Clinical and economic impact of the nonresponder phenomenon – implications for systems based discovery

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Molecular diversity is a hallmark of life. Unfortunately, given that the clinical benefit of a drug can only be realized under certain genetic/molecular conditions, such heterogeneity can mean the difference between survival and death. For most targeted therapies it appears that such conditions are met in only a small percentage of patients, particularly in the monotherapy context. Notwithstanding, the nonresponder phenomenon can be viewed as a low-hanging fruit among medical needs, with a large body of scientific knowledge surrounding the target and the diseased system. This knowledge, together with information about the molecular sources of nonresponse, provides a rational framework upon which novel intervention strategies can be built. Driven by such molecular considerations and the enormous economic implications, new levels of innovation are urgently required. Systems level patient characterization coupled with innovative *in silico* strategies hold great promise and suggest a future of theranostic-linked combination therapies, optimized cohort selection and rational prioritization of clinical opportunities.

Introduction

When a drug is administered to a patient it begins a complex journey defined by diverse molecular liaisons. These sequential interactions are not only essential to the passage, metabolism and removal of a drug from the patients system but also define the molecular basis of observed clinical outcomes. For targeted therapies, the drug (or a metabolite thereof) interacts with and modulates the activity of target proteins within diseased systems, working to offset the influence of disease causing anomalies. Unfortunately, when tested against an entire patient population, a drug can elicit a diversity of physiological responses, ranging from complete remission, to adverse event, to no response whatsoever. Not only does this highlight the molecular diversity inherent in patient populations and their underlying disease cases but also defines an under-appreciated aspect of unmet medical needs.

Borrowing from the tenets of Karatsuba's 'divide and conquer' strategy [1], biologists have made great strides in defining the molecular composition of diverse cellular systems, including those refractory to therapy. While this strategy has resulted in a comprehensive and invaluable molecular parts list, the idea that it might provide a blueprint for modulating drug response rates has convincingly been dispelled. As Jules-Henri Poincaré (1854–1912) correctly emphasized 'Science is built up with facts as a house is with stones. But a collection of facts is no more a science than a heap of stones a house' [2]. Such philosophy succinctly captures the next phase of the challenge, where we seek to 'conquer' on the basis of the results of the 'divide'; a phase of integrative systems based discovery. With this goal in mind, let us examine the key issues surrounding the nonresponder phenomenon from market to molecular considerations, and detail how systems based discovery might bring us closer to surmounting this problem effectively.

The economics of nonresponse

While the nonresponder problem afflicts all therapeutic areas, it is particularly pronounced in clinical oncology. Here, response rates necessary for marketing approval remain low and, as a result, significant populations of patients are left without effective sources of therapeutic impact or hope. From a market perspective, the implications of the nonresponder phenomenon are quite

