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Informative diagnostics for personalized medicine

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Abstract

Some of the most celebrated triumphs of chemical biology are molecularly-targeted therapeutics to combat human disease. However, a grand challenge looms as informative diagnostic strategies must be developed in order to realize the full impact of these promising pharmaceutical agents.

Almost exactly ten years ago, the preliminary sequence of the human genome was released,^{1, 2} instantly grabbing the attention of the biomedical research community and signaling the presumptive arrival of the age of personalized medicine. The ensuing decade has seen several notable successes in the deployment of personalized therapies for cancer; however the widespread translation of genomic insight into individualized disease treatment has yet to be fully realized.

The chemical biology community has been incredibly successful in utilizing ‘omic technologies to illuminate potential targets for disease intervention, and adapting high throughput screening methodologies to facilitate the discovery of therapeutics that can act to either destroy or restore normal, healthy function to diseased cells. The most successful example of a molecularly targeted therapeutic for personalized medicine is imatinib, which is a small molecule inhibitor of kinase signaling that was developed to selectively act on cancers that have the *BCR-ABL* oncogene (the result of a reciprocal translocation between chromosomes 9 and 22).³ This drug, marketed as Gleevec in the United States, has found wide clinical use in the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors, amongst other cancers. Inspired by the success of imatinib, chemical biologists continue to use similar approaches to drug discovery and target validation in generating an ever increasing list of molecularly targeted therapeutics that are promising for personalized medicine applications.^{4–11}

However, by comparison with these drug discovery efforts there has been a relative dearth of activity directed towards creating informative companion diagnostic methods to support the development of new drugs in the clinic. For molecularly-targeted drugs in particular, identifying the subset(s) of responsive patients is even more important, since the compounds can be ineffective if the appropriate causative factors are missing. A notable exception that highlights the importance of diagnostics in support of targeted therapeutics is found in trastuzumab,¹² a humanized monoclonal antibody sold as Herceptin and used to treat Her2 positive breast cancers. Importantly, Genentech worked together with the diagnostic company DAKO to develop assays that directly detected Her2 over expression, thereby providing a robust method of pre-identifying a subset of responsive breast cancer patients prior to treatment. The striking success of this pharmaceutical-diagnostic collaboration—sometimes referred to as an Rx/Dx relationship—can serve as a successful model as chemical biologists aim to fully exploit the incredible power of molecularly-targeted therapeutics for personalized medicine.

There are numerous ways in which chemical biologists can and should contribute to the central goal of acquiring detailed biomolecular information from individual patients. Efforts to tackle this challenge can be sub-divided into two synergistic objectives (Fig. 1): 1) the creation of informative *in vitro* diagnostic platforms, and 2) the further improvement of enabling *in vivo* imaging tools.

Upstream of an *in vitro* diagnostic platform, there are outstanding opportunities for chemical biologists to both identify and create affinity recognition strategies for disease biomarkers, which may be discovered at the genomic, transcriptomic, proteomic, or metabolomic levels. In the clinic, informative biomarkers may assume different roles,¹³ including use as pre-clinical diagnostic biomarkers for pre-symptomatic detection, prognostic biomarkers that forecast disease progression, and theragnostic biomarkers, which suggest the most appropriate treatment strategy—such as Her2 in the case of trastuzumab. While some biomarkers may have value in multiple roles, it is important to note that this will not always be true. Caution should be taken from prostate specific antigen, which for years has been used as a diagnostic biomarker but offers almost no prognostic information, contributing to overaggressive treatment regimens for prostate cancer.¹⁴ Moreover, some conditions may require the quantitation of multiple biomolecules in order to completely unravel more complex disease mechanisms. Chemical biologists are well-versed in many of the tools required to discover new biomarkers, including array-based nucleic acid technologies and mass spectrometry based proteomic strategies.¹⁵ However, additional efforts are needed in developing approaches for higher-precision genomic, transcriptomic, and proteomic analysis methods so that subtle changes in expression can be used as informative measures of disease onset and progression. Notably, these endeavors will not necessarily be subject to the same constraints faced by an eventual diagnostic platform since they are aimed at biomarker discovery as opposed to clinical detection, and therefore raw capability, as opposed to practicality, is of paramount importance.

