Dynamic Targeting in Cancer Treatment

Zhihui Wang¹²* and Thomas S. Deisboeck³*

¹ Mathematics in Medicine Program, Houston Methodist Research Institute, Houston, TX, United States
² Department of Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, TX, United States
³ Department of Radiology, Harvard-MIT (HST) Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, United States

With the advent of personalized medicine, design and development of anti-cancer drugs that are specifically targeted to individual or sets of genes or proteins has been an active research area in both academia and industry. The underlying motivation for this approach is to interfere with several pathological crosstalk pathways in order to inhibit or at the very least control the proliferation of cancer cells. However, after initially conferring beneficial effects, if sub-lethal, these artificial perturbations in cell function pathways can inadvertently activate drug-induced up- and down-regulation of feedback loops, resulting in dynamic changes over time in the molecular network structure and potentially causing drug resistance as seen in clinics. Hence, the targets or their combined signatures should also change in accordance with the evolution of the network (reflected by changes to the structure and/or functional output of the network) over the course of treatment. This suggests the need for a “dynamic targeting” strategy aimed at optimizing tumor control by interfering with different molecular targets, at varying stages. Understanding the dynamic changes of this complex network under various perturbed conditions due to drug treatment is extremely challenging under experimental conditions let alone in clinical settings. However, mathematical modeling can facilitate studying these effects at the network level and beyond, and also accelerate comparison of the impact of different dosage regimens and therapeutic modalities prior to sizeable investment in risky and expensive clinical trials. A dynamic targeting strategy based on the use of mathematical modeling can be a new, exciting research avenue in the discovery and development of therapeutic drugs.

Keywords: drug discovery, mathematical modeling, network medicine, signaling pathway, therapeutic target, translational research

INTRODUCTION

Cancer is a multifactorial and remarkably heterogeneous disease. Its initiation, progression, invasion, and metastasis processes all involve multiple molecular signaling mechanisms. The diversity of molecular and cellular properties across tumors from different patients, and even across cancer cells from the same patient, makes it extremely difficult to find a “one-size-fits-all” solution for therapeutic targeting of cancer. Thus, tailored targeted therapies based on each individual tumor’s characteristics are required in order to optimize treatment efficacy, minimize toxicity and drug side-effects, and ultimately lead to more cost-effective patient management by giving the most...
appropriate drugs at the optimum dose to every patient in need (Topol, 2014; Ryall and Tan, 2015). This is the essential concept of precision medicine.

From a systems biology perspective, cancer can be viewed as a network disease caused by dysregulation of molecular signaling pathways that determine various physiological cellular processes, such as growth, division, differentiation, and apoptosis (Creixell et al., 2012). These signaling pathways are not isolated from each other, but form a complex, interconnected network with numerous regulatory feedback loops and redundant pathways that together confer significant evolutionary robustness. Still, substantial advances have been made in development of targeted therapies based on detailed mechanistic understanding of these signaling networks, and as a result, some targeted drugs are emerging for clinical use (Yildirim et al., 2007; Hopkins, 2008). However, despite positive treatment responses in some patients, a large fraction of patients fail to benefit from these targeted therapies, even when molecular markers have been used to stratify patients into groups that are expected to respond to the therapy. Taking an approved ErbB-targeted drug (Herceptin) as an example, only about half of all patients with ErbB2-amplified metastatic breast cancer respond to the drug, and of those who do respond in the beginning, most eventually develop resistance (Garrett and Arteaga, 2011). This pattern of initial response followed by relapse is not unique to ErbB-targeted therapies, but has been seen for most molecularly targeted inhibitors (Al-Lazikani et al., 2012).

