

Early patient stratification is critical to enable effective and personalised drug discovery and development

With the current chances of an efficacious outcome in Phase II for novel mechanisms being in the region of 1 in 5, we argue the need for personalised drug discovery and development to be executed at the beginning of the process and that the pharmaceutical industry's future successes will likely depend upon effectively enacting this paradigm.

It is well known that the drug discovery and development process is lengthy, expensive and prone to failure¹⁻³. This high failure rate is a significant factor in the pharmaceutical industry's productivity problems, subsequent mergers and downsizing⁴. Starting from the selection of a novel target in Discovery, through the multiple steps to regulatory approval, the overall probability of success is less than 1%¹. Given the time and resources needed to investigate a novel biological mechanism, ie one that has not been tested in humans before, success rates as low as these yield an unsustainable business model. In the face of a negative return-on-investment for new chemical entity drug discovery and development (DDD)² and constricted healthcare budgets that demand improved drugs to warrant reimbursement, an alternative approach must be identified to provide patients with new and better therapies as well as sustain the industry. The central tenet of this paper is

that the data-driven matching of patients to the appropriate investigational therapy in early drug development is critical to the industry's success, overall cost reductions in healthcare spending and to the delivery of effective, personalised and innovative medications to patients.

Phase II challenge

Of the multiple hurdles in DDD that must be overcome, successfully establishing efficacy in Phase II is one of the most significant. For novel mechanisms, the likelihood of an efficacious outcome in Phase II is approximately 20%⁵. One of the major challenges in DDD is to understand why this success rate is so low, as the selection of the biological mechanisms and the identification and development of agents to manipulate those mechanisms are most often based on state-of-the-art science. As an industry, we need to better understand why some investigational agents are successful in Phase II and most others are not.

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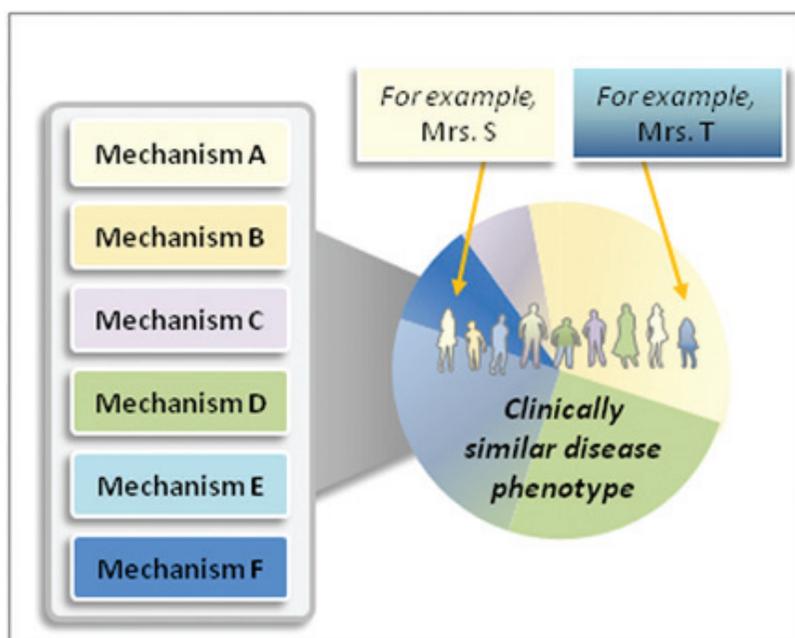


Figure 1

Conceptualising the multimechanistic contributions to disease. There are multiple mechanistic pathways that can result in disease classified by clinical phenotype (eg, tumour type, atherosclerosis, diabetes, etc). Reconfiguring how we think about disease and developing new treatments is crucial to achieving meaningful breakthroughs in patient health. Consider that different mechanistic wedges represent Mrs S and Mrs T. Treating them with a mismatched drug that does not influence the dominant, respective causal mechanism of their diabetes mellitus will likely result in a negative clinical result. These 'apparent' failures will also force the selection of more regulatory (biological) mechanisms that may be less relevant to the disease. As a result, the clinical manifestation of their disease, but not its cause, is treated

In consideration of the major factors required for Phase II success with novel mechanisms of action, several possibilities warrant discussion. These include: 1. The investigational agent did not yield the required pharmacology; 2. The biological target or mechanism is not relevant to the disease; and 3. The biological target is correct, but only for a subset of patients.

Inadequate pharmacology

The first and most obvious reason that an investigational drug may fail to yield an efficacious response in Phase II is that the agent did not exert the desired pharmacology. That could be due to several causes, including suboptimal drug levels from high clearance, low bioavailability, high protein binding, or safety issues that restrict dosing. Some of these issues have been obviated by modern drug metabolism, pharmacokinetic and safety testing methods undertaken in the preclinical phase of drug development.

