged. The drug resistance problem in HIV was successfully tackled by introducing combination therapies, which are now routinely tailored to each patient's individual drug-resistance profile. As a result, HIV infection has been transformed from a uniformly fatal disease into a severe but manageable chronic condition. State-of-the-art HIV therapy provides the most elaborate example of personalized medicine that has yet been realized for any disease. In this Perspective, we have reviewed the building blocks of personalized medicine in HIV and cancer therapy, and have identified a number of lessons from HIV therapy that might be informative for shaping the future of personalized cancer therapy (BOX 3). With an increasing number of targeted cancer drugs entering routine clinical practice and high-throughput sequencing emerging as a powerful diagnostic platform, it is likely to become feasible to devise personalized cancer therapies in much the same way as is common practice for HIV infection.

However, the most substantial obstacles to the routine use of patient-specific combination therapies in cancer may turn out to be neither technical nor scientific, but regulatory and economic[30]. By definition, the application of each patient-specific combination therapy is limited to a small number of patients, making it impossible to validate all clinically useful drug combinations in adequately powered clinical trials. Importantly, this problem is neither due to our limited understanding of cancer biology nor due to inadequate statistical or computational methods. Instead, it is deeply rooted in the heterogeneity of human cancers and thus is conceptually unavoidable. If each tumour is indeed a "disease never before encountered in the clinic" (REF. 67), clinical trials with few treatment groups and many patients per group might no longer be the most appropriate method for validating combination therapies against cancer. Rather than focusing on a tiny subset of combination

Box 3 | **What can be learnt from HIV therapy for personalizing cancer treatment?**

Over the past 20 years, HIV therapy has spearheaded personalized medicine in terms of targeted drug development, molecular diagnostics and the rational design of patient-specific combination therapies. Several aspects that have contributed to the success of HIV therapy may be relevant for devising the future of personalized cancer therapy.

- HIV drug resistance can be predicted from viral genotype data. Currently achieved prediction accuracies are considered sufficient for guiding treatment decisions in clinical practice[16,20].
- Drug resistance predictions were initially carried out using expert-curated mutation tables, but computational methods are now complementing this approach[12,18,19].
- State-of-the-art statistical learning algorithms[77] give rise to resistance predictions that are at least as accurate, robust and clinically useful as manually curated expert rules[16,20].
- The prediction of resistance phenotypes was facilitated by the development of databases that collect viral genome sequences and matched cellular resistance phenotypes that are based on primary patient samples[17].
- First-line combination therapies for HIV infection have been validated in clinical trials and are partly available as off-the-shelf combination drugs. Patient-specific therapy design is initially required only for a minority of patients who are infected with non-wildtype viruses.
- Once the first-line combination therapy fails owing to drug resistance, patient-specific combination therapies against drug-resistant viruses are devised on a case-by-case basis and are often given without prior validation in clinical trials.
- Several methods for viral resistance prediction have found regulatory approval as part of diagnostic kits for HIV genotyping. By contrast, more advanced interpretation systems have not yet been approved by either the US Food and Drug Administration or the European Medicines Agency, but they are nevertheless widely used for tackling drug resistance in clinical practice.
- Expert panels have developed guidelines for areas of HIV therapy that are insufficiently covered by governmental regulation[12,18,19].

therapies and validating them in classical clinical trials, a more powerful approach would be to validate guidelines that stipulate how drugs that are approved as single agents should be combined in a rational and robust manner. Although it will probably take years for regulatory agencies to develop a comprehensive framework regulating this scenario, and for pharmaceutical companies to negotiate collaboration agreements for validating drug combination, the example of HIV therapy provides cause for optimism that progress towards personalized cancer treatment may still be fairly swift. In HIV therapy, expert panels have stepped in when regulatory guidance was insufficient, devising guidelines on how to select optimal drug combinations[12,18,19]. And academic researchers took the lead when there was insufficient financial incentive for pharmaceutical companies to explore combination therapies with drugs owned by different companies. The clinical reality of patient-specific HIV therapy has important implications for personalized medicine. On the one hand, it shows that pragmatic solutions do emerge fairly quickly when there is considerable medical need, and that these solutions can be viable in the absence of a detailed regulatory framework. On the other hand, it underlines the need for adapting regulatory procedures and economic incentives to the new reality of patient-specific combination therapies against drug-resistant disease.

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Competing interests statement

The authors declare no competing financial interests.

FURTHER INFORMATION

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