The disappointing response rate of targeted therapies is partly due to the resilience of oncogenic signaling networks that will often bypass a single hit through an abundance of the highly non-linear built-in feedback loops and alternative pathways that can compensate for therapeutic impact. To solve this "escape" problem, multiple therapies can be used together or in sequence, i.e., combination therapy, which can potentially block these parallel or alternative pathways activated in cancer cells (Fitzgerald et al., 2006). Since these therapeutic drugs may be administered at a smaller dosage for each individual drug, a combination therapy may stop oncogenic signaling or further delay resistance to treatments, while simultaneously minimizing overlapping toxicity. In theory, a combination approach would seem to have the potential to block alternative pathways, but, while there have been clinical successes, as with monotherapy they have not led to cure or long-term control for all patients (Chong and Janne, 2013; Yap et al., 2013; Sachs et al., 2016; Lopez and Banerji, 2017). One problem lies in the complexity of signaling networks, making it difficult to simply guess a priori which drug combinations are synergistically effective and which are not. Given the number of targeted drugs currently available and in clinical development, it is time-consuming and expensive to do unbiased screening of the large number of possible drug combinations at their clinically relevant dose and dosing schedules. Therefore, there is a major need for approaches that will allow us to identify effective drug combinations where two or more drugs work synergistically to suppress malfunctioning signaling.

Testing potentially clinically relevant drug combinations using mathematical models (see Box 1) offers a reasonable yet relatively simple and expeditious way to accomplish this task by computationally examining multiple targets through extensive parameter perturbation analyses (Araujo et al., 2005; Iyengar et al., 2012; Barbolosi et al., 2016). This approach allows for rapid and low-cost examination of the drug and target combination parameter space, including identification of potentially optimal drug combinations through mathematical methods, ultimately providing valuable insights which would be difficult (if not impossible) to achieve through traditional experimental and clinical trial methods and techniques. In the end, these models can help to narrow down and prioritize different target combinations prior to experimental validation.

**NETWORK REWIRING**

It has been extensively reported that cancer cells or cell populations adapt or evolve in response to targeted therapies, in part by rewiring molecular mechanisms to overcome the inhibitory effects of initial treatments (Gillies et al., 2012; Logue and Morrison, 2012; Azad et al., 2015; Kolch et al., 2015; Stuhlmiller et al., 2015). This rewiring may involve alterations of signaling pathways, such as addition or deletion of edges in the network, modification of reaction rates, and changes in molecular concentrations, all of which may ultimately contribute to treatment resistance, either directly through rendering the drug ineffective or indirectly by leading to activation of alternative pro-survival or anti-apoptotic pathways. There are many other biological, biochemical, and biophysical factors [e.g., genetic alteration of individual cells, outgrowth of existing resistant subclones under selection pressure from treatment, altered effectors in DNA repair, pathway-independent acquired resistance, up-regulation of efflux pumps in cellular membranes, protein level oscillations within cells even in the absence of treatment, and physical barriers that may limit diffusive and convective drug transport (Minchinton and Tannock, 2006; Garraway and Janne, 2012; Brocato et al., 2014; Stewart et al., 2015; Cristini et al., 2017)] that may also contribute to cancer resistance to treatment, but rewiring of signaling pathways very likely plays an important role as a mechanism of acquired resistance. This implies that pharmacologically targeting the compensatory mechanisms (which have emerged due to this rewiring) should help to improve treatment efficacy and patient outcome (Solit and Rosen, 2011; Akhavan et al., 2013; Camidge et al., 2014).

