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Systems biology embedded target validation: improving efficacy in drug discovery

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Abstract

The pharmaceutical industry is faced with a range of challenges with the ever-escalating costs of drug development and a drying out of drug pipelines. By harnessing advances in –omics technologies and moving away from the standard, reductionist model of drug discovery, there is significant potential to reduce costs and improve efficacy. Embedding systems biology approaches in drug discovery, which seek to investigate underlying molecular mechanisms of potential drug targets in a network context, will reduce attrition rates by earlier target validation and the introduction of novel targets into the current stagnant market. Systems biology approaches also have the potential to assist in the design of multidrug treatments and repositioning of existing drugs, while stratifying patients to give a greater personalisation of medical treatment.

DISAPPOINTING PROGRESS FOR DRUG DISCOVERY IN THE POST-GENOMIC ERA

The standard model of drug discovery is in a bind of increasing costs and risks and decreasing efficiency; regulation is failing to reflect scientific advances while industry productivity flatlines.¹ The average cost for the development of a new drug has been estimated at between \$800 million and \$2 billion, with high levels of attrition due to lack of efficacy (sidebar 1).² Drug discovery was until the late 20th century a straight, phenomenological process: a library of compounds was administered to an animal model, and then potential rescue of disease phenotypes was measured. This approach sought to characterize a disease as a series of symptoms rather than investigating underlying molecular mechanisms. Screening was both laborious and haphazard because drug targets and drug mechanisms of action were in most cases not known. As such we remained ignorant of the molecular effects of these drugs. Even for some of the most common drugs such as aspirin, we still lack knowledge on their full effects.³ Developments in the fields of signalling networks, robotics, high-throughput arrays and the human genome project have transferred drug discovery away from this phenomenological process towards a more targeted approach. We have moved to a more ‘rational’ targeted screening, in which a specific molecular target is first identified and subsequently a compound is sought that interacts with it. This can happen on a much larger scale than the earlier phenotypic screening.

With the successful completion of the human genome project in 2003,⁴ there was a hope that researchers would now have the sequence of all genes, and consequently information on all proteins. This vast amount of molecular information would allow for an identification of many more targets, with a concomitant boost to drug discovery.^{5, 6} In reality, progress in drug development has been modest: over the last 30 years, an average of 18 new drugs are approved by the US Food and Drug Administration every year, with a more or less steady rate of introduction of drugs with novel targets.⁷ Drug attrition remains very high, though this is increasingly due to a lack of efficacy, whereas previously the primary cause was toxicity.

This article focuses on why progress in drug development has not lived up to expectations, and how systems biology has the potential to move away from reductionism and deliver significant, cost-effective improvements to the drug discovery process. We put forward a concept where systems biology can improve the discovery of new targets based on a network wide understanding of their functions and by affording a more stringent and rational approach to target validation in the early stages of the process.

WHY DID DRUG DISCOVERY NOT SKYROCKET?

The negligible advances in drug discovery in the genomic age appear to reflect an on-going conservatism in research and development, where conceptual thinking has not kept pace with the new technological capabilities of the –omics sciences that have revolutionised biological discovery. Firstly, focus has not shifted beyond the previously favoured targets, despite the fact that advances in a variety of –omics fields and high-throughput assay development have changed molecular biology into a data-rich science (sidebar 2). We are only using a small segment of the possible targets. The rate of innovation in terms of exploiting drug targets has been stable over the past 30 years, despite the dramatic increase in investment for drug target research. If we consider targets that are encoded by the human genome (excluding for instance virus-encoded targets), less than a quarter of the drugs newly approved each year are targeting novel molecules. In 2011, only 435 of the estimated 30000 genes in the human genome were used as effect-mediating drug targets (with 989 unique approved drugs targeting them). Even more striking is that these targets all belong to a few protein classes. For instance, 36% of these targets are G-protein coupled receptors.⁷ Today's drug discovery efforts in the cancer field are focused on kinases, due to success stories like the Abl-kinase inhibitor imatinib mesylate (Gleevec), and reagents targeting receptor tyrosine kinases such as the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor receptors (VEGFRs).^{8,9}

Omics technologies have the potential to point out a less obvious, broader range of drug targets beyond the limited set of protein families that are currently taken into consideration, providing a more holistic view on the biological system. In the human genome for instance, the numbers of protein phosphatases and receptor tyrosine kinases are within the same order of magnitude.¹⁰ This implies that the versatility of functions and specificity of these kinases and phosphatases could also be similar, making phosphatases possible targets of interest.^{11, 12} This idea has been put forward before, but the use of systems biology approaches now allows for the consideration of more mechanistic and dynamic detail during target identification, and could therefore reinforce rationales that consider less conservative targets.¹² For instance, proteomics has characterized how a protein phosphatase 4 complex conveys sensitivity to cisplatin¹³, and how phosphatases shape the kinetics of ERK activation and cell fate decisions^{14, 15}.

While numbers of novel drug targets remain uninspiring, understanding of the underlying molecular functions of the majority of drug targets on cellular or organismal physiology is also surprisingly poor. Put simply, for the majority of possible targets we still do not know what they do in the context of the biomolecular networks they are embedded in, inhibiting a truly rational drug design. Molecular knowledge on drug targets is mostly based on very crude methods such as knock-out mice. These methods generally do not give us detailed molecular information to differentiate effects due to their diverse functions that include different aspects such as scaffolding effects, subcellular

compartmentalisation and catalytic activities. There is also a need for a deeper understanding of disease states based on the states of biological networks.

SYSTEMS BIOLOGY: CONSIDERING THE COMPLEX BIOLOGICAL NETWORK ENVIRONMENT

One important aspect that current reductionist approaches neglect is that drug targets are part of complex dynamic biological networks. The topology and dynamics of these networks effectuates tight control of signalling responses and their resulting biological effects, and these features should be exploited for drug discovery purposes.¹⁶⁻¹⁸ It is at this point that a systems biology approach has the potential to really improve the drug discovery process, by considering possible targets in the context of their surrounding network.