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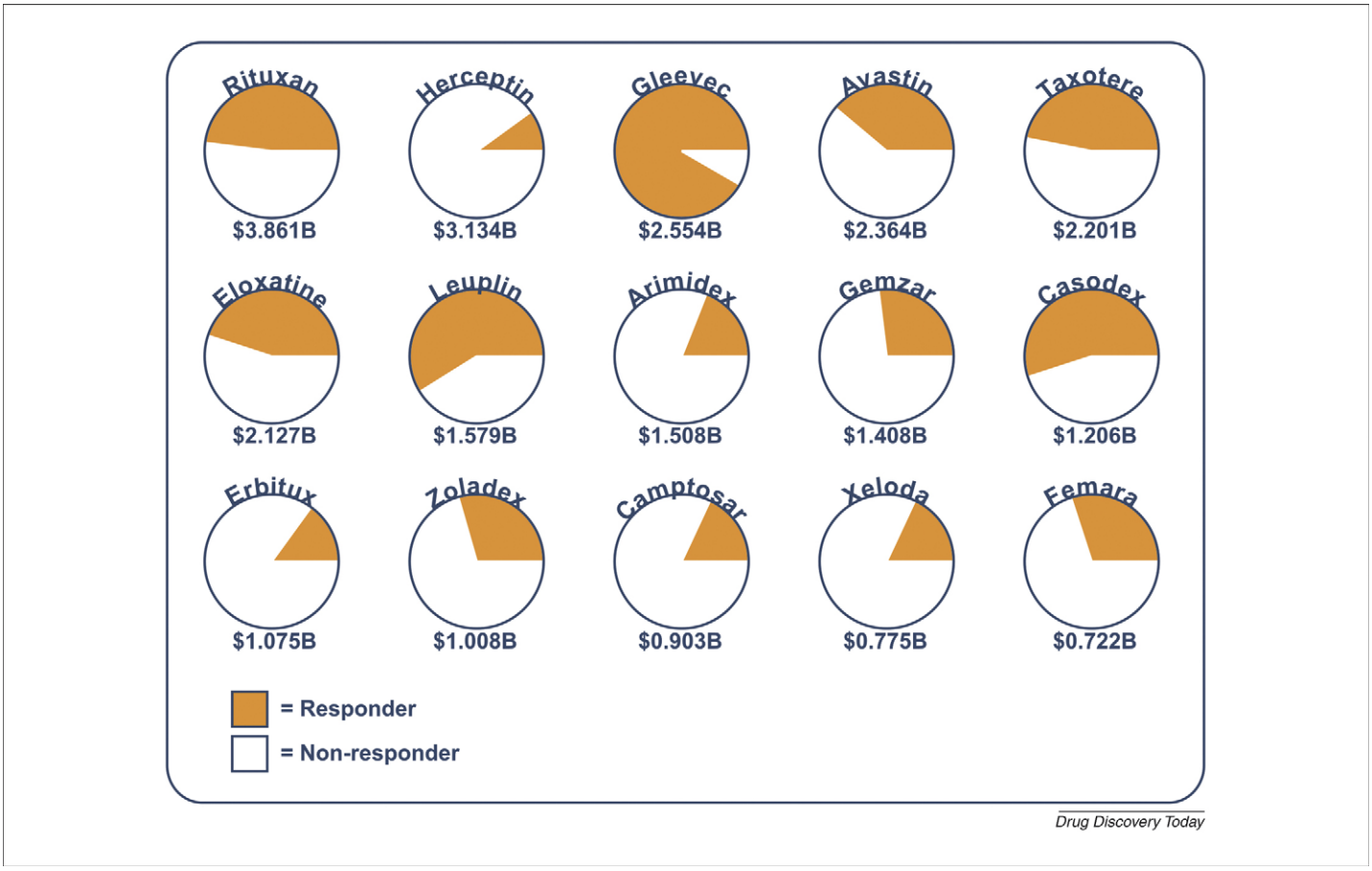

FIGURE 1

Overview of top oncology drug sales for 2006 [3] with associated responder/nonresponder ratios (including combo-therapies). Response rates were determined from product label information at http://www.fda.gov.

startling. In 2006, for example, the top 15 selling onco-therapeutics generated sales of approximately US$ 26.43 billion (Fig. 1) [3]. Within this group of drugs the average un-weighted overall response rate is ~35%, with the distribution of values ranging from a 10% response rate (for herceptin) up to ~90% (for gleevec/imatinib). Perhaps not surprisingly, a clear correlation is seen between overall response rate and the sales volume, with four of the top five best selling onco-therapeutics showing response rates of around 40% or more. Empirical estimates based on these data suggest that ~65% of cancer patients do not respond to conventional therapeutic options. The enormity of the problem – and indeed potential – is further emphasized by the fact that the figures quoted here are limited to the top 15 oncology drugs. Not only has the arrival of newer therapies expanded this market but it also does not consider other therapeutic areas such as neurology. It is therefore conceivable that even single figure percentage increases in response rates can improve prognosis for large populations of patients and drive significant market capture. Moreover, these data also stress the importance of identifying the right patients for the right drug as early as possible.

The financial implications of the nonresponder problem are not limited to marketed drugs. Indeed, a much more difficult sum to quantify is the industry-wide loss incurred as a result of clinical failure during the drug development process. Again, much of this failure can be attributed to the high numbers of nonresponders within the trial population. Recent experience has demonstrated that small subgroups of patients do indeed respond during trials, with *post hoc* genomic analysis often revealing strong correlative evidence favoring use of the drug in certain genetic backgrounds [4,5]. While helping to define a path to market, however, such retrospective analyses still come at significant cost, with the FDA demanding prospective clinical studies to validate such *post hoc* results. Clearly, a process that can capitalize on the prospective identification/prioritization of putative responders before clinical testing could improve the chances of success in any disease setting. Here, putative cohort participants would be molecularly screened for (a) aberrations in components associated with the drugs activity and (b) for comedications that may impinge on drug function and system sensitivity. Such a process should clearly be supported by innovative new approaches to systems based data analysis, where clinically representative disease models are used to generate clinical hypotheses.