Even before treatment, signaling networks are rewired in cancer cells compared to normal cells. Here, we briefly discuss several recent studies working toward understanding how signaling networks are rewired in cancer cells, and discuss how identification of these alterations can enable more effective cancer treatment. Creixell et al. (2015) performed systems-based research to evaluate whether cancer mutations perturb signaling networks and, if so, by what mechanisms. Using their collected global exome sequencing and proteomic data on the same set of cancer cell lines, some mutations were found to create new phosphorylation sites or destroy existing ones within a signaling network, or shift the network structure by upstream or...
downstream rewiring of the mutated signaling node. A variety of rewiring modes were identified, including constitutive activation and inactivation of kinase and SH2 domains, upstream and downstream rewiring of phosphorylation-based signaling, and the extinction and genesis of phosphorylation sites. Their results indicate that signaling networks are both dynamically and structurally rewired in cancer cells. More recently, Latysheva et al. (2016) investigated the interaction properties and structural features of more than two thousand fusion-forming proteins, and provided insight into the genome-scale molecular principles upon which fusion proteins could escape cell-death regulation and rewire signaling networks in cancer. Notably, using an integrated experimental and computational approach, Halasz et al. (2016) predicted and then validated feedback inhibition of insulin receptor substrate 1 (IRS1) by the kinase p70S6K in a zebrafish (Danio rerio) xenograft model to confer resistance to EGFR inhibition through extensive analysis of a perturbation data set targeting epidermal growth factor receptor (EGFR) and insulin-like growth factor 1 receptor (IGF1R) pathways in a panel of colorectal cancer cells. Some studies (Pandey et al., 2014) also point to transient or short-term pathway alterations resulting from one drug as causing increased sensitivity to a second drug delivered at a later time. Morton et al. (2014) designed a nanoparticle system that successfully delivered two different drugs with varying models of action to the tumor in a sequential manner. The first drug inhibited an oncogenic pathway through rewiring that sensitized the cells to DNA damage-induced apoptosis, and the second was a genotoxic drug that took advantage of the vulnerable state of the cancer cells to kill them with enhanced efficiency. Their results highlight how understanding the ways that signaling pathways change or rewire in response to treatment or drug exposure is essential for improving current translational and clinical research.

RE-IDENTIFICATION AND RE-TARGETING

To predict cellular behavior, it is required to assess temporal- and state-based network dynamics in response to perturbations such as those induced by targeted drugs. It is thus highly rational to examine the newly rewired and altered molecular network [or networks, as some studies have found evidence that the dominant network is different at different tumor sites (Pestrin et al., 2009; Bhamidipati et al., 2013; Russo et al., 2017)], which arises after the extinction and genesis of phosphorylation sites. Their results indicate that signaling networks are both dynamically and structurally rewired in cancer cells. More recently, Latysheva et al. (2016) investigated the interaction properties and structural features of more than two thousand fusion-forming proteins, and provided insight into the genome-scale molecular principles upon which fusion proteins could escape cell-death regulation and rewire signaling networks in cancer. Notably, using an integrated experimental and computational approach, Halasz et al. (2016) predicted and then validated feedback inhibition of insulin receptor substrate 1 (IRS1) by the kinase p70S6K in a zebrafish (Danio rerio) xenograft model to confer resistance to EGFR inhibition through extensive analysis of a perturbation data set targeting epidermal growth factor receptor (EGFR) and insulin-like growth factor 1 receptor (IGF1R) pathways in a panel of colorectal cancer cells. Some studies (Pandey et al., 2014) also point to transient or short-term pathway alterations resulting from one drug as causing increased sensitivity to a second drug delivered at a later time. Morton et al. (2014) designed a nanoparticle system that successfully delivered two different drugs with varying models of action to the tumor in a sequential manner. The first drug inhibited an oncogenic pathway through rewiring that sensitized the cells to DNA damage-induced apoptosis, and the second was a genotoxic drug that took advantage of the vulnerable state of the cancer cells to kill them with enhanced efficiency. Their results highlight how understanding the ways that signaling pathways change or rewire in response to treatment or drug exposure is essential for improving current translational and clinical research.