Advances in a variety of -omics fields have massively increased the amount of data we can gather. Systems biology approaches allow for a reduction of the information noise in these large datasets by carving out functional relationships, and for the integration of different types of data into hypothesis-driven mathematical models. Systems biology provides an integrative, multidisciplinary approach that aims to integrate these different types of high-throughput data through knowledge and techniques derived from a diverse range of other disciplines, including engineering, information science and mathematical modelling. This enables a wider signalling network in all its complexity to be considered, instead of adopting the linear, reductionist approaches taken so far. Network based methods are not yet commonly employed in drug development, however they already have proven useful in deciphering molecular mechanisms of diseases, often with very complex traits. A network-based approach combining interactome, co-expression and co-morbidity data, for instance, was used to predict candidate genes for lipid and lipoprotein traits. Despite the fact that these candidate genes had not been picked up in GWAS studies, the predictions were validated by the identification of novel disease-associated SNPs.¹⁹ Similarly, integrative systems biology approaches combining expression and interaction data into networks have been successful in indicating molecular mechanisms of diseases in different fields, such as the classification of metastatic versus non-metastatic breast cancer²⁰ and respiratory diseases^{21, 22}, where different public-private partnership consortia have been set up to apply -omics and systems biology techniques to biomarker discovery.²³

Dynamic, mechanistic mathematical models facilitate a holistic perspective on a drug target, revealing the complex environment it exists in, bringing to light new information that would otherwise have remained obscured. Perturbation of a target will have knock-on effects on the rest of the network, and modelling these effects will show which way the network can be best perturbed to achieve the desired effect, and therefore which node in the network could be a suitable target candidate. This could for instance be the catalytic activity of a specific node, the expression of a specific component, but also a particular protein-protein interaction. A tangible example where the surrounding network should be considered is kinase inhibitors, one of the major focuses of drug development programs in the pharmaceutical industry. Type I kinase inhibitors lock the kinase in its active state, while type II kinase inhibitors lock it in the inactive state. The target is in a different conformation depending on what kinase inhibitor is used, and this will affect the binding of different partners of the kinase in the network, and will therefore have a different effect on the network dynamics.²⁴ Omics techniques such as proteomics can help monitor interactions of specific drugs and the effects of drugs on the signal transduction network of cells at a large scale, including off-target and secondary effects.^{25, 26} Mathematical modelling on the other hand can help to integrate these

rather static high-throughput data in a more dynamic model that better reflects the biological system.¹⁸ We currently do not know of any new drugs in clinical trial that are based on dynamic modelling of signalling networks.

However mathematical modelling has already been used to support the FDA approval of Ranolazine, a treatment for chronic angina, by showing that drugs that reduce the late sodium current in cardiac cells would have therapeutic potential against arrhythmias, therefore indicating the method of action of the drug.^{27, 28} Similarly, computational modelling of the interaction of two commonly used anti-arrhythmic drugs, lidocaine and flecainide with sodium channels in the heart could accurately predict the clinically beneficial dosing of these compounds.²⁹ This is an important advance, as these compounds have a narrow therapeutic window and can exacerbate arrhythmia when dosed incorrectly. Another example is the development of chronotherapy for cancer, which has shown that both efficacy and side effects of chemotherapy are modulated by the circadian rhythm.³⁰ The development of scheduled treatment cycles as well as the elucidation of underlying mechanisms is heavily based on mathematical modelling providing an excellent example of how systems biology approaches can be used in the clinic.³⁰⁻³³ While these developments are encouraging, there are still many challenges ahead. It took more than 4 decades until Denis Noble's pioneering work on a computational heart model led to hard evidence that modelling can produce useful and clinically relevant results that can explain the mechanism of drug actions, guide drug development and dosing.³⁴ The reasons for this slow uptake only may be guessed but plausibly include an inherent scepticism against hard-core mathematics in the biomedical sciences, which traditionally prefer a more intuitive approach. On the other hand, it takes a lot of data and validation to generate clinically relevant and reliable computational models. Importantly, it is not the data quantity that is lacking, but modelling requires particular types of data, such as kinetic biochemical data and data that allow reconstructing network structures, which are not routinely measured. The heightened awareness and understanding of modelling approaches will hopefully accelerate the closing of this gap. Again, chronotherapy is a good example where modelling found its way into clinical application rather quickly.

Drug-target networks are also increasingly being used in network biology. These models utilize protein interaction networks (interactome networks), and include specific drugs and knowledge on their targets.^{7, 35, 36} Research at a large drug-interaction network comprising of 989 approved drugs and their targets again indicated that most drugs share similar target interaction profiles and that we are only targeting a limited part of the proteome. Such studies confirm that the pharmaceutical industry has a tendency to target already validated target protein, causing an abundance of follow-on drugs.^{7, 36}

These types of networks are not only useful for meta-analysis of current drug discovery. By using a specific drug-target interactome network related to myocardial infarction called My-DTome, that comprised of approved and other drugs, Azuaje *et al.* were able to identify novel associations between drugs, targets and myocardial infarction related molecular mechanisms in a modular manner. This disease-specific network not only allowed for research at drug-drug interaction, adverse effects and multidrug treatment, but also indicated possible repositioning of unrelated non-cardiovascular drugs and pointed at different miRNA as potential novel targets for myocardial infarction treatment.³⁵

A SYSTEMS BIOLOGY EMBEDDED TARGET VALIDATION AS POSSIBLE SOLUTION

We propose that the lack of drug efficacy causing attrition during clinical drug development (side-bar 1) is due to insufficient target validation in the pre-clinical stage. We put forward a systems biology embedded concept that will significantly increase the efficacy of the drug development process (figure 1). Considering complex spatiotemporal dynamics controlled by multiple negative or positive feed-forward and feedback loops can shed a different light on where to hit the disease network.¹⁶ For instance, phosphatases can significantly alter signalling dynamics, often more than kinases, and could therefore be good targets to alter signalling dynamics. However, there is a need for a deeper understanding of these dynamics to decipher the sensitivity and specificity that is necessary for therapeutics.¹² We feel that the further development of dynamic computational models can automatically lead to a broader use of systems biology techniques in the drug discovery field.