The nonresponder phenomenon also raises other interesting, although less direct, market opportunities. The mere existence of the problem tells us that, while a patient's disease may phenotypically conform to a particular diagnosis, it may still be subtly distinct at the molecular level. Such distinction is important enough to render the patient refractory to approved therapies and, as such, one may argue, defines a new class of unmet medical needs. The implication here is that by defining molecularly distinct disease subtypes we can provide a more accurate definition of the disease and its rate of occurrence. From a regulatory standpoint, this may enable

authorities to grant orphan drug status to therapies directed at these refractory subgroups, since populations now have a higher chance of falling below the limits of the 200,000 patient threshold. For companies, this could imply significant tax advantages and market exclusivity upon successful development of a therapy, although it remains to be seen whether authorities will grant the same recompense to subgroup-directed medicines as exist today under standard orphan status agreements.

Systems based implications of the nonresponder problem

If there is a single positive to be gleaned from the nonresponder problem it is that it actually forces us to seek new levels of innovation in systems based discovery. Today, it provides the impetus to acquire and rationalize patient-specific molecular information with the wealth of knowledge surrounding drugs and their *in vivo* interaction partners on a system-specific level. Characterizing the inter-patient differences in genes associated with the *in vivo* activity of therapeutic molecules will allow us to classify the range of anomalies most likely to impinge on drug responsiveness. Evidence to date suggests that such anomalies will be cancer- and therapy-specific, meaning a no 'one size fits all' approach. So how might we optimally approach the problem?

A first important step is to define and understand the 'parts-list' and molecular connectivity of individual onco-systems and their relationship to available therapies (Fig. 2). This implies the need for representative cancer-specific *in silico* disease models, demanding the integrated potential of 'omics' and computational technologies. For example, while text-mining of full-text publications is essential to creating an initial 'proteo-anatomical' disease model, the connectivity of this model must be optimized through analysis of relevant expression information that is specific to the tumor/histopathological subtype under investigation. Strategies that emphasize a bias for the human specificity and physiological relevance of incorporated data will help avoid the problems of empirical pathway representations, which often utilize information from inappropriate cellular systems and experimental settings. Such models represent mosaics of molecular information and often fail to respect the context-dependent functionality of many proteins. New cell ontologys are therefore required and should enable us to prioritize data quickly coming from those cell-types with the greatest relevance to the disease under study. Moreover, given that patient-derived data are requisite to producing accurate models, all efforts to expedite the public availability of these data should be encouraged.

By integrating the wealth of knowledge surrounding drugs and their *in vivo* interaction partners, such clinical focus sets the stage for several important innovations. Foremost among these opportunities are (a) the ability to prioritize prospectively those cancers most likely to respond to a given targeted therapy, (b) the ability to prioritize prospectively those patients most likely to respond, especially during the cohort selection process and (c) the ability to modify the treatment regimen of patients with intrinsic or evolving resistance to a therapy strategically.

The right indication for a drug candidate

Today, the pressure to capture the broadest market possible upon initial drug launch – typically one of the 'big four' tumor types:

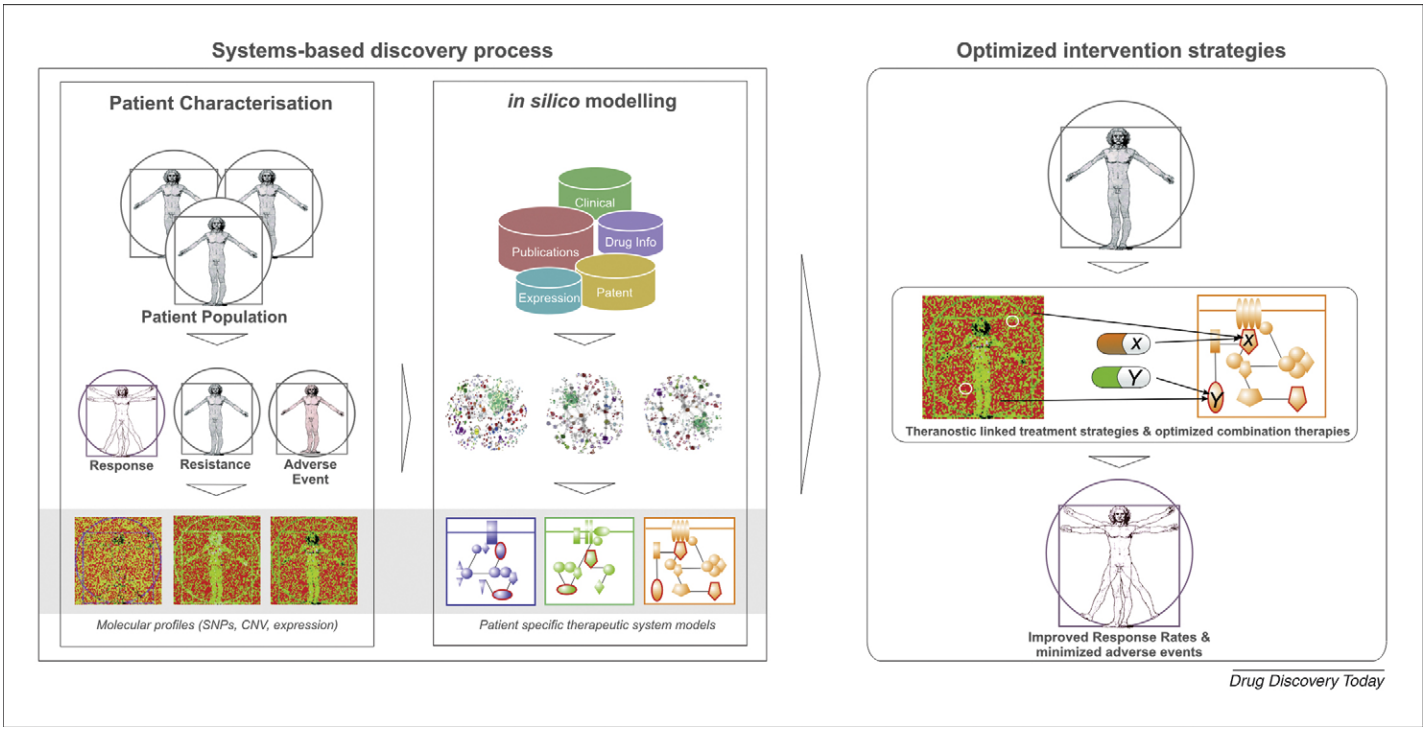

FIGURE 2

Schematic overview of a systems based approach to the nonresponder problem. Patient disease systems are first characterized, with resulting data rationalized against *in silico* disease models. Such models are defined using only cell and disease relevant information, using processes such as bibliome mining and expression analyses. Once patient- or cohort-specific information has been assessed against these models, clinicians may be in the position to define rectifying treatments. Such insights should facilitate the emergence of novel theranostic signatures and accompanying (multicomponent) therapies for marketed and developmental drugs.

breast, prostate, lung or colon cancer – remains a key decision bias. Under this pretext, we must question whether the choice of therapeutic area was the optimal one to begin with and whether enough human-specific molecular information is being considered in prioritizing particular cancers for clinical testing. Not only is it difficult to achieve incremental improvement over existing standards of care but the underlying biology of the 'big four' may not necessarily be the most suitable to a drug candidate, especially when compared to that of less common cancers.

As the history of imatinib development successfully demonstrates, the molecular composition of rare cancers such as CML can be exquisitely sensitive to the mode of action of a targeted therapy [6]. Not only can this result in extremely high response rates but can also provide the perfect starting point for expanded approval into alternative indications. This is because clinical use and sometimes even off-label administration of approved therapies across numerous cancer types can lead to clinically compelling findings, a feat next to impossible in traditional drug development approaches. By administering the drug as early as possible to humans in diverse clinical contexts, we become less dependent on results from model systems and their subsequent influence on strategic decisions. Moreover, community-wide efforts to understand the biology of a drug (e.g. its promiscuity profile) are often enhanced upon marketing approval, and with this comes an expanded understanding of its fuller therapeutic potential. It should therefore be emphasized that when it comes to strategic decisions, the biology of human cancer must take precedence over market considerations because it is biology that ultimately determines a drug's success or failure. Given this important perspective, can systems based discovery provide a new path forward?

