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Personalized Cancer Models for Target Discovery and Precision Medicine

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Abstract

Although cancer research is progressing at an exponential rate, translating this knowledge to develop better cancer drugs and more effectively match drugs to patients is lagging. Genome profiling of tumors provides a snapshot of the genetic complexity of individual tumors, yet this knowledge is insufficient to guide therapy for most patients. Model systems -usually cancer cell lines or mice – have been instrumental in cancer research and drug development, but translation of results to the clinic is inefficient, in part, because these models do not sufficiently reflect the complexity and heterogeneity of human cancer. Here, we discuss the potential of combining genomics with high throughput functional testing of patient derived tumor cells to overcome key roadblocks in both drug target discovery and precision medicine.

Roadblocks to Advancing Precision Oncology

Developing new cancer medicines is very inefficient. It is estimated that only 5–15% of investigational cancer drugs reach clinical approval [1, 2]. Cancer models systems such as cell lines or mice are instrumental in cancer research because they are amenable to functional assays [3–6]. Using model systems, both hypothesis-driven and unbiased screening approaches have been used to discover and mechanistically evaluate oncology targets and drugs and most if not all currently used drugs were developed using such approaches. However, hypothesis-driven research is limited by current knowledge and cannot predict all possible targets and therapeutic options. Also, typically used models such as cancer cell lines and mice do not completely capture the complex genetic and epigenetic landscape that each patient represents. For these and other reasons, translation of findings from model systems to the clinic is inefficient and remains as a significant barrier to progress [3, 7–9].

Recently, DNA sequencing and other -omics approaches have been used to describe the genetic aberrations of human cancers with the expectation that this information will increase

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precision in assigning drugs to patients. The obvious appeal of this approach is that the data is obtained from actual human tumors and can be carried out on fixed samples, pathology slides, or blood samples, enabling clinical application. However every tumor carries a complex mosaic of genetic and epigenetic alterations (Figure 1) with largely unpredictable effects on phenotype and predicting which drug will work for any given patient based on genomic analysis alone is not straightforward [10, 11]. Future approaches in precision medicine will need to account for this genetic complexity.

We suggest the broader use of patient derive tumor organoids (PDTOs) as a model system will help overcome some of these roadblocks. Several key advantages are: 1) PDTOs phenotypically and genomically resemble the tumor from which they were derived, 2) PDTOs can be subjected to functional studies, including high throughput drug testing, in a clinically relevant time frame and can be studied both *in vitro* and after transplantation into mice *in vivo*, and 3) Results from PDTOs can be compared to each patient's clinical history in a co-clinical trial format.

Cancer Genomics: A Language in Need of Translation

The Cancer Genome Atlas (TCGA)ⁱ, the International Cancer Genome Consortium (ICGC)ⁱⁱ, and other large scale efforts have provided an unprecedented view of the genomic landscape of cancer [12]. There is no doubt that computational biology approaches will exploit this information to enhance our understanding of the underlying mechanisms of cancer. For example, pan-cancer comparisons reveal common molecular features and underlying pathologies between disparate tumor types, suggesting future therapies may be based on these features rather than tissue type [13–15].

While there are spectacular examples of success of genome guided therapy, for example, imatinib for BCR-ABL fusion chronic myelogenous leukemia (CML) [16–18] and the ALK inhibitor crizotinib for ALK-rearranged non-small cell lung cancers [19–21], these are limited and not applicable to the majority of cancer patients. Indeed, common genetic alterations such as amplification of the MYC oncogenes, (~28% pan-cancer) [15], mutations of the RAS family (~16% of cancers) [22], or alterations of tumor suppressor genes such as TP53 (mutated in 50% of cancers) [23] are difficult to target directly and currently lack FDA approved drugs.