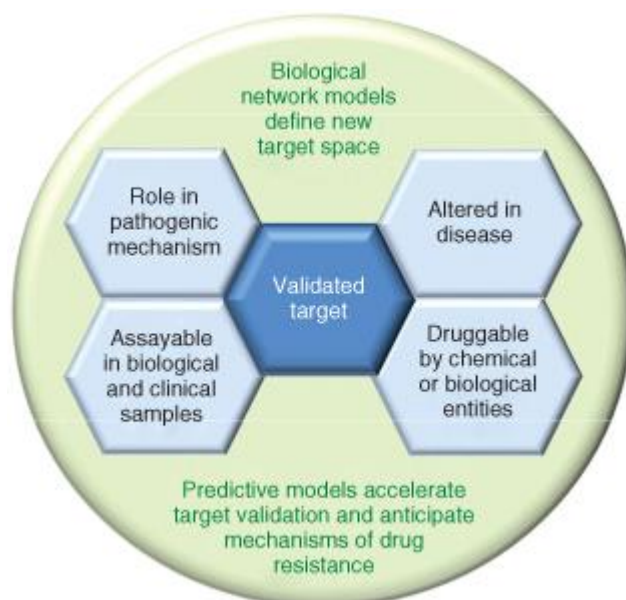


Figure 1: A systems biology concept of drug target validation as a mechanistic, diagnostic and therapeutic package. This concept comprises that a validated target plays a role in the pathogenic mechanism, is altered in disease, is druggable by chemical or biological entities and is assayable in biological and clinical samples.

Systems biology network models can define a new target space, and will seek to thoroughly validate the target earlier in the process, before going further into the clinical phases of the drug development process. By taking a less reductionist view, this target space can be broader than what is considered a potential target now. Using systems biology approaches from the outset of the process will enable target validation to be a continuous process. We propose that preclinical target validation should be considered as a package that includes the following elements: a good target should be shown to be altered in disease, and play a role in the pathogenic mechanism early on in the drug development process. This comprises a mechanistic systems level analysis of the function of the target in a network context and the early study of the alterations of the target and its effects in clinical samples. In this way the pathogenesis can be tackled specifically, and the development of tests to assay the target and its biochemical effects are a direct prelude to the development of accompanying diagnostic tests that can guide preclinical animal studies and eventually clinical

studies with human patients.

In addition, a good target has to be 'druggable'. However, what is currently considered 'druggable' is often narrowly and conservatively conceived. Drug development has in the last decades been focused around small molecular weight chemical compounds. There has also been an emphasis on the 'rule-of-5': poor absorption or permeation into cells is deemed more likely when the number of hydrogen-bond donors >5, the number of hydrogen-bond acceptors >10, the relative molecular mass >500 and the calculated logP (cLogP)>5.³⁷ Taking also into account more favourable production costs, this means a good drug is small and hydrophobic chemical compound, for instance selectively binding to hydrophobic pockets. However, most natural product-based drugs, biomimetics and biologics such as antibodies or siRNAs do not correspond to these rules, but are proving themselves valid alternatives. Biologics have had a higher success rate in clinical trials than small molecules. There was an approximately 32% approval rate for biologics versus an approximately 13% approval rate for small-molecule drugs first tested in humans between 1993 and 2004.³⁸ If one for instance would take into account protein transporters, a wider range of drug types could be considered, less constrained by matters of lipophilicity.³⁹ The use of antibodies for example allows for a more rational target based screening, as they can be made against a wide range of targets, and high target specificity. We think that the more recent focus on biologics is a way forward to broaden our scope of possible drug targets. Considerable efforts should therefore be made to overcome the hurdles that prevent biologics from being widely used, such as the higher costs for production, and problems with for instance oral delivery.⁴⁰

The predictive mathematical models employed in systems biology can significantly accelerate this type of target validation described above, not only by identifying the most effective targets, but also by facilitating the drug development process. As with all model systems, computational models are imperfect. The knowledge of the network interactions, and especially dynamics, is often incomplete. However, through our proposed iterative target validation process, data that are generated during the drug discovery and development process are being fed back into the model so that the model can be constantly refined and extended, for instance to include more biological readouts as the model moves with the drug(s) through the development process. Therefore, the target also should be assayable in biological and clinical samples. There is a need to co-develop very specific diagnostic, molecular assays, hand in hand with the development of the drugs. The same predictive models can also anticipate mechanisms of drug resistance and possibly point out side effects. They can therefore help identifying clinical risks before the clinical trial phase. Providing more and earlier checkpoints for deciding the best course of action, e.g. abandoning the target or reconsidering the target in a combinatorial treatment context, will lower the risk of attrition in clinical trials.

SYSTEMS BIOLOGY AND THE DESIGN OF MULTIDRUG TREATMENT

The pharmaceutical industry's research and development strategies are based primarily on the premise that high-affinity and high selectivity binding to a single disease-linked target will provide efficacious and well-tolerated drugs. Therefore, this thinking governs the drug discovery and development process.^{17, 40} This reductionist view of targeted screens follows a 'one gene, one drug, one disease' rule. However, a disease phenotype is rarely the consequence of an abnormality in a single gene or gene product, but rather it is the result of various pathological processes that interact in a complex network. Biological networks often require simultaneous changes in multiple nodes to

modify a phenotype, and the multiple hit theory for cancer has been widely accepted for a long time.^{41, 42} Indeed, drug-target networks show that a lot of approved drugs have multiple targets.^{7, 36} Although it is commonly assumed that a decrease of selectivity will increase the occurrence of side effects and toxicity, we may need to rethink this argument. Partially inhibiting an ensemble of disease relevant targets actually may have a higher efficacy and less side effects than the highly selective and full inhibition of a single target. Indeed, this 'polypharmacology' seems to be key to the efficacy of some drugs.^{17, 43} Unfortunately, it is extremely difficult to purposefully develop polypharmacological drugs,⁴⁴ and approaches towards that end are only starting to be developed.⁴⁵ Thus, in lieu of developing polypharmacological compounds, we combine drugs. Drug combinations or 'cocktails' such as the four-drug combination cyclophosphamide, doxorubicin, vincristin and prednisone for the treatment of non-Hodgkin's lymphoma, and bleomycin, etoposide and cisplatin for testicular cancer, are commonly used in cancer therapy, but are usually the result of empirical observations and could benefit from a more rational preclinical design.^{46, 47}