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FIGURE 1 | Illustration of the dynamic targeting strategy. The molecular signaling network changes or evolves with selective treatment. For instance, in this schematic, at time point 1, A1 emerges as the most critical node, hence during the first treatment period, A1 will be targeted with anti-A1. Assuming this to be of sub-lethal impact, the network rewires due to A1 inhibition, but the cell still finds a way to upregulate proliferation, so the treatment continues. At time point 2, A2 emerges as the top target, so the therapeutic regimen will attempt to inhibit A2 (together with A1) for the second treatment period. The network again rewires due to A2 inhibition, and the cell finds yet another way to bypass the A2 route and continues to proliferate. At time point 3, B1 becomes the top target, so the next treatment cycle will target B1 (together with A1 and A2). This process will continue until growth control is optimized and relapse to rapid replication does not occur. For each target at each treatment stage, exactly how much drug (dose) and how often to apply it (frequency) will require careful evaluation and should be different across patients. That is, other than depicted in the schematic for simplification purposes, the network adaptation is likely not hard-wired or rigidly dependent on external therapeutic pressure, but rather it undergoes a dynamic transition through an intrinsic optimization process. To manage side effects, a basic strategy could be to maximize the modulation effects on the top target specific to each treatment iteration, while keeping the “pressure” on prior targets at their respective “maintenance” minimum yet necessary dosing/frequency levels. Top targets are highlighted in yellow when the target identification process is performed. R: receptor; A1, A2, B1, B2: signaling molecules of the network.

could instead be intended to modulate it up or down to redirect the network output. The second question is how frequently should the tumor system be re-examined in order to identify new targets or target combinations? While this is generally cancer type- and treatment-specific, it should also be patient-specific – yet remaining mindful of operational constraints and economics involved when translating this concept into a clinical setting. Still, in our opinion, every time a patient sees a diminishing therapeutic yield from, let alone fails a particular targeted treatment, the molecular network should be re-evaluated to potentially adjust the targeting strategy. We note that the timeline shown in Figure 1 is merely a schematic, and it follows that new network configurations (and thus the target hit-list) will differ in how fast they evolve, as would the drug dose and dosing schedules (determined uniquely for each drug delivered) for the individualized patient treatment plan.

In our dynamic approach, targets will emerge sequentially through “selection” imposed by targeted treatment and the perturbations it causes and reconfigurations the network stabilizes to. This is geared toward optimizing tumor growth control and as such differs from current combinatorics approaches (Gillies et al., 2012; Logue and Morrison, 2012), where the “most impactful” target combination is assessed once and then applied a priori, which should also incur more unexpected on-target or off-target side effects. We note that based on current reports on cell signaling (Tanay et al., 2005; Wei et al., 2016; Young et al., 2017), there are reasons to believe that there is some form of phase transition for network adaptability or maximum carrying capacity for the selection pressure or stress applied by a treatment, beyond which the cell simply dies. Rather than trying to kill all the cancer cells as efficaciously as possible, which is often impossible because of, e.g., detection limits and delivery challenges, our goal is to achieve maximum control over disease progression with minimal side effects, hence the sequential probing approach implemented in dynamic targeting.

Admittedly, there are many challenges in implementing this dynamic targeting strategy in current clinical practice. For example, immunotherapy is known to not always yield a tumor response within a time frame that other treatments may have shown, and some patients may experience initial increased size of tumor lesions with subsequent decreased tumor burden [this phenomenon is called pseudoprogression (Hodi et al., 2016)]. If a molecular targeted therapy is used together with immunotherapy, then we should give this type of combination
importance of dynamic targeting in cancer treatment. We note we here discuss two recent examples to demonstrate the combinations would then be handed over to conventional individualized, computationally validated drug targets and necessary; the mathematically narrowed down selection of identifying effective drug target combinations progressively with quantitative wet lab studies to facilitate the process of computer model simulations can be effectively integrated corresponding network perturbations in a dynamic fashion.

As another example, to understand the dynamic, non-linear behavior of signaling pathways in cancer, Bernardo-Faura et al. (2014) developed an adaptive model to study and predict changes in network architecture (i.e., topology) over time in response to drug treatment based on fuzzy logic, a method that has been widely used in computation and engineering. Using the model, they tested the dynamics of the mitogen-activated protein kinase (MAPK) pathway (which was composed of 10 signaling intermediates) against a dataset derived from a melanoma cell line that was exposed to different pharmacological kinase inhibitors over 4 days. They found that, although Sorafenib (an inhibitor) was considered to have the capability to prevent phosphorylation of MEK1/2, which should in turn suppress.