Pointing to the difficulties in implementing genome guided precision medicine, a recent study reported that whole exome sequence analysis of 737 advanced cancers identified a somatic mutation with a matching an FDA approved drug in only three cases (0.4%). Another 71 cases (9.6%) had mutations matched to a drug without current FDA approval [24]. Other studies have suggested a higher percentage of “actionable targets” [25, 26] but the clinical utility of these targets remains to be demonstrated [10, 11, 27]. In recent clinical trials, only ~10–15% of patients were matched to targeted therapies based on genomic evaluations [28, 29] emphasizing challenges to existing clinical trial designs in precision

ⁱ<https://cancergenome.nih.gov/>

ⁱⁱ<http://icgc.org/>

oncology [30–32]. There is a need for additional approaches, including model systems, to translate complex genomics into actionable targets. Recognizing this need, large-scale efforts have been initiated to generate living biobanks of patient derived tumor models; for example the NCI's Human Cancer Model Initiativeⁱⁱⁱ, with a focus on conditionally reprogramed cell models or organoids or the NCI's Patient Derived Models Repository^{iv} with a focus on patient derived xenografts (PDX).

Drug Profiling of Patient Derived Tumor Cells: Both Functional and Personal

Beginning with the groundbreaking work of Dr. Jane Wright, who pioneered *in vitro* drug profiling, drug testing on patient derived cells has been pursued as a strategy to more accurately assign drugs to patients [33, 34]. These early studies demonstrated some success but were handicapped by a number of key factors including the limited number of drugs, mostly genotoxic and non-specific chemotherapies, and imperfect culture methods. For example the use of high serum concentrations which can inhibit the growth of tumor initiating cells, non-physiological oxygen levels which induce culture stress through generation of reactive oxygen species (ROS), and the lack of appropriate growth and developmental factors [35] hampered early attempts to culture tumor cells. Historically, cancer cell lines were selected for rapid proliferation on plastic and so differ in both growth kinetics and heterogeneity from the primary tumors. Other confounding factors in assaying drug responses *in vitro* included the lack of sensitive and accurate cell viability assays, or high-content phenotypic read-outs, and the absence of molecular or genomic data to serve as biomarkers.

A number of breakthroughs have improved on all aspects of *in vitro* drug testing of patient derived tumor cells, including improved cell culture conditions, more sensitive phenotypic assays, and increased number of highly selective gene-targeted agents (Figure 2) [36–38]. The use of low oxygen incubators, serum free media, optimal tissue culture vessels, extracellular matrix and matrigel have improved culture take rate, enabled expansion of 3D organoids preserving fidelity to the original tumor [39–43]. Importantly, tumor derived organoid models phenotypically and genetically resemble the tumor from which they were derived [24, 40, 44, 45], enabling phenotypic analysis in the appropriate and personalized genetic context.

Other advances include improved high throughput methods leading to highly accurate, quantitative cell viability assays [10, 46]. Acoustic liquid handling, as well as improved laboratory automation have increased the precision of miniaturized assays and facilitated the evaluation of drug combinations. Decreasing the number of cells required for each assay saves time, reduces the possibility of emergence of subclones, and enables testing of hundreds of drugs, within days to weeks from sample retrieval [24, 47]. High-throughput automation enables drug combinatorics studies to measure the effect of inhibiting multiple

ⁱⁱⁱ<https://ocg.cancer.gov/programs/HCMCI>

^{iv}<https://pdmr.cancer.gov/>

pathways simultaneously or in sequence, with the aim of overcoming resistance to single agents [48].

Recent studies have begun to test the predictive value of *in vitro* organoid testing. Novel drug combinations identified in PDOs were validated in PDX models and led to regression of chemoresistant, recurrent cancers [24]. Also, drug sensitivity of tumor derived organoids was concordant with patients' retrospective evidence and genomic features [40, 49]. In another example, *in vitro* testing of organoid cultures derived from neuroendocrine prostate cancer was able to distinguish responders from nonresponders to alisertib, an aurora A kinase inhibitor that is under clinical testing [50]. These and other examples are encouraging but more work needs to be done to establish the degree of utility and limitations of *in vitro* drug sensitivity testing.