One of the reasons why systems biology approaches are not yet generally applied early on in the drug discovery process is that the pharmaceutical industry is slow to change and generally rather risk averse. Buy-in will depend on the successes of currently running public-private partnerships on systems biology²³, and the continuously on-going development of large-scale mathematical models. It could therefore take some time before we see the first drug that is the result of a full systems biology embedded development. However, the rational design of drug combinations is one of the areas where systems biology approaches can make an imminent clinical impact. Systems biology tools can help in predicting synergistic or counteracting effects of combinatorial drugs.⁴⁸ Synergistic effects of combinations of, for instance, phosphatase-targeting drugs and tyrosine kinase inhibitors could be studied through mathematical modelling.¹² There are several examples in the literature where data-driven mathematical modelling has been used to design efficacious multi-treatments based on complex features in specific dynamic signalling networks for diseases such as multiple myeloma, breast cancer and melanoma, often resulting in surprising findings.⁴⁹⁻⁵² Targeting two components of a three-tiered kinase module as the MAPK Raf-MEK-ERK pathway, for instance, may at first glance seem redundant. However, a systems level analysis⁵² showed that this module consists of a kinases cascade that affords signal amplification and a negative feedback from ERK back to Ras and Raf, thus featuring the design properties of a negative feedback amplifier, which is used in electronic circuits for noise reduction during signal amplification. In the biological context these properties make MEK a difficult target as the negative feedback keeps adjusting the amplifier strength thereby maintaining the output constant over a wide range of MEK inhibition. Weakening the feedback strengths by inhibiting Raf by 50% conveys full sensitivity to MEK inhibition. Although inhibiting two consecutive components in the same pathway seems counterintuitive from a biological point of view, mathematical modelling followed by experimental validation revealed the success of this strategy (figure 2).⁵² Indeed, this combination has also proven its worth in the clinic. A phase 1 and 2 trial of combined treatment with dabrafenib, a selective BRAF inhibitor, and trametinib, a selective MEK inhibitor showed that progression-free survival was significantly improved compared to monotherapy.⁴⁹ Mathematical modelling does not only predict which drug combinations can synergise, but also in which sequential order the drugs should be administered. A data-driven mathematical model that was based on the expression levels or activation states of 36 signalling proteins in multiple signalling pathways was used to analyse the response of triple negative breast cancer cells (TNBC) to the EGFR inhibitor erlotinib and the DNA-damaging

doxorubicin, when applied individually and in combination.⁵⁰ Interestingly, the study showed that pretreatment, and not co-treatment or post-treatment, with EGFR inhibitors significantly rewires the signalling network of these cancer cells sensitizing them to subsequently applied DNA damaging agents.