**PILOT EXAMPLES**

We here discuss two recent examples to demonstrate the importance of dynamic targeting in cancer treatment. We note that both examples do not represent a full implementation of the dynamic targeting process. However, they reflect the necessity for novel approaches addressing network rewiring to find new, complementary drug targets or their combinations in an effort to truly improve survival and the probability of long-term remission if not cure in cancer treatment.

Lee et al. (2012) studied three cell lines from triple-negative breast cancer (i.e., estrogen receptor-, progesterone receptor-, and HER2 oncogene-negative) for their responses to seven genotoxic drugs and eight signaling inhibitors in various combinations and dosing schedules. They found that combination treatment with EGFR inhibitor (erlotinib) and DNA-damaging chemotherapy (doxorubicin) led to substantial killing of cancer cells, but only when the EGFR inhibition was used before the chemotherapy by at least 4 h. This combination treatment led to the rewiring of oncogenic signaling pathways, which has the potential to make cancer cells more susceptible to death. That is, the observed response relates to the dynamic effects on the molecular interaction network, which was rewired in response to EGFR inhibition, during which the cells once again became susceptible to death triggered by DNA damage. Since it was challenging to directly examine rewiring pathways by using wet lab experiments alone, they constructed a data-driven model based on partial least squares regression which was then used to correlate cellular responses with different forms of drug treatment. This study is significant, as it provides strong evidence that the timed application of signaling inhibitors causes the rewiring of signaling pathways in tumor cells and renders them more susceptible to subsequent chemotherapy. Other studies, such as Huether et al. (2005), also pointed to changes in apoptotic signaling pathways from a targeted therapy increasing chemotherapeutic sensitivity, with time dependence. Moreover, as also shown in other clinical research (Andre et al., 2003, 2004, 2009), this study by Lee et al. (2012) demonstrates that not only the selection of optimal drug combinations, but also the sequence and timing of the administration of the multiple therapeutic drugs were critical to maximize treatment efficacy. Goldman et al. (2015) also reported that if a chemotherapy drug pair is administered in the right temporal sequence combinations, the leading drug could induce a phenotypic cell state transition, thereby making the cancer vulnerable to the partner agent. Interestingly, they even proposed the use of mathematical modeling to optimize sequential treatment with two drugs to take advantage of rewiring in response to the first drug.

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Lastly, for any type of cancer, it should be kept in mind that only a subset of patients could benefit from a particular drug treatment. Hence, molecular diagnostics and imaging markers (Ransohoff and Gourlay, 2010; Reis-Filho and Pusztai, 2011; Jafari et al., 2017; Sepulveda et al., 2017) will be critical to correctly identify patient cohorts that are best suited for different targeted therapies, in addition to assessing response to therapy and monitoring patients for adverse drug reactions. Many other significant challenges related to further understanding tumor heterogeneity, tumor-host interactions, and immune response, etc. (Gatenby et al., 2010; Andre et al., 2013; Enriquez-Navas et al., 2016; Ibrahim-Hashim et al., 2017; Zhang et al., 2017) certainly exist in translating this strategy to clinical application. Further discussion of those challenges is beyond the scope of this article, as we only focus on introduction of a new concept, but it is worth emphasizing that many details with respect to technology, clinical care, regulation, and reimbursement need to be addressed in order to translate this concept into a reality.