Drugging Non-Mutated Cancer Vulnerabilities: Synthetic Lethality and Lineage Dependencies

Despite the improvements in *in vitro* drug testing of patient derived cells, its clinical utility is limited by the number of available anticancer drugs. There are currently only ~ 100 cancer genes being targeted in the clinic yet the human genome contains at least 22,000 coding genes [51]. Thus, in addition to more predictive model systems, there is a corresponding need for more targeted agents. The majority of drug development efforts focus on genes that are mutated in cancer such as activated oncogenes [52]. While there are obvious benefits to focusing on such targets and their downstream signaling components, a broader approach to target discovery will almost certainly provide increased opportunities. Cancers have many vulnerabilities beyond mutated genes, for example, synthetic and collateral lethal genes, developmental pathways, lineage dependencies and other non-oncogene addictions [53].

An example of successful targeting of lineage dependencies is given by Bruton's tyrosine kinase (BTK). Although BTK is not mutated in B cell malignancies, it is an effective target because it is required for B cell development. Ibrutinib (Imbruvica), a small molecule inhibitor of BTK, was recently approved for chronic lymphoid leukemia and mantle cell lymphoma [54] and patients have shown dramatic responses. An example of targeting synthetic lethal genes in the clinic is given by the success of PARP inhibitors Olaparib, Rucaparib and Niraparib for use in BRCA mutant breast, ovarian, and perhaps other cancers with defects in the homologous recombination (HR) pathway of DNA repair [55].

However, a challenge with targeting non mutated genes is identifying associated biomarkers to help select which patients might respond. For example, in recurrent ovarian cancers, Niraparib provides benefit to some but not all BRCA mutant cases as well as BRCA wild type cases [56]. Also, we have identified exceptional responders to PARP inhibitors in organoid cultures from a range of pediatric and adult solid tumors without clear links to BRCA pathway status. Recent pan-cancer analysis identified high frequency alterations in DNA damage response genes, which could act as biomarkers to guide the broader use of drugs such as PARP inhibitors that target DNA repair pathways [57].

Clearly, the therapeutic space of cancer dependencies and associated biomarkers is still largely undiscovered and because it includes genes that may not be mutated, novel approaches are required for their discovery. In line with this, the mission of the NCI's Cancer Target Discovery and Development (CTD²) Network is to employ a variety of approaches to identify the next generation of cancer targets [58]^V.

High throughput testing of gene function through functional genomic approaches can be used to sort through hundreds to thousands of genes to identify candidate cancer drug targets. There are several functional genomic platforms in use, including arrayed siRNA and pooled shRNA and CRISPR screens, each with strengths and weaknesses [59–62]. Regardless of platform, these assays have typically been performed using cancer cell lines because of ease of procurement and ability to expand large numbers of cells required for pooled screening approaches.

Technical advances now make it possible to perform functional genomic screens and target discovery using patient-derived tumor cell cultures (Figure 3). Arrayed siRNA screening is a suitable platform for this application for a number of reasons [47, 63]. Because of miniaturization, fewer cells are required which enables the use of early passage cells and limits the emergence of subclones. One can quantify on a genome scale the phenotype of depleting one gene at a time (one gene/well) simultaneously, thereby capturing, with increased sensitivity, effects on cell viability. The use of arrayed screens and high content microscopy enables detection of multiple phenotypes such as DNA damage, signaling pathways, differentiation, migration, or apoptosis [63–67]. In our experience, targets identified using this platform have shown a high rate of validation using orthogonal methods [65, 68] and as discussed below, gave rise to a successful clinical trial.

Identifying biomarkers for targets discovered in cancer cells is challenging because of their inherent genetic complexity (Figure 1). The aggregate of genetic and epigenetic alterations that co-exist in any given cancer can modify the phenotypic