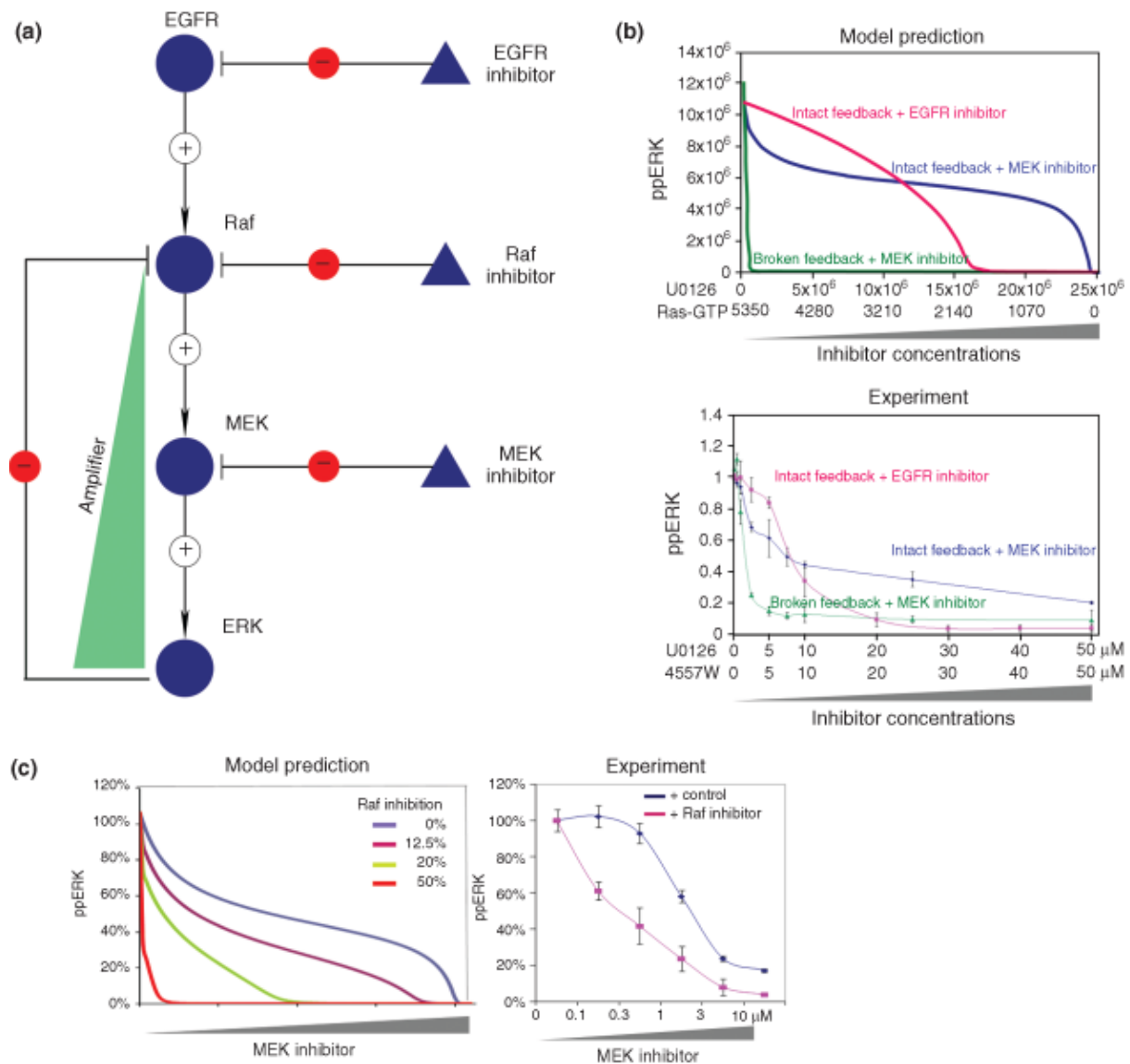


Figure 2: Using mathematical modelling to study drug targets in a network environment can lead to surprising conclusions. (a) The three-tiered kinase Raf-MEK-ERK module shows features of a negative feedback amplifier, providing robustness to change.⁵² Simulations using a mathematical model, which have been experimentally validated, suggest that to reduce downstream ERK activity, one needs to either (b) target outside the negative feedback or (c) target both MEK and Raf.

SYSTEMS BIOLOGY IN LATER PHASES OF DRUG DEVELOPMENT, PERSONALIZED MEDICINE AND REPOSITIONING OF EXISTING DRUGS

Later in the drug development process, systems biology approaches can help to improve the effectiveness of clinical trials by enabling trials with smaller cohorts and a flexible trial design that optimizes benefits for the trial patients.^{2, 53} These adaptive clinical trials can aim, for example, to optimize dose finding during the trial, integrate diagnostic monitoring, and allow crossovers

between treatment groups based on projections of treatment efficacies and benefits. This idea is appealing, especially in the context of personalized medicine, where clinical trials also need to become personalized. Even a back of the envelope calculation shows that, in keeping the currently used templates for clinical trial design, we will find neither the number of patients nor the money to run all the required highly differentiated trials. Thus, there is an urgent need to develop the statistical and modelling tools that will enable adaptive clinical trials. Methods used to model biochemical networks and social networks are promising seeds for approaches to tackle the challenges of adaptive clinical trial design.

Systems biology approaches also can help us to re-think how we dose and apply medication. Pharmacokinetics/pharmacodynamics and dose-response modelling are well established, but could further benefit from systems biology tools.^{54, 55} For instance, considering compartmentalization and organ specific effects may help understanding drug turnover in more mechanistic details. A particularly pressing challenge is how we can exploit genetic information that is now widely and rapidly becoming available for improving pharmacokinetic and pharmacodynamic profiling for individual patients. As already mentioned, an example of the progress that can be made using modelling approaches is the pioneering work in the emerging field of chronobiology.³³ Here, administration of a drug is timed according to the physiological rhythms of the patient in order to optimize efficacy. Indeed, it is widely accepted that the timing of glucocorticoid administration affects the efficacy of the treatment, and the same could apply to other types of drugs.⁵⁶

Thus, using systems biology models to predict the outcome of combinatorial treatments or different regimen could become key to not only accommodate but also analyse the long held clinical view that every patient is different and responds differently to therapy. A mathematical model can for instance be used to stratify patients, by predicting drug resistance based on the expression of specific biomarkers, such as has been shown for trastuzimab resistance.⁵⁷ As such, systems biology tools can, through 'systems medicine', lead to a more personalized medicine.^{58, 59}

Finally, the network centred perspective of systems biology also provides a natural home for efforts of drug repositioning. All drugs have side effects, some caused by the inhibition of the intended target, but more often caused by off-target effects. Can we turn side effects into main mechanisms of action? As the supply of new molecular entities is running low while we are simultaneously sitting on a wealth of information on drug side effects, drug repositioning is becoming an attractive option in particular for personalized medicine. The poster-children of drug repositioning are thalidomide and sildenafil. Thalidomide was developed as a mild sedative and sleeping pill. Prescribed to pregnant women because of its lack of apparent side effects it triggered a catastrophic avalanche of limb malformations in babies. Although the exact mechanism of thalidomide action is still elusive, it is an effective inhibitor of angiogenesis.⁶⁰ This property has positioned a thalidomide derivative to become a frontline treatment for multiple myeloma and leprosy.⁶¹ The phosphodiesterase 5 (PDE5) inhibitor Sildenafil was originally developed for treating hypertension. Instead, it became a blockbuster drug for the treatment of erectile dysfunction, and its wondrous metamorphosis is still ongoing revealing potential new applications in the treatment of disease as diverse as stroke, cognitive dysfunction and gastric ulcers.⁶¹ Using systematic search tools to mine drug-target networks, clinical data and -omics profiles of patients, we should be able to exploit drug side effects and identify new applications known drugs.^{35, 62, 63} This could form a very cost-effective way of

generating new efficacious drugs.