Despite achieving predicted drug exposure, however, the *in vivo* human pharmacology still may not reflect the preclinical testing regimens, including cell lines or animal pharmacology. To address this, many clinical studies strive to incorporate mechanistic (pharmacodynamic) biomarkers, to ensure that the biological target is being manipulated. These biomarkers are distinct from efficacy biomarkers. Examples include: increase in circulating GLP-1 level with DPP-IV inhibition⁶, an increase in HDL level following CETP inhibi-

tion⁷, increase in soluble $\alpha\beta$ CSF level from gamma secretase inhibition⁸, or mitotic cells following Aurora A kinase inhibition⁹. A significant difficulty with mechanistic biomarkers, however, is that the required degree of change in these markers is often derived from animal models of disease and as such lack the translatability to the human condition.

Disease relevance

The second consideration for the lack of demonstrable Phase II efficacy is that the biological target or mechanism is not relevant to the disease under study. If the target is not relevant in humans, then how was it selected? In general, the rationale for selecting that target for prosecution is multifaceted, including input from human genetics, observational clinical studies (eg, a measure related to the target is abnormal), and animal experiments. In most therapeutic areas, however, concrete decisions regarding the pursuit of a specific programme often hinge on animal models of disease. Examples of animal models of disease include: Apo E knockout mouse for atherosclerosis; the rat conditioned avoidance behaviour model of schizophrenia; the mouse tumour transplant model, or the *ob/ob* mouse model of diabetes¹⁰⁻¹³. From these models, partial correction of the abnormality may be achieved by knocking out or overexpressing a specific gene (biological target) or through the use of a pharmacological tool. A positive outcome, signalling potential human efficacy with a pharmacological agent is a 'go forward' result, ie, the project team is armed with evidence that the exerted pharmacology will yield a salutary outcome in people. Yet the problem with animal models of disease is that they very often do not reflect the human circumstance (eg, avastimibe in animal models of atherosclerosis, among others)¹⁴⁻¹⁸. If they did, then one would expect that success rates in Phase II would be significantly higher than 20%. Intuitively, this is not surprising, as the physiology and associated pharmacology of the test species is likely to be very different from that of the human despite similar and apparent clinical manifestations (eg, elevated glucose). Thus, a positive animal model result might be due to a target that is relevant to the animals *per se*, and much less so to humans.

It is important to acknowledge the potential value of animal models of disease to identify a promising target for future exploration in humans. That is, animal models of disease can lead to new ideas that can be explored in humans.

It is a much more demanding application, however, to use the animal model to make decisions about the predicted therapeutic efficacy of an investigational drug. Moreover, in order to confidently employ even a simple, dichotomous (positive vs negative) response, scientists must have a reasonable idea of how that preclinical change predicts the clinical response. For many reasons, that is very hard to do.

Phenotypically similar but etiologically heterogeneous diseases

The last consideration of causality for the low Phase II success rates is that the biological target is relevant to the disease only in a subset of patients, or is important but only in combination with other disease-driving mechanisms. Currently, the classification of many diseases and the resulting selection of therapy are based on the clinical presentation. For example, the diagnosis of diabetes mellitus is based on an elevated blood glucose or glycosylated hemoglobin value. For type 2 diabetes mellitus, however, it is the integrated impact of several factors that yield the patient's blood glucose value.

Consider two patients, Mrs S and Mrs T, both of whom are 65 years of age and have fasting plasma glucose concentrations of 180mg/dL (10mM). Despite the same diagnosis of diabetes mellitus, the manner in which their respective blood glucose concentrations came to be 180mg/dL can be very different. At the next level of separation or stratification, Mrs S and Mrs T may differ in how much insulin their beta cells can produce counterbalanced by target tissue sensitivity to insulin. Peeling the layers of the 'pathophysiologic onion' further is a trove of literature-generated possibilities supporting differential contributions in our hypothetical patients from inflammation, fuel availability, genetic abnormalities, counter-regulatory hormones, autonomic nervous system activity, etc. Thus, these two patients may differ on multiple variables that, when summated, produce a glucose of 180mg/dL.

Diabetes mellitus is chosen as an example because, at face value, it is a relatively simple disease, first diagnosed in antiquity by some simple biomarkers, ie the taste and volume of urine. Despite a simple and obvious clinical presentation, however, there are multiple factors that differentially contribute to any individual patient's presentation (Figure 1). The same thought process is applicable to rheumatoid arthritis, Alzheimer's disease, atherosclerosis, cancer, ie that there are often multiple ways to attain the same 'apparent' clinical state.

Incongruence between razor-like selectivity of an investigational drug and clinical classification of disease

In contrast to the more classical manner in which diseases are characterised, the discovery and development of new therapeutics is focused on the creation of agents with a high degree of molecular specificity. New drug candidates, whether NCEs or monoclonal antibodies, are designed to possess a high degree of biological selectivity. There are two main reasons for this. First, it is highly desirable to specifically attack the target of interest and prevent 'unwanted' specificity spillover on to other mechanisms that are similar to the intended biological target¹⁹. This spillover has been hypothesised to play a role in unwanted side-effects of the new agent.