For newly discovered proteomic biomarkers, the development of stable and high affinity capture agents represents a significant hurdle—one that chemical biologists are uniquely suited to attack. Monoclonal antibodies are by far the most commonly used capture agent for immunoassays, and while advances in hybridoma technology have led to the commercial availability of many thousands of antibodies, the cost and production time required to generate high quality monoclonal antibodies against emerging biomarkers is often rate limiting. As substitutes for antibodies that feature more facile generation and improved stability, a number of alternative capture agents have been explored,¹⁶ including aptamers¹⁷ and multivalent peptide scaffolds,¹⁸ amongst many other exciting prospects. Chemical biologists have and will continue to pioneer new capture agent development strategies given their aptitude in techniques such as ligand selection (e.g. SELEX), library syntheses, and bead-based screening approaches.

Chemical biologists should also work in stride with analytical chemists and engineers to develop enabling clinical measurement tools, lending their expertise in more conventional biological assays to expedite the validation of emerging approaches. Driven by cost considerations, limited patient sample sizes in some situations, and a desire for higher per assay information content, many of the most promising emerging technologies are based upon micro- or nanotechnologies and often leverage massively scalable fabrication techniques, such as those originally developed to support the microelectronics industry. Perhaps most critical to keep under consideration during the development of prospective diagnostic technologies are issues surrounding the applicability and practicality of an assay to the challenges faced when working with real-world clinical samples (Box 1). Specifically, diagnostic assays must be amenable to either “as collected” or minimally-processed samples, must be mass producible on a scale that is consistent with the demand, and

applicable to clinical laboratories. Recent trends towards high information content measurements have also placed an increasing impetus on multiparameter analysis, as single biomarkers have limited diagnostic utility in many cases, and quantitation of multiple biomolecular signatures can help compensate for natural heterogeneities within a population that are independent of disease state.

Box 1

Technology design ideals for diagnostic technologies

1. The technology must work for clinically-relevant samples, including body fluids and tissue biopsy samples.
2. The technology must be cost effective and scalable, consistent with clinical demand.
3. Rapid time-to-result will enable physicians to rapidly assess and treat disease.
4. Multiplexed analysis is essential as patient-to-patient heterogeneity limits the utility of single biomarkers.
5. Ability to perform genomic, transcriptomic, *and* proteomic analyses would increase the generality of the technology.

In addition to *in vitro* biomolecular diagnostics, advanced imaging technologies such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are playing an increasingly important role in managing the treatment of disease, and the development of informative diagnostic imaging probes is an area where chemical biology can lead significant advances.¹⁹ Disease relevant small molecule metabolic probes, active site binders, engineered proteins, and novel imaging tags, such as magnetic and optically active nanoparticles, will continue to provide physicians with increasing clarity as to the spread of disease.

The development of informative diagnostic methodologies is absolutely critical if the biomedical research community is to realize the full potential of molecularly-targeted therapeutics. Although early successes from the modern drug discovery process have offered hope for the personalized treatment of disease, a grand challenge now lies in the development of individualized diagnostic tools—a challenge that must be met in order to translate this promise into the improved treatment of human disease. Chemical biologists are well-positioned to lead this charge by expanding their efforts to include the development of informative clinical diagnostic methodologies, which should include collaborations with scientists who offer expertise in emerging technologies that may just be appearing on the horizon.

The practical achievement of individualized therapeutics appears to be increasingly within our grasp and its eventual realization will have profound consequences throughout the field of chemical biology. Most directly affected will be the pharmaceutical industry, which has already begun to move away from the “blockbuster drug” model. While some have suggested that this is a looming crisis for the industry, it can be alternatively viewed as an incredible opportunity. For example, the ability to utilize innovative diagnostic measurements to pre-identify groups of patients that have a high likelihood of responding to a particular molecularly targeted drug will revolutionize the clinical trial process, improving rates of success and dramatically reducing the number of drug candidates lost after substantial financial investment. Furthermore, informative *in vitro* and *in vivo* diagnostic tools will lead to a paradigm shift in the overall perception of disease, replacing organ-

specific views (eg. lung cancer) with broader perspectives that recognize similarities in causative disease factors (eg. mutated *EGFR*) as expanded opportunities for molecularly targeted treatment strategies, ultimately leading to a wider deployment of the powerful therapeutic agents that are the fruits of many chemical biologists' labor.

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Figure 1.
Beyond drug discovery and target validation, there are numerous opportunities for chemical biologists to accelerate the realization of personalized medicine.