Sidebar 1: Drug development attrition

The overall development rate of novel drug compounds has remained largely constant over the last six decades. However, the costs per newly FDA approved drug has steadily increased and has reached into billions of dollars.⁶⁴ Until the 1990s one major factor influencing this overall cost was the long development times of 10-15 years. The last two decades have however seen even larger increases due to “development risk” – i.e. the risk of attrition due to efficacy, safety or commercial concerns.³⁸ This risk seems to be the most limiting factor in new molecular entity (NME) output. Since about two thirds of the cost stem from clinical development, many potential compounds never make it out of preclinical discovery.⁶⁵ Those that do are tested for safety in Phase I and then for efficacy in subsequent Phases II and III. While the risk of failure in any of these Phases is high, Phase II forms the biggest hurdle: only 18% of development projects pass this stage. 51% of attrition is due to insufficient efficacy, 29% to strategic and 19% to safety reasons. Interestingly, even drugs that fall into the latter two categories still have issues relating to efficacy, like lack of differentiation or advantage over existing drugs.⁶⁶ In recent years Phase III failures have been around 50%. Again, more than two thirds of these failures can be attributed to efficacy issues, and only 21% to safety concerns.⁶⁷

Sidebar 2: -OMICS data and the necessity for systems biology

Life science and medical research has traditionally followed a reductionist approach – reducing large and complicated processes into simple components to make them more accessible to experimentation and interpretation.⁶⁸ In the last decade, through substantial advances in technologies like next generation sequencing large scale datasets have become not only more thorough but also more readily available. In addition, dynamic technologies like transcriptomics, proteomics and metabolomics are now becoming widely available in robust high throughput formats. RNA sequencing supplements DNA mapping with a second layer of information, and proteomics is used to study protein expression profiles, protein-protein interactions and posttranslational modifications. As sensitivity increases and quantification of these data becomes more and more accurate, they are opening integrative ways to identify disease states and monitor them.⁶⁹ Thanks to concomitant advances in computing power, Genome Wide Association Studies, or GWAS, have become feasible in the past years. This has resulted in projects such as HapMap, containing information on millions of genetic variants (SNPs). These inherent trait analyses can be associated with common diseases and also can provide information on drug targets.⁷⁰ All these – omic technologies generate large sets of data and integrating them requires computational tools and methods borrowed from disciplines such as chemistry, mathematics, physics, engineering and information sciences. The utilization of these multidisciplinary tools results in the ability to consider complex biological systems, moving away from reductionism.

Conclusion

Systems biology approaches have the potential to significantly improve drug discovery through the provision of tools that reflect the complex network environment that drugs and their targets exist in.

Such a multidisciplinary approach could have a positive impact on the on-going current problems with lack of efficacy during drug development by improving target identification and target validation. Systems biology can help to broaden the conservative views adopted by the pharmaceutical industry of possible targets. This will have to coincide with a more opened up concept of what a 'druggable' target is. However, the greatest potential for significant advances with systems approaches can be made on target validation. This should be a continuous process, in which predictive models are being set up from the start and with the provision of continuous feedback from target validation assays. Systems biology will provide the tools needed for a rational design of multidrug treatment, for repositioning of known drugs, and for personalized treatment.

We feel that public-private partnerships will be necessary for drug discovery to truly benefit from the advances in systems biology. To interrogate how systems biology can contribute more to more clinical needs and to formulate which specific issues have to be addressed, the European Commission has funded the Coordinating Action Systems Medicine consortium (CASyM, www.casym.eu) under the Seventh Framework Programme for Research to formulate a roadmap that will guide this European-wide implementation of systems medicine. CASyM aims to be integrative, bringing all stakeholders in this multidisciplinary field together. This includes researchers, physicians, pharmaceutical industry and policy makers, as well as the patient him or herself.

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References

1. Forda SR, Bergstrom R, Chlebus M, Barker R, Andersen PH. Priorities for improving drug research, development and regulation. *Nat Rev Drug Discov* 2013, 12:247-248.
2. Orloff J, Douglas F, Pinheiro J, Levinson S, Branson M, Chaturvedi P, Ette E, Gallo P, Hirsch G, Mehta C, et al. The future of drug development: advancing clinical trial design. *Nat Rev Drug Discov* 2009, 8:949-957.
3. Pathi S, Jutooru I, Chadalapaka G, Nair V, Lee SO, Safe S. Aspirin inhibits colon cancer cell and tumor growth and downregulates specificity protein (Sp) transcription factors. *PLoS One* 2012, 7:e48208.
4. Program USDoEG. International consortium completes Human Genome Project. 2003. Available at: http://web.ornl.gov/sci/techresources/Human_Genome/project/50yr/press4_2003.shtml.
5. Chanda SK, Caldwell JS. Fulfilling the promise: drug discovery in the post-genomic era. *Drug Discov Today* 2003, 8:168-174.
6. Reiss T. Drug discovery of the future: the implications of the human genome project. *Trends Biotechnol* 2001, 19:496-499.
7. Rask-Andersen M, Almen MS, Schioth HB. Trends in the exploitation of novel drug targets. *Nat Rev Drug Discov* 2011, 10:579-590.
8. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001, 344:1031-1037.
9. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, et al. Activating mutations in the epidermal growth

- factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004, 350:2129-2139.
10. Alonso A, Sasin J, Bottini N, Friedberg I, Friedberg I, Osterman A, Godzik A, Hunter T, Dixon J, Mustelin T. Protein tyrosine phosphatases in the human genome. *Cell* 2004, 117:699-711.
 11. Barr AJ. Protein tyrosine phosphatases as drug targets: strategies and challenges of inhibitor development. *Future Med Chem* 2010, 2:1563-1576.
 12. Nguyen LK, Matallanas D, Croucher DR, von Kriegsheim A, Kholodenko BN. Signalling by protein phosphatases and drug development: a systems-centred view. *FEBS J* 2013, 280:751-765.
 13. Gingras AC, Caballero M, Zarske M, Sanchez A, Hazbun TR, Fields S, Sonenberg N, Hafen E, Raught B, Aebersold R. A novel, evolutionarily conserved protein phosphatase complex involved in cisplatin sensitivity. *Mol Cell Proteomics* 2005, 4:1725-1740.
 14. Bluthgen N, Legewie S, Kielbasa SM, Schramme A, Tchernitsa O, Keil J, Solf A, Vingron M, Schafer R, Herzel H, et al. A systems biological approach suggests that transcriptional feedback regulation by dual-specificity phosphatase 6 shapes extracellular signal-related kinase activity in RAS-transformed fibroblasts. *FEBS J* 2009, 276:1024-1035.
 15. Hornberg JJ, Bruggeman FJ, Binder B, Geest CR, de Vaate AJ, Lankelma J, Heinrich R, Westerhoff HV. Principles behind the multifarious control of signal transduction. ERK phosphorylation and kinase/phosphatase control. *FEBS J* 2005, 272:244-258.
 16. Araujo RP, Liotta LA, Petricoin EF. Proteins, drug targets and the mechanisms they control: the simple truth about complex networks. *Nat Rev Drug Discov* 2007, 6:871-880.
 17. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol* 2008, 4:682-690.
 18. Kholodenko BN, Hancock JF, Kolch W. Signalling ballet in space and time. *Nat Rev Mol Cell Biol* 2010, 11:414-426.
 19. Sharma A, Gulbahce N, Pevzner S, Menche J, Ladenvall C, Folkersen L, Eriksson P, Orho-Melander M, Barabasi AL. Network based analysis of genome wide association data provides novel candidate genes for lipid and lipoprotein traits. *Mol Cell Proteomics* 2013.
 20. Chuang HY, Lee E, Liu YT, Lee D, Ideker T. Network-based classification of breast cancer metastasis. *Mol Syst Biol* 2007, 3:140.
 21. Turan N, Kalko S, Stincone A, Clarke K, Sabah A, Howlett K, Curnow SJ, Rodriguez DA, Cascante M, O'Neill L, et al. A systems biology approach identifies molecular networks defining skeletal muscle abnormalities in chronic obstructive pulmonary disease. *PLoS Comput Biol* 2011, 7:e1002129.
 22. Diez D, Goto S, Fahy JV, Erle DJ, Woodruff PG, Wheelock AM, Wheelock CE. Network analysis identifies a putative role for the PPAR and type 1 interferon pathways in glucocorticoid actions in asthmatics. *BMC Med Genomics* 2012, 5:27.
 23. Wheelock CE, Goss VM, Balgoma D, Nicholas B, Brandsma J, Skipp PJ, Snowden S, Burg D, D'Amico A, Horvath I, et al. Application of 'omics technologies to biomarker discovery in inflammatory lung diseases. *Eur Respir J* 2013, 42:802-825.
 24. Dar AC, Shokat KM. The evolution of protein kinase inhibitors from antagonists to agonists of cellular signaling. *Annu Rev Biochem* 2011, 80:769-795.
 25. Pan C, Olsen JV, Daub H, Mann M. Global effects of kinase inhibitors on signaling networks revealed by quantitative phosphoproteomics. *Mol Cell Proteomics* 2009, 8:2796-2808.
 26. Rix U, Hantschel O, Durnberger G, Remsing Rix LL, Planyavsky M, Fernbach NV, Kaupe I, Bennett KL, Valent P, Colinge J, et al. Chemical proteomic profiles of the BCR-ABL inhibitors imatinib, nilotinib, and dasatinib reveal novel kinase and nonkinase targets. *Blood* 2007, 110:4055-4063.
 27. Noble D, Noble PJ. Late sodium current in the pathophysiology of cardiovascular disease: consequences of sodium-calcium overload. *Heart* 2006, 92 Suppl 4:iv1-iv5.

28. Belardinelli L, Shryock JC, Fraser H. Inhibition of the late sodium current as a potential cardioprotective principle: effects of the late sodium current inhibitor ranolazine. *Heart* 2006, 92 Suppl 4:iv6-iv14.
29. Moreno JD, Zhu ZI, Yang PC, Bankston JR, Jeng MT, Kang C, Wang L, Bayer JD, Christini DJ, Trayanova NA, et al. A computational model to predict the effects of class I anti-arrhythmic drugs on ventricular rhythms. *Sci Transl Med* 2011, 3:98ra83.
30. Ortiz-Tudela E, Mteyrek A, Ballesta A, Innominato PF, Levi F. Cancer chronotherapeutics: experimental, theoretical, and clinical aspects. *Handb Exp Pharmacol* 2013:261-288.
31. Ballesta A, Dulong S, Abbara C, Cohen B, Okyar A, Clairambault J, Levi F. A combined experimental and mathematical approach for molecular-based optimization of irinotecan circadian delivery. *PLoS Comput Biol* 2011, 7:e1002143.
32. Innominato PF, Giacchetti S, Moreau T, Smaaland R, Focan C, Bjarnason GA, Garufi C, Iacobelli S, Tampellini M, Tumolo S, et al. Prediction of survival by neutropenia according to delivery schedule of oxaliplatin-5-Fluorouracil-leucovorin for metastatic colorectal cancer in a randomized international trial (EORTC 05963). *Chronobiol Int* 2011, 28:586-600.
33. Altinok A, Levi F, Goldbeter A. Identifying mechanisms of chronotolerance and chronoefficacy for the anticancer drugs 5-fluorouracil and oxaliplatin by computational modeling. *Eur J Pharm Sci* 2009, 36:20-38.
34. Mirams GR, Davies MR, Cui Y, Kohl P, Noble D. Application of cardiac electrophysiology simulations to pro-arrhythmic safety testing. *Br J Pharmacol* 2012, 167:932-945.
35. Azuaje FJ, Zhang L, Devaux Y, Wagner DR. Drug-target network in myocardial infarction reveals multiple side effects of unrelated drugs. *Sci Rep* 2011, 1:52.
36. Yildirim MA, Goh KI, Cusick ME, Barabasi AL, Vidal M. Drug-target network. *Nat Biotechnol* 2007, 25:1119-1126.
37. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev* 2001, 46:3-26.
38. DiMasi JA, Feldman L, Seckler A, Wilson A. Trends in risks associated with new drug development: success rates for investigational drugs. *Clin Pharmacol Ther* 2010, 87:272-277.
39. Kell DB. Finding novel pharmaceuticals in the systems biology era using multiple effective drug targets, phenotypic screening and knowledge of transporters: where drug discovery went wrong and how to fix it. *FEBS J* 2013.
40. Gashaw I, Ellinghaus P, Sommer A, Asadullah K. What makes a good drug target? *Drug Discov Today* 2011, 16:1037-1043.
41. Ashley DJ. The two "hit" and multiple "hit" theories of carcinogenesis. *Br J Cancer* 1969, 23:313-328.
42. Hartman JLt, Garvik B, Hartwell L. Principles for the buffering of genetic variation. *Science* 2001, 291:1001-1004.
43. Hopkins AL, Mason JS, Overington JP. Can we rationally design promiscuous drugs? *Curr Opin Struct Biol* 2006, 16:127-136.
44. Metz JT, Hajduk PJ. Rational approaches to targeted polypharmacology: creating and navigating protein-ligand interaction networks. *Curr Opin Chem Biol* 2010, 14:498-504.
45. Dar AC, Das TK, Shokat KM, Cagan RL. Chemical genetic discovery of targets and anti-targets for cancer polypharmacology. *Nature* 2012, 486:80-84.
46. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, Glick JH, Coltman CA, Jr., Miller TP. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med* 1993, 328:1002-1006.
47. Ramaswamy S. Rational design of cancer-drug combinations. *N Engl J Med* 2007, 357:299-300.