Second, this approach also reflects the way that we are trained to conduct experiments, ie to focus on, or manipulate, one variable at a time. Modern experimental methods, particularly since Ronald Fischer, have imprinted on generations of scientists that a well-conducted experiment should be able to conclude that a change in the dependent variable was a direct consequence of the manipulation of an independent variable. The conduct of trials in this manner will assure that the outcomes are likely and specifically due to the intended manipulation. If the tested molecule affects other biological targets beyond the primary, then how would we know that the intended mechanism is key to the new therapy's efficacy?

The ability to selectively manipulate individual targets within large families of related targets with razor-like precision explains in part the attractiveness of monoclonal antibodies, or newer modalities such as antisense oligonucleotides or siRNA. Although the approach to manipulating one molecular target at a time is very appealing (in more than one way), it stands in contrast to how most diseases are characterised, ie there is a mismatch between how we currently define disease and the approach to developing therapies and our standard discovery process lacks the basic tools to address multi-variate disease etiology. That is, to more effectively treat disease, we need to directly treat its causes within the relevant patient subpopulation.

Consider the following hypothetical Phase II study of a new investigational agent to lower glucose, illustrated in Figure 2. Based on published literature, there is good rationale that a specific biologic target, ABCD, may be important in worsening insulin resistance. Assume that the recruited study population consists of typical patients with type 2 diabetes, classed by their glucose values. The

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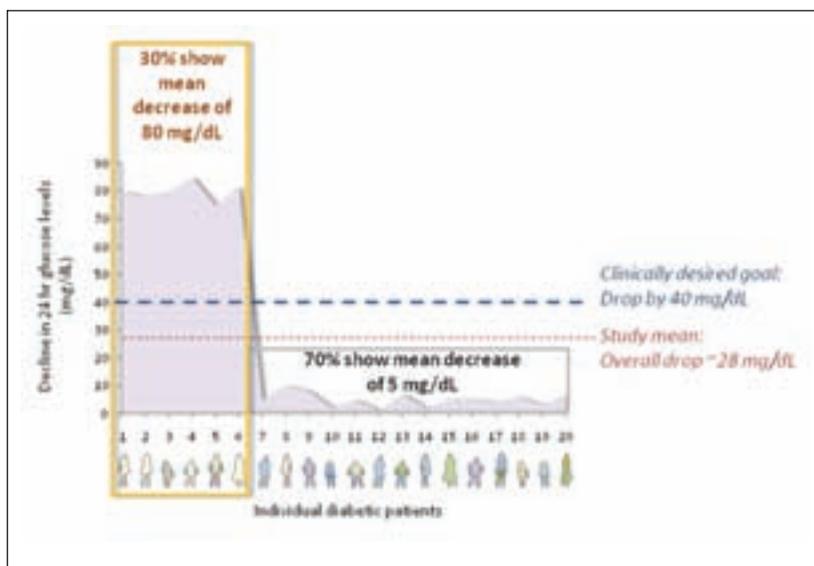


Figure 2

Graphic illustration of the impact of subpopulation responses on overall study outcome in a Phase II trial of an investigational drug for diabetes. Without segmentation of the patient population prior to the conduct of the trial, the robust response of the smaller subpopulation is diluted by the lackluster response in 70% of the trial participants. Y-axis indicates magnitude of decline in plasma glucose concentrations

clinically and commercially desired goal for the outcome of the study is a drop in 24-hour mean glucose by 40mg/dL. However, the overall drop is ~28mg/dL and the trial is deemed a failure, ie the mechanism does not have the necessary efficacy to be useful and marketable. Additional *post hoc* analysis of the data suggests that there are two populations of responses: one in which the mean decline in 24-hour glucose is 80mg/dL, representing 30% of the study population, and a second group of the remaining 70% which yielded a mean decrease of 5mg/dL. It is clear from the analysis that the robust response of 80mg/dL was diluted by the tepid response in the larger group.

At this point, however, the team is challenged wondering if the upper 30% was truly distinct from the remainder. Or perhaps it was simply the nature of statistical distributions and the observed 30% occurred by chance. Assuming that there were no obvious pharmacokinetic differences between the groups, the project team will likely be unable to separate responders from non-responders and the project ends short of the conduct of another trial, even a limited one. Even if the team manages to identify potential stratification biomarkers, it is very difficult to retrofit a patient subpopulation analysis on a completed trial. First, if there is separation from the *post hoc* analysis, then another prospective trial would be necessary to achieve proof-of-concept (POC). This inefficient process would be shunned by most given limited resources and the prevailing doubt of resurrecting a failed drug. Second, the trial was designed to fit a product profile/marketing plan that contains specific assumptions for population size and efficacy.