We have already emphasized the need for human/system-specific disease models across all cancer types. A database of such models can facilitate a process of 'comparative systeomics' involving *in silico* comparison of independent cancers. Not unlike the premise of comparative genomics, this strategy can be used to identify those cancers whose molecular composition and architecture is most consistent with a probable successful outcome. Once prioritized, the putative response of top scoring cancer types to drug candidates can be assessed in a preclinical setting, with resulting information used to guide the development strategy. Clearly, such a process could ensure that the most appropriate cancer type is chosen at the beginning of the drug development process and that maximum biological input is achieved during the decision process.

The right patient for a given trial

System-specific disease models provide a global, real-time appreciation of those factors that, if perturbed, stand a greater likelihood of causing nonresponsive disease. As such, they can provide a prospective prioritization of genes for functional analyses and facilitate hypothesis-driven clinical trial design. For example, the molecular status of key genes can be assessed as a basis for trial inclusion/exclusion. Those patients whose genotype is most consistent with a probable therapeutic response should be prioritized for trial participation. Alternatively we can also consider a scenario where primary and secondary endpoints are established once the molecular characteristics and associated functional implications of the trial population are defined. Such a process would certainly demand stringent regulatory guidance, but may help to obviate the present need for prospective trials following retrospective discoveries. Resulting clinico-molecular data from trial patients can also be incorporated into existing models and used to understand their functional implications at the system level, or to further optimize the disease model for follow-on studies. Moreover, by using molecular information derived from trial participants, such models can be constructed for responders and nonresponders. Such intra-trial comparative analysis can greatly facilitate the identification of those factors involved in nonresponsive disease.

The right drug(s) for a given patient

Ever since the publication of the human genome, the term 'personalized medicine' has been warmly embraced by the clinical oncology community and not without reason. Implicit in its definition is the hope of utilizing a patient's genotype to prescribe a drug(s) with the highest safety, efficacy and likelihood of response to a specific condition. While great attention has been afforded to the identification of biomarkers to determine a patient's likelihood of response, such knowledge also provides the basis for designing new therapeutic intervention strategies. Interestingly, it may be argued that nonresponsive disease is a low-hanging fruit among medical needs, since extensive clinico-molecular information already exists. Given the diversity of causative anomalies, however, future approaches will focus first on identifying the source of resistance and then developing a rectifying intervention on the basis of this information.

For target-dependent sources of resistance, the approach is, in principle, straightforward and focused on assessing the mutational/expression status of the target gene (Fig. 3). As the case for BCR-ABL exemplifies, efforts to redress target-based resistance have focused on the development of second generation drugs, with higher affinity and greater structural compatibility with the associated target [7]. For systems based sources of nonresponse, the issue is clearly much more challenging with many combinations of variable and mechanism possible. In the case of pathway-independent resistance, involving drug transport proteins for example, it may be sufficient to monitor plasma drug concentrations and modify dosage regimens accordingly [8]. In fact, this can be viewed as a very basic necessity in the clinical management of nonresponsive disease today, especially in cases where unexpected adverse events occur.

Little effort has as yet been dedicated to exploring globally pathway-dependent resistance, as well as to examining its potential for defining compensatory therapies. While such therapies could involve single drugs whose affinity profile encompasses multiple specific targets, the most tractable scenario is one where multiple system components are targeted using rational combinations of targeted agents. Again, the nature of such combinations will be determined by the molecular source(s) of resistance and the strategy required to overcome their influence. Notwithstanding, by aligning specific combinations of genetic aberration with appropriate treatment measures, such theranostic-linked multicomponent therapies hold great promise for rationally redressing intrinsic and emergent nonresponsive disease (Fig. 4).

Present challenges

An important question today is whether available technologies and information can provide immediate impact in surmounting