48. Feala JD, Cortes J, Duxbury PM, Piermarocchi C, McCulloch AD, Paternostro G. Systems approaches and algorithms for discovery of combinatorial therapies. *Wiley Interdiscip Rev Syst Biol Med* 2010, 2:181-193.
49. Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, Demidov LV, Hassel JC, Rutkowski P, Mohr P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med* 2012, 367:107-114.
50. Lee MJ, Ye AS, Gardino AK, Heijink AM, Sorger PK, MacBeath G, Yaffe MB. Sequential application of anticancer drugs enhances cell death by rewiring apoptotic signaling networks. *Cell* 2012, 149:780-794.
51. Peng H, Wen J, Li H, Chang J, Zhou X. Drug inhibition profile prediction for NFkappaB pathway in multiple myeloma. *PLoS One* 2011, 6:e14750.
52. Sturm OE, Orton R, Grindlay J, Birtwistle M, Vyshemirsky V, Gilbert D, Calder M, Pitt A, Kholodenko B, Kolch W. The mammalian MAPK/ERK pathway exhibits properties of a negative feedback amplifier. *Sci Signal* 2010, 3:ra90.
53. Antman E, Weiss S, Loscalzo J. Systems pharmacology, pharmacogenetics, and clinical trial design in network medicine. *Wiley Interdiscip Rev Syst Biol Med* 2012, 4:367-383.
54. Andersen ME, Thomas RS, Gaido KW, Conolly RB. Dose-response modeling in reproductive toxicology in the systems biology era. *Reprod Toxicol* 2005, 19:327-337.
55. Chien JY, Friedrich S, Heathman MA, de Alwis DP, Sinha V. Pharmacokinetics/Pharmacodynamics and the stages of drug development: role of modeling and simulation. *AAPS J* 2005, 7:E544-559.
56. Arvidson NG, Gudbjornsson B, Larsson A, Hallgren R. The timing of glucocorticoid administration in rheumatoid arthritis. *Ann Rheum Dis* 1997, 56:27-31.
57. Faratian D, Goltsov A, Lebedeva G, Sorokin A, Moodie S, Mullen P, Kay C, Um IH, Langdon S, Goryanin I, et al. Systems biology reveals new strategies for personalizing cancer medicine and confirms the role of PTEN in resistance to trastuzumab. *Cancer Res* 2009, 69:6713-6720.
58. Hood L, Galas D. P4 Medicine: personalized, predictive, preventive, participatory: a change of view that changes everything. 2008. Available at: http://www.cra.org/ccc/files/docs/init/P4_Medicine.pdf
59. Vandamme D, Fitzmaurice W, Kholodenko B, Kolch W. systems medicine: helping us understand the complexity of disease. *Q J Med* 2013.
60. Ito T, Ando H, Handa H. Teratogenic effects of thalidomide: molecular mechanisms. *Cell Mol Life Sci* 2011, 68:1569-1579.
61. Ladizinski B, Shannon EJ, Sanchez MR, Levis WR. Thalidomide and analogues: potential for immunomodulation of inflammatory and neoplastic dermatologic disorders. *J Drugs Dermatol* 2010, 9:814-826.
62. Keiser MJ, Setola V, Irwin JJ, Laggner C, Abbas AI, Hufeisen SJ, Jensen NH, Kuijter MB, Matos RC, Tran TB, et al. Predicting new molecular targets for known drugs. *Nature* 2009, 462:175-181.
63. von Eichborn J, Murgueitio MS, Dunkel M, Koerner S, Bourne PE, Preissner R. PROMISCUOUS: a database for network-based drug-repositioning. *Nucleic Acids Res* 2011, 39:D1060-1066.
64. Munos B. Lessons from 60 years of pharmaceutical innovation. *Nat Rev Drug Discov* 2009, 8:959-968.
65. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, Schacht AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat Rev Drug Discov* 2010, 9:203-214.
66. Arrowsmith J. Trial watch: Phase II failures: 2008-2010. *Nat Rev Drug Discov* 2011, 10:328-329.
67. Arrowsmith J. Trial watch: phase III and submission failures: 2007-2010. *Nat Rev Drug Discov* 2011, 10:87.

68. Ahn AC, Tewari M, Poon CS, Phillips RS. The limits of reductionism in medicine: could systems biology offer an alternative? *PLoS Med* 2006, 3:e208.
69. Milward EA, Daneshi N, Johnstone DM. Emerging real-time technologies in molecular medicine and the evolution of integrated 'pharmacomics' approaches to personalized medicine and drug discovery. *Pharmacol Ther* 2012, 136:295-304.
70. Kingsmore SF, Lindquist IE, Mudge J, Gessler DD, Beavis WD. Genome-wide association studies: progress and potential for drug discovery and development. *Nat Rev Drug Discov* 2008, 7:221-230.