Further development with a redesigned Phase II endpoint in selected patients may not meet the marketing criteria and incur tremendous additional cost, as the programme is set back by about two years while the biomarker development and repeat studies take place.

There are current examples available that illustrate this point, largely advanced in oncology. Consider first the example of KRAS mutations and EGF receptor (EGFR) inhibition. It has been clearly demonstrated that KRAS mutations abrogate the positive effects of agents such as panitumumab²⁰⁻²¹. In these studies, subjects with metastatic colon cancer and KRAS mutations and who received panitumumab fared no better than those treated with standard therapy. In subjects with wild type KRAS, a demonstrable effect on progression-free survival due to panitumumab was observable²⁰⁻²¹. Imagine, however, that the first trial(s) with panitumumab or other EGFR antagonists unknowingly included many subjects with the mutation. The false negative conclusion from those studies could have been that panitumumab (or other EGFR antagonists) was not effective. Similarly, Her2 overexpression is the critical factor determining the responsiveness of patients with breast cancer to trastuzumab. As Her2 overexpression is present in only ~20% of patients with breast cancer, it is easy to project that, without pre-planning, a trial of women with breast cancer and no stratification would have likely yielded a negative result²² (Figure 3). Moreover, given the cardiotoxicity associated with trastuzumab²³, without patient stratification there would have been many more adverse effects without its benefit.

It is the premise of the authors that, beyond oncology, there are likely many of these subsets of patients who suffer from apparently similar clinical disease, but whose molecular underpinnings are likely different. Similar ideas have been expressed for rheumatoid arthritis²⁴, ulcerative colitis²⁵ as well as diabetes²⁶. If this is true, then trying to create molecularly-refined therapeutics without defining the appropriate patient populations markedly inflates the probability of failure. The industry will likely continue to have productivity problems from Phase II failures until this incongruence is adequately addressed. The only other alternative is that new agents are produced against targets that are proximal in a pathway or have key regulatory or broad-spectrum functions, such as those used in oncology or anti-inflammatory agents that are broadly immunosuppressive. The problem with these targets is that they will likely have more adverse effects associated with their use.

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Breaking the cycle: methods for determining patient stratification/disease segmentation early in drug discovery and development

In order to address this problem, knowledge regarding important molecular drivers in a disease needs to be acquired early, preferably before target selection for the investigational drug occurs. It can be argued that this work is already ongoing – it is the nature of biomedical research sponsored by a variety of esteemed organisations such as the NIH. Although these research endeavours are key to future success, what is also needed for more effective application of their rendered knowledge are methods to integrate these observations from individual experiments into a more holistic picture of the dynamic biology of the system. As discussed above, most research focuses on one variable at a time in order to more decisively conclude the relationship of that specific variable to experimental outcome. It needs to be recognised, however, that multiple elements are changing within that biological system. In order to understand them better, these elements need to be integrated.

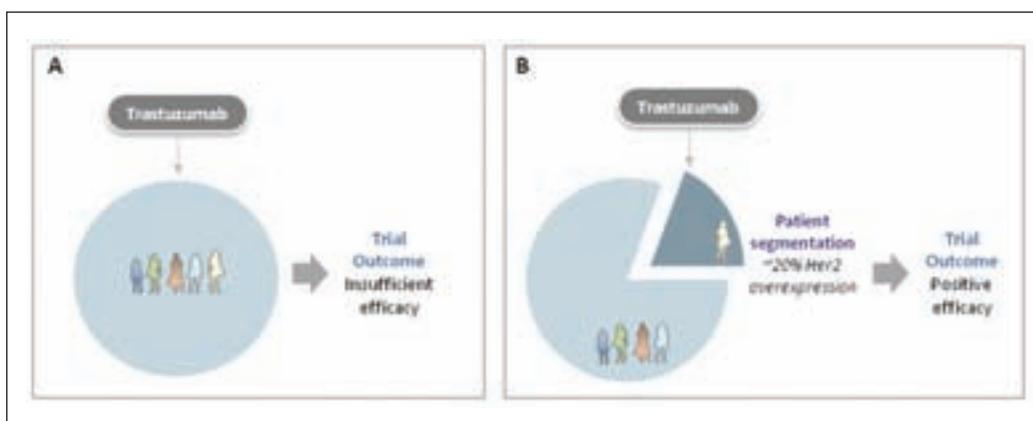
With the advent of the molecular biology revolution, a wide array of technologies has been developed to systematically and comprehensively characterise disease at a variety of biological levels. Over the past 20 years, the human genome has been sequenced; gene expression arrays have started to provide a comprehensive description of mRNA expression levels; proteomics and metabolomics have yielded broad assessments of protein and metabolite levels; and, most recently, Next Generation Sequencing provides access to whole genome information, not to mention microRNA focused arrays and SNP arrays. Although these methodologies have produced a lot of information, the ability to interpret the data at a mechanistic level in a similarly systematic way has

been lagging. In addition, the transformation of collections of data into insight (across these methodologies) has not been well developed.

