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Development of Cures in the Era of Genomic Medicine

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Cancer, in contrast to many other somatic disorders of mankind, is a semi-autonomous from its human host deregulation of cells where complex genetic, epigenetic and metabolic changes lead to a cancer phenotype- incessant growth, resistance to apoptosis, and perpetual mutations and clonal evolution. In depth understanding of biology of tumors has lead not only to spectacular cures and major advancements in the well-being of cancer patients, but it also propelled forward other fields of Medicine where similar pathological processes are at play. In fact, genetic and regulatory changes in cancer cells tend to involve pathways that are usually spared from germline alterations due to incompatibility with normal tissue and organ development [1]. Conversely, non-neoplastic disorders tend to affect genes and metabolic pathways that are more regulatory in nature and more peripheral to the life-sustaining pathways in mammalian cells [2]. Despite these differences, cancer medicine has been offering itself as a unique testing ground for manipulation of these core biological processes in humans.

From perturbation of DNA replication with chemotherapy DNA poisons, the field of oncology moved on to develop a new class of anticancer agents targeting components of cellular signaling systems, usually a kinase of a cell surface receptor that are functionally up-regulated or are products of an amplified gene. This approach is meeting with some success in specific tumor types: for example, trastuzumab against human epidermal growth factor receptor 2 (HER2) in breast cancer cells, bevacizumab against vascular endothelial growth factor (VEGF), cetuximab against epidermal growth factor receptor (EGFR), sorafenib against B-RAF. The lessons and challenges are instructive to other areas of drug development in several ways.

Firstly, success of anti-cancer drug therapy seen in the minority of responders depends on the presence of a mutated or amplified oncogene which is the target for the drug. Identification of such critical activated oncogenes (harboring so-called "driver mutations") in an individual's tumor and matching these oncogenes with a specific drug provides a better chance of clinical benefit. In this respect, "centrality" [3] of the oncogenic driver for the genesis of malignancy, and the rapidity of its pharmacological inactivation [4,5] are the key elements to successful inactivation of the entire signaling system in a given cancer cell. In addition, comprehensive evaluation of multiple molecular targets (mutationally active gene and gene expression patterns) in a patient's tumor [6] may make it possible to identify essential driver mechanisms, or serve as a rationale for combination of specific therapeutic agents, thus giving the patient a viable therapeutic alternative.

Secondly, we have learned that manipulation of a biological system almost invariably leads to selection of "escapees", i.e. in the context of cancer therapy clones of tumor cells that are resistant to the treatment. Similar principles are true for antimicrobial therapy, antiviral and, perhaps, in autoimmune disorders where epigenetic changes may lead to loss of self-tolerance in a subset of T cells [7]. Despite initial responses, patients' tumors eventually progress on these therapies, and the durable responses are seen only in the minority of patients.

Thirdly, as cancer physicians, we have begun training ourselves as clinical cell biologists. It is done very much with the sense that cancer process is uniquely personal. Not only is it personal on the human level as the majority of patients over time face limited opportunities for rational and effective therapies for their tumors. It is also personal, or "personalized", on the level of therapy decisions because we recently came to realization that cancers, even of the same histological and tissue origin type, share only about 10-15% of most common mutations in their genomes [8]. Cancer, as many other human illnesses, is a polygenic disease that arose in a step-wise fashion through sequential acquisition of genomic and epigenetic alterations. Today, the clinical evidence from retrospective analyses [9] and prospective series [10,11] strongly suggests that matching cancer genetic alterations with the specific agent is highly effective [12]. Targeted agents by inhibiting an oncogenic driver in a cancer cell can often cause a rapid and irreversible collapse of the cellular signaling system leading to cancer cell apoptotic death, and to ultimate spectacular therapeutic benefit.

Seeing the promise of innovation, we cannot tolerate status quo as the majority of cancer patients have only 1-2 "textbook" treatment options. Upon progression, many of these young and active individuals may participate in Phase I or Phase II studies of new anticancer agents if they meet the usually strict eligibility criteria and have access to centers that can evaluate investigational agents. When patients participate in these studies, the new agents give response rates of between 5% on average in a Phase I setting, particularly when combined with cytotoxic agents and 10-12% (on average) in a Phase II setting. The problem that needs to be addressed is that in the majority of tumors the driver oncogenic pathways and the points of therapeutic vulnerability are never investigated.

The problems that need to be addressed are:

1. Analytical problem. Integration of information from multiple platforms available to characterize individual cancer (sequencing, transcriptome, proteome profiling, copy number alterations) needs integration on the systems level in order to appreciate the dominant oncogenic mechanism. Such mechanism can be a single oncogenic mutation (driver mutation, e.g. EGFR, BRAF, ABL, KIT), or an oncogenic pathway activated epigenetically (e.g. VEGF in VHL deficient tumors). Currently, such algorithms to identify key oncogenic mechanisms are underdeveloped.

2. Models. Existing preclinical models based on cancer cell lines are NOT predictive of clinical cancers, and that leads to devastatingly low success rate for new drug development. Recent data from immediate human-to-mouse tumor grafts

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showed high predictability of the response in the patient of mouse xenografts trials [13,14].

3. Therapeutic strategy. It has become evident that single-agent interventions in cancer not unexpectedly induce rapid emergence of resistance either via secondary mutations or epigenetic mechanisms. In clinical trials, early attempts to combine agents are often ineffective due to lack of detailed understanding of the interactions between targeted pathways, or a "blanket" approach not taking into account biological differences between individual's tumors. We proposed a concept of synthetic lethality for rational design of targeted drugs combinations [15]. Using siRNA screening approach, we demonstrated that inactivation of critical signaling nodes produced an irreversible deregulation of multiple kinases targets, and an ultimate cancer cell death. We now are interested to test if this approach is valid in the clinic.

4. Socio-economic challenges. With costs of genome sequencing falling exponentially, many individuals will be able to afford their somatic cells genomically profiled to characterize the basic disease mechanisms. Yet, these tools are beyond reach for many vulnerable Americans hit with financial challenges of cancer diagnosis itself. It remains to be seen how soon insurance companies are going to embrace and pay for these services which, on the long run, can be tremendously cost-saving by avoiding futile and ineffective therapies.

Looking to the future of genome-powered medicine and to cancer medicine in particular, we need to start with basic information gathering to characterize cancer genomes of individual patients using next generation sequencing and transcriptome and proteome profiling. Furthermore, geneticists and omics trained pathologists will inevitably become new members of the cancer treatment team. Such teams will also include experts in bioinformatics with skills in pathway modeling, an approach that will provide patients and clinicians with essential molecular targets for pharmacological interventions aimed to disrupt individual patient's cancer signaling systems. By linking such genomic integrative analysis with the clinical database and scientific evidence, we will be able to further develop the genomic medicine. Such genomic medicine will define: i) the targets for individual patients; and ii) the likely-to-benefit population for future interventional clinical trials with rational (i.e. cancer mechanism-based) selection of therapeutic agents or their combinations.

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