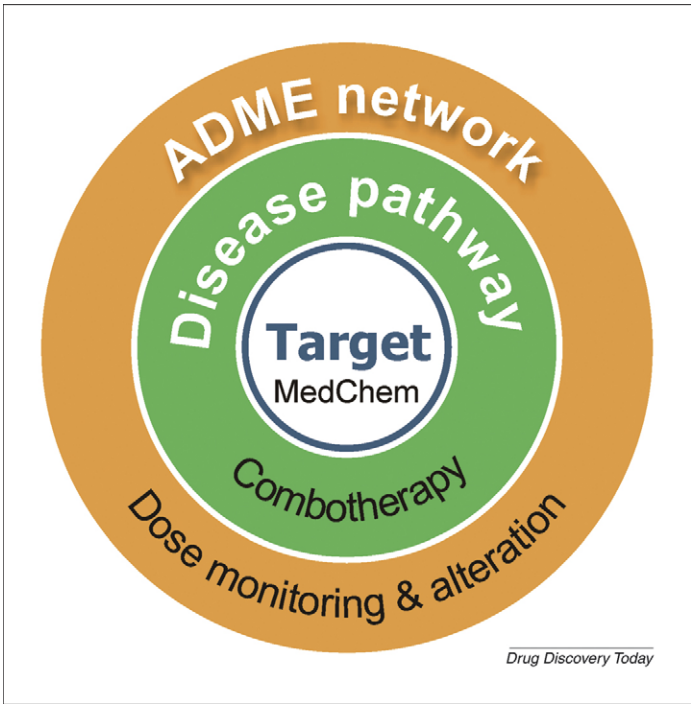

FIGURE 3

A synopsis of the primary domains of nonresponse and some of the approaches that may be taken to redress these aberrations. Central to the issue are perturbations in the target protein (i.e. target-based resistance). In this context, medicinal chemistry (MedChem) has been helpful in redressing the problem by producing follow-on compounds with lower sensitivity to structural changes in the drug-binding domain. Systems based sources of resistance include disease pathway-dependent mechanisms and those affecting the passage of the drug to the diseased system – typically affecting ADME processes (i.e. disease pathway independent resistance). In the latter case, dose monitoring may be employed to ascertain whether the therapeutic index of the drug is maintained. Dosing regimens may be optimized accordingly. For aberrations affecting disease pathway components, rationally designed combination therapies may be the method of choice. Here, the concept of theranostic-linked drug combinations will play a key role in defining the molecular source of resistance and providing mechanism-based treatment strategies.

such refractory behavior? I certainly believe so, but only under the prerequisite that we are willing to challenge certain established concepts with a view to achieving a new level of innovation on several fronts. For example, our target-centric appreciation of drug mode-of-action has clear limitations as does our over-reliance on poorly congruous model systems with their often tenuous relationship to the human disease state. In the former instance, emergent data are allowing us to step confidently beyond Ehrlich's prevalent 'magic bullet' concept in favor of more-encompassing therapeutic strategies. Such strategies should seek to capitalize on the nature of the system as a whole rather than the sole function of a specific target. Here, the term 'system' is intended to encompass numerous levels of definition; from pathway, to tumor, to patient. Just as we should now embrace chemical promiscuity as a fact of life, so we must approach the molecular heterogeneity of tumor tissue and the inherent genetic diversity of patient populations. Immediate emphasis on the rational design of patient-tailored multitargeted drug combinations is thus essential.

New *in silico* strategies that capitalize on existing tomes of clinical data must be developed, with comorbidity, comedication and side-effect information certain to provide novel, clinically relevant targets and mechanistic hypotheses. By obviating model organism dependencies, such focus on human-specific data is essential to reaching new levels of clinical insight. Moreover, a new and exciting discipline of 'computational molecular pathology' could thus emerge, and with it a more expeditious path to clinical discovery than previously possible. These strategies will be highly dependent on the elaboration of accurate computational models of human disease systems and their subsequent interplay with clinico-molecular information. To ensure success, it is imperative that such models be built based on data-derived solely from relevant cell and disease subtypes. These system-specific knowledge models will enable us to ask whether the molecular composition, architecture and activity of a cancer might influence the response to targeted therapies. Such models will certainly also facilitate the prediction of rectifying combination treatments and allow us to prioritize cancers for clinical testing against