In the quest to understand patient subsets in a specific disease, most analyses have systematically focused on genetic data. The most effective of these analytical methods have focused on using the data as rich fingerprints, rather than indications of disease pathophysiology. Numerous examples exist of the generation of *post hoc* classifiers able to distinguish responders and non-responders to given interventions using genetics. For example, seminal work by Golub et al resulted in a much deeper understanding of AML subsets²⁷. Similar work using genetics led to the identification of numerous variables driving common diseases, albeit weakly²⁸. Although there are isolated examples of how broad analysis impacted research portfolios (cf PCSK9)²⁹⁻³⁰, overall this type of work did not result in the revolution of research portfolios or more widespread implementation of early patient stratification in clinical studies.

Briefly, there are three reasons for the limited application or utility of these abundant and interesting results. First, most rare variants only identify small segments of a disease population and the methodology does not take into account non-genetic drivers of disease. This means that extremely small populations can be identified as likely responders, making DDD commercially non-viable. Second, there is a large gap between the identification of a disease-driving genetic variant and the development of a specific therapy to address that variant. This gap is only becoming wider as we discover more non-coding change variants as disease drivers. Finally, many classifiers based on the *post hoc* signature approach lack statistical robustness in the follow-on trials. This ‘replication attrition’ has resulted in disappointing performance for strong

Figure 3
Illustrating the problem of the ‘all-comers’ approach. In panel A, if trastuzumab was studied in breast cancer patients without Her2 overexpression, the likely clinical outcome would have been insufficient efficacy. By preselecting subjects who would likely respond, an important treatment was identified for a subpopulation of breast cancer patients (panel B)



potential biomarkers, likely resulting from a 'hitchhike effect': that is, many analytes with very low predictive ability hitchhiking along with a small number of real markers of disease in the initial trials (eg³¹).

There has been a growing movement to make these large individual datasets interpretable at the mechanistic level. In other words, rather than observing changes, can we conclude what drove those changes at the patient level and use these drivers as stratification? Broadly, two analytical frameworks have been developed. The first is one where an *a priori* model of the disease is developed and relationships between entities in the model developed based on a deep, but non-systematic understanding of the disease. These computational and dynamic models are then used to simulate known endpoints and are validated against observed measures. Most times, these endpoints are measured dynamically over time to increase the ability to identify agreements and disagreements of the model with the patient data. This approach was used successfully to understand important issues in DDD, such as response to EGFR inhibitors in the context of NSCLC³², as well as (lack of) response to p38 inhibitors in RA³³. These examples validate the utility of such an approach, but also point to the fact that dynamic molecular data are hard to obtain from primary patients data. As a consequence, validation is often dependent upon cell-based model systems, leaving open the issue of translatability.

Other approaches use no *a priori* knowledge to understand drivers of a specific disease context based on primary patient data and no assumptions are made about the distributional characteristics of the data or the equations to represent them. These approaches result in the ability to identify driving mechanisms of specific disease outcomes. The pioneering work by Schadt and colleagues in diabetes using such an approach has resulted in the identification of mechanistic drivers of the disease³⁴⁻³⁶.

These approaches still need *a priori* reduction in complexity of the data, as network construction requires the number of observations to be bigger than the number of variables. With an average of six million SNPs differentiating one human from another, one can see that without a reduction in complexity, these approaches are hard to use. Gene expression data have been used in combination with genetic differences to constrain the potential space for such a biological network³⁷. Other approaches have used prior biological knowledge to constrain the search space. Such

approaches have advantages because they identify drivers with prior biological validation, but leave parts of the data unused. In the context of DDD however, prior biological validation is an important driver, since it implies the availability of tools for development and testing and in that context these constraints may well not be limiting. A preliminary report from Drubin et al²⁵ suggests that diseases such as ulcerative colitis or specific malignancies can be sub-classified into their respective key molecular contributors using prior knowledge and a primary human dataset to constrain it. Taken together, integration of complex datasets can yield important discoveries. However, effective use of these tools requires having the right tools in the analytic toolbox, good understanding of the limitations of each approach, and ability to acquire the appropriate datasets.

Implications for changing the current drug discovery and development paradigm

It is important to consider the possible outcomes of segmenting a disease population. The most desirable is that the selected population reflects a substantial proportion and absolute number of patients with the disease (eg >30%). As in the aforementioned example in type 2 diabetes mellitus, this subset would likely have significantly greater efficacy. However, it is also possible that segmenting a disease population may only yield small cohorts (eg <10%). Low prevalence subpopulations such as this could be hard to justify. For example, consider a Phase II trial that requires 100 subjects. If the ratio of screened to enrolled subjects is 2:1 for example (need to screen two subjects for every one enrolled), then for a subtype prevalence of 10% the project team would need to screen 2,000 subjects to enrol the 100. And if the screening process is complex and/or expensive, then the screening process alone could be very burdensome. If the project advances to Phase III, then this issue is magnified further (the same could be said for clinical practice). Finally, commercial considerations could make pursuit of this subpopulation impractical – because of the low prevalence, the cost of the medication would make it impractical in comparison to other therapies. Although potentially daunting, sponsors should/could make an informed decision depending on the prevalence of the general disease and its subpopulation, the availability of alternative effective therapies, and the magnitude of observed efficacy. It is the basis for a formulary approach to DDD.