To implement the dynamic targeting strategy, it would be prohibitive to evaluate the sheer number of mathematically possible drug target combinations multiple times over the course of treatment in preclinical animal models, let alone in a clinical setting. We therefore need, and should take additional assessments have a favorable cost to benefit ratio. Lastly, for any type of cancer, it should be kept in mind that only a subset of patients could benefit from a particular drug treatment. Hence, molecular diagnostics and imaging markers (Ransohoff and Gourlay, 2010; Reis-Filho and Pusztai, 2011; Jafari et al., 2017; Sepulveda et al., 2017) will be critical to correctly identify patient cohorts that are best suited for different targeted therapies, in addition to assessing response to therapy and monitoring patients for adverse drug reactions. Many other significant challenges related to further understanding tumor heterogeneity, tumor-host interactions, and immune response, etc. (Gatenby et al., 2010; Andre et al., 2013; Enriquez-Navas et al., 2016; Ibrahim-Hashim et al., 2017; Zhang et al., 2017) certainly exist in translating this strategy to clinical application. Further discussion of those challenges is beyond the scope of this article, as we only focus on introduction of a new concept, but it is worth emphasizing that many details with respect to technology, clinical care, regulation, and reimbursement need to be addressed in order to translate this concept into a reality.

To implement the dynamic targeting strategy, it would be prohibitive to evaluate the sheer number of mathematically possible drug target combinations multiple times over the course of treatment in preclinical animal models, let alone in a clinical setting. We therefore need, and should take full advantage of, large-scale unbiased methods based on mathematical modeling to evaluate and prioritize potential drug target combinations as early as possible. Indeed, mathematical network modeling has been helpful in identifying promising targets and effective combinations of existing targets (Wang et al., 2007, 2008, 2009, 2011b, 2012, 2014; Zhang et al., 2009; Miller et al., 2013; Wang and Deisboeck, 2014; Schoeberl et al., 2017). Once proven reliable, these models can be used to exhaustively test the efficacy of a large number of single drug and drug combinations by correlating signaling outputs with corresponding network perturbations in a dynamic fashion. Computer model simulations can be effectively integrated with quantitative wet lab studies to facilitate the process of identifying effective drug target combinations progressively over the course of treatment when treatment efficacy needs to be evaluated or a new treatment method is considered necessary; the mathematically narrowed down selection of individualized, computationally validated drug targets and combinations would then be handed over to conventional preclinical testing.
the activation of ERK1/2, the observed ERK1/2 profile was not consistently inhibited, suggesting a signaling rearrangement compared to the original MAPK pathway. While the rewired interaction could not be specifically identified with the model, the potential underlying biological mechanisms could range from genetic mechanisms (such as mutations) to spatiotemporal pathway regulations. This result also proved an interesting point: that some biological mechanisms may enable the cell to enhance certain pathways or prevent some reported interactions from happening in order to trigger a specific response, depending on the context or cell type (Jones et al., 2008). This adaptive modeling approach can be used to characterize dynamic signaling rearrangements that grant tumors the ability to maintain proliferation and develop resistance.

CONCLUSION

Using the same drug or drug combinations throughout the course of treatment has been proven ineffective to overcome the pathway crosstalk and redundant signaling mechanisms, which are thought to be responsible (at least in part) for the modest responses observed in current trials of targeted therapies. Focusing on long-term tumor control rather than eradication, we introduce a dynamic targeting strategy, proposing that the target “signature” should change accordingly as the signaling network adapts during the course of treatment. Of course, this critically depends on being able to analyze the molecular networks readily and sufficiently, and mathematical models present an ideal platform for testing and optimizing drug combinations whenever target re-identification is needed. Ultimately, one may be able to predict the range of emerging target configurations, so that personalized, multi-tiered treatment can become proactive as opposed to being reactive to the network’s intrinsic ability to adapt. Compared to current preclinical and clinical oncology practice, our concept offers a faster, more effective, and thus arguably more economic approach to explore a large number of potential treatment strategies to identify an optimal, patient-specific therapeutic regimen.

AUTHOR CONTRIBUTIONS

Both authors made a substantial contribution to researching data for the article, discussions of content, writing, and reviewing and editing of the manuscript before submission.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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