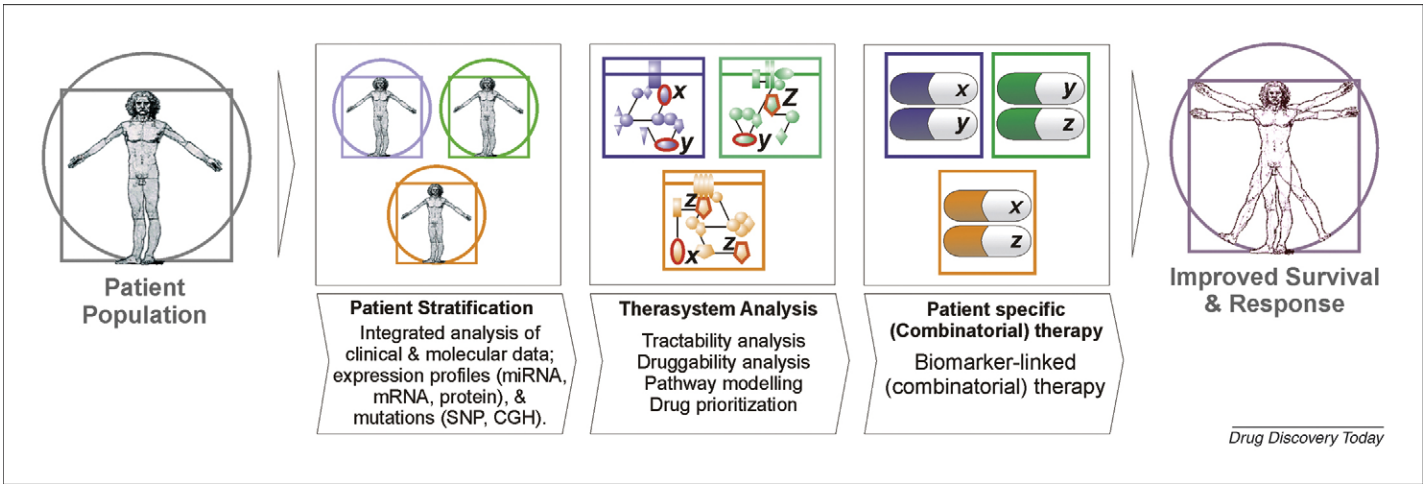

FIGURE 4

Schematic overview of a process for predicting patient-specific combination therapies. Patient disease systems are characterized at the molecular level, preferably within the context of large, well controlled, clinical trials. Disease subtypes are thus defined, with the information used to produce *in silico* disease models. These models are subsequently used to prioritize chemistry for combinatorial testing in a preclinical setting. Such a process can be used to define additional drugs to sensitize resistant patients to the effects of a targeted therapy.

developmental compounds. For those predicted to be refractory, or of low likelihood to respond, combination therapies might again be proposed. This strategy could also prove highly effective in repositioning existing therapeutic assets within such drug combinations.

While the prize is clearly great, the challenges to such *in silico*-driven approaches to the nonresponder problem are significant; challenges that are not only technological but also practical in nature. From a clinical perspective, the process is dependent on characterizing a disease system, which requires the provision of diseased tissue. To be successful, clinicians must either overcome the reticence to biopsy pre- and post-treatment or develop new noninvasive methods to provide equivalent data. Considering the mortality rates and range of side effects experienced by cancer patients undergoing chemotherapy (e.g. hair-loss) and/or targeted treatment (e.g. extreme skin rash) are biopsies really too much to ask? Greater understanding about the nature and prevalence of resistant disease subtypes is also required, as is regulatory emphasis and recognition of the issue; after all, the problem of nonresponse represents perhaps the greatest of all unmet medical needs.

Education is also a key factor and much can still be done to bridge the gap between the clinical and molecular research fields. New *in silico* strategies and methodologies will play a crucial role in marrying these autonomous information domains, meaning that many of today's bioinformaticians must strive to become tomorrow's computational molecular pathologists, preferably in close collaboration with clinical mentors. Clinical researchers, by contrast, should also embrace the potential of emergent computational approaches, providing the guidance necessary to ensure their clinical relevance. At the same time, medical *curricula* can also be enhanced to prepare clinicians for the conceptual novelties of information-driven medicine.

Concluding remarks

In an era where targeted therapies are emerging as key components in our therapeutic armamentarium, it is the issue of nonresponse which is attracting ever-growing attention. There is little doubt that, if greeted with community-wide effort and collaboration, rational solutions to this problem will change the nature and practice of not only the drug development process but also that of therapeutic intervention itself. It is reassuring to note that, after years of emphasis on model systems, technological advancements are today enabling us to characterize human disease directly from patient sources. For a given trial population we can now decipher and compare molecular systems associated with specific clinical outcomes. Given that such information derives not from a model system but from real patients, the molecular insights promise unique and applicable insights into the molecular basis of human disease. This, in turn, will help guide the development of future therapeutic strategies that focus on the nature of the system as a whole rather than the function of a specific target. From this perspective, we are clearly witnessing the beginning of an exciting revolution in medical science.

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