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Implications for combination development

There is another alternative, however. There may be a larger subpopulation of patients in whom more than one mechanism contributes to the manifestation of disease. This construct, in fact, is likely the most often observed scenario in common, non-monogenic diseases. In many therapeutic areas, including oncology, metabolic diseases, inflammatory diseases, etc, combination therapy is the most common treatment paradigm that patients see. The prevalent use of combinations suggests that healthcare providers intuitively recognise that more than one drug is needed to effectively change clinical manifestations of disease. That is, the correction of more than one mechanism is a necessary part of therapy. In this alternative, instead of seeking solely one dominant path to manipulate (see discussion, *vide supra*), several molecular pathways may need to be adjusted to bring about clinically meaningful treatment outcomes.

The selection of combinations, however, should be data-driven, rather than based on individual agents that appear to have some monotherapeutic

efficacy and are simply combined in anticipation of achieving greater additive efficacy. Similar to the application of anti-viral cocktails in the treatment of HIV, different facets of the pathobiology should be selectively attacked. To do so, the advanced planning and analysis as described above for single targets is critical to enable this effort. Moreover, sponsors would need to focus on the combination as the final product, rather than the individual components. The reason for doing so is that it changes the preparatory work that would be done as well as expectations from any single component.

Combinations also have appeal regarding drug safety. In the current paradigm, single target therapeutic agents are often designed to inhibit the biological mechanism to the greatest extent possible. If the targeted mechanism plays a critical biological role, then excessive inhibition can create a genetic-like syndrome and yield adverse complications of therapy. In some cases, these complications can force restriction of dosing and a less-than-desired response. By not requiring maximal inhibition of a single target, intelligent combinations have the potential to open new therapeutic possibilities.



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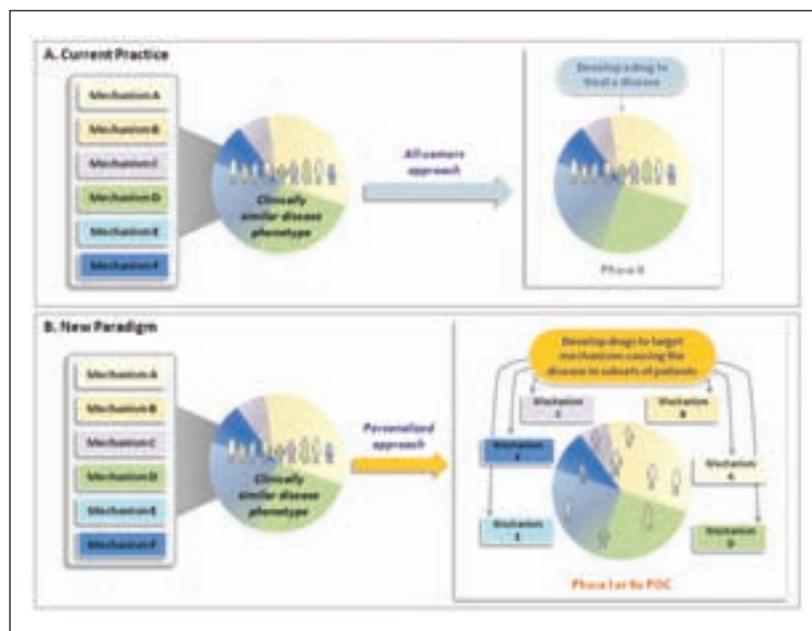
Addressing stakeholder concerns

It is expectable that stakeholder groups may have concerns about the recommended approach of subselecting patient populations. Scientists may be concerned about putting all of their efforts into a programme that hinges on the correct, early identification of the response group. What if the analysis is wrong? How would the complexity of a combination need to be managed? Commercial colleagues might be concerned that the market size and total reimbursement could be too small to underwrite the costs of discovering, developing and marketing this agent.

These are legitimate concerns that can be addressed. There is a risk if only a specific subtype were to be studied in a Phase IIa POC study. If that result were negative, then it would not be clear whether the general group of patients would have responded differently. To address that concern, a sponsor could stratify its Phase II study by including the subselected as well as the more general patients in a balanced design. That way, a comparison between the selected subpopulation and the entire population could be provided to the sponsor. A data-driven choice could then be made by the team, including additional molecular analyses on both populations. This is similar to the study design for trastuzumab efficacy in HER-2 positive and negative subjects. Commercial colleagues can use these data to project market capture of subgroup efficacy versus the entire disease population.

Conclusions

The essence of personalised healthcare, ie identifying and treating the key, causal factors in a patient's disease, is a popular topic that has been well discussed by others^{24,38}. This paper specifically focuses on the need for personalised drug discovery and development from the beginning of the process. The pharmaceutical industry's Phase II future successes will likely depend upon effectively enacting this paradigm. To successfully execute a personalised healthcare approach to drug discovery and development, including the possibility of combinations, it is critical to categorise patient subtypes in advance (Figure 4). By doing so, biological targets can be carefully chosen and appropriate mechanistic biomarkers identified in advance of the investigational compound entering the clinic. Modern analytical tools exist that make molecular subsegmentation of disease now possible. It is critical to recognise that advance planning is necessary to enable this approach. Without it,



sponsors will most often be reactive to Phase II data and likely be saddled with the same Phase II success rates.

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Figure 4

Contrasting the current paradigm for drug development and the new paradigm of personalised drug discovery and development. In current practise (panel A), despite recognition that a disease can have one or more mechanistic drivers, drugs are developed to manipulate the clinical aspect of disease. For inclusion in the clinical trial, subjects are generally not selected by mechanism. In a personalised approach, patients are matched to the mechanisms causing the clinical manifestation of their disease (panel B). This new paradigm has significant implications for the definition of disease, market sizes, and success rates

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References

- 1 Fryburg, DA. Do technical and commercial biases contribute to the pharmaceutical industry's productivity problems? An analysis of how reordering priorities can impact productivity. *Drug Discov Today*. 2010 Jun 25.
- 2 David, E, Tramontin, T, Zimmel, R. Pharmaceutical R&D: the road to positive returns. *Nat Rev Drug Discov*. 2009 Aug;8(8):609-10.
- 3 Paul, SM, Mytelka, DS, Dunwiddie, CT, Persinger, CC, Munos, BH, Lindborg, SR et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat Rev Drug Discov*. 2010 Mar;9(3):203-14.
- 4 Malik, NN. Drug discovery: past, present and future. *Drug Discov Today*. 2008 Nov;13(21-22):909-12.
- 5 Arrowsmith, J. Trial watch: Phase II failures: 2008-2010. *Nat Rev Drug Discov*. 2011 May;10(5):328-9.
- 6 Gustavson, SM, Dai, H, Preston, GM, Somayaji, V, Hirshberg, B, Calle, RA. Effects of multiple doses of the DPP-IV inhibitor PF-734200 on the relationship between GLP-1 and glucose in subjects with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2011 Feb;91(2):e45-9.
- 7 Brousseau, ME, Schaefer, EJ, Wolfe, ML, Bloedon, LT, Digenio, AG, Clark, RW et al. Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. *N Engl J Med*. 2004 Apr 8;350(15):1505-15.
- 8 Potter, WZ. Dose ranging for trials through biomarkers of drug effects. *J Nutr Health Aging*. 2010 Apr;14(4):310-1.
- 9 Chakravarty, A, Shinde, V, Taberero, J, Cervantes, A, Cohen, RB, Dees, EC et al. Phase I assessment of new mechanism-based pharmacodynamic biomarkers for MLN8054, a small-molecule inhibitor of Aurora A kinase. *Cancer Res*. 2011 Feb 1;71(3):675-85.
- 10 Francia, G, Cruz-Munoz, W, Man, S, Xu, P, Kerbel, RS. Mouse models of advanced spontaneous metastasis for experimental therapeutics. *Nat Rev Cancer*. 2011 Feb;11(2):135-41.
- 11 LeRoith, D, Gavrilova, O. Mouse models created to study the pathophysiology of Type 2 diabetes. *Int J Biochem Cell Biol*. 2006;38(5-6):904-12.
- 12 Meir, KS, Leitersdorf, E. Atherosclerosis in the apolipoprotein-E-deficient mouse: a decade of progress. *Arterioscler Thromb Vasc Biol*. 2004 Jun;24(6):1006-14.
- 13 Olsen, CK, Brennum, LT, Kreilgaard, M. Using pharmacokinetic-pharmacodynamic modelling as a tool for prediction of therapeutic effective plasma levels of antipsychotics. *Eur J Pharmacol*. 2008 Apr 28;584(2-3):318-27.
- 14 Macleod, MR, Fisher, M, O'Collins, V, Sena, ES, Dirnagl, U, Bath, PM et al. Good laboratory practice: preventing introduction of bias at the bench. *Stroke*. 2009 Mar;40(3):e50-2.
- 15 Pound, P, Ebrahim, S. Supportive evidence is lacking for report on animal studies. *BMJ*. 2002 Nov 2;325(7371):1038.
- 16 Hart, BA, Amor, S, Jonker, M. Evaluating the validity of animal models for research into therapies for immune-based disorders. *Drug Discov Today*. 2004 Jun 15;9(12):517-24.
- 17 Zadelaar, S, Kleemann, R, Verschuren, L, de Vries-Van der Weij, J, van der Hoorn, J, Princen, HM et al. Mouse models for atherosclerosis and pharmaceutical modifiers. *Arterioscler Thromb Vasc Biol*. 2007 Aug;27(8):1706-21.
- 18 Lindner, MD. Clinical attrition due to biased preclinical assessments of potential efficacy. *Pharmacol Ther*. 2007 Jul;115(1):148-75.
- 19 Fradkin, JE, Eastman, RC, Lesniak, MA, Roth, J. Specificity spillover at the hormone receptor – exploring its role in human disease. *N Engl J Med*. 1989 Mar 9;320(10):640-5.
- 20 Ciardiello, F, Tortora, G. EGFR antagonists in cancer treatment. *N Engl J Med*. 2008 Mar 13;358(11):1160-74.
- 21 Roberts, PJ, Stinchcombe, TE, Der, CJ, Socinski, MA. Personalized medicine in non-small-cell lung cancer: is KRAS a useful marker in selecting patients for epidermal growth factor receptor-targeted therapy? *J Clin Oncol*. 2010 Nov 1;28(31):4769-77.
- 22 Sarker, D, Workman, P. Pharmacodynamic biomarkers for molecular cancer therapeutics. *Adv Cancer Res*. 2007;96:213-68.
- 23 Ewertz, M, Jensen, AB. Late effects of breast cancer treatment and potentials for rehabilitation. *Acta Oncol*. 2011 Feb;50(2):187-93.
- 24 Littman, BH. Tocilizumab and missed personalized medicine opportunities for patients with rheumatoid arthritis? *Arthritis Rheum*. 2009 May;60(5):1565-6.
- 25 Drubin, D, NL, C, J, P, AA, VH, BPF, RD, K, editors. Predictive classifiers for response to c-Met targeted therapies in lung and colon cancer [abstract]. American Association for Cancer Research; 2011 April 2; Orlando, FL.
- 26 Malandrino, N, Smith, RJ. Personalized medicine in diabetes. *Clin Chem*. 2011 Feb;57(2):231-40.
- 27 Golub, TR, Slonim, DK, Tamayo, P, Huard, C, Gaasenbeek, M, Mesirov, JP et al. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. *Science*. 1999 Oct 15;286(5439):531-7.
- 28 Winckler, W, Burt, NP, Holmkvist, J, Cervin, C, de Bakker, PI, Sun, M et al. Association of common variation in the HNF1A gene region with risk of type 2 diabetes. *Diabetes*. 2005 Aug;54(8):2336-42.
- 29 Abifadel, M, Varret, M, Rabès, JP, Allard, D, Ouguerram, K, Devillers, M et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nature genetics*. 2003;34(2):154-6.
- 30 Steinberg, D, Witztum, JL. Inhibition of PCSK9: a powerful weapon for achieving ideal LDL cholesterol levels. *Proceedings of the National Academy of Sciences of the United States of America*. 2009;106(24):9546-7.
- 31 Ein-Dor, L, Kela, I, Getz, G, Givol, D, Domany, E. Outcome signature genes in breast cancer: is there a unique set? *Bioinformatics*. 2005 Jan 15;21(2):171-8.
- 32 Hendriks, BS, Griffiths, GJ, Benson, R, Kenyon, D, Lazzara, M, Swinton, J et al. Decreased internalisation of erbB1 mutants in lung cancer is linked with a mechanism conferring sensitivity to gefitinib. *Syst Biol (Stevenage)*. 2006 Nov;153(6):457-66.
- 33 Hendriks, BS, Hua, F, Chabot, JR. Analysis of mechanistic pathway models in drug discovery: p38 pathway. *Biotechnol Prog*. 2008 Jan-Feb;24(1):96-109.
- 34 Schadt, EE, Friend, SH, Shaywitz, DA. A network view of disease and compound screening. *Nat Rev Drug Discov*. 2009 Apr;8(4):286-95.
- 35 Chen, Y, Zhu, J, Lum, PY, Yang, X, Pinto, S, MacNeil, DJ, et al. Variations in DNA elucidate molecular networks that cause disease. *Nature*. 2008 Mar 27;452(7186):429-35.
- 36 Emilsson, V, Thorleifsson, G, Zhang, B, Leonardson, AS, Zink, F, Zhu, J et al. Genetics of gene expression and its effect on disease. *Nature*. 2008 Mar 27;452(7186):423-8.
- 37 Guido, NJ, Wang, X, Adalsteinsson, D, McMillen, D, Hasty, J, Cantor, CR et al. A bottom-up approach to gene regulation. *Nature*. 2006 Feb 16;439(7078):856-60.
- 38 Bates, S. Progress towards personalized medicine. *Drug Discov Today*. 2010 Feb;15(3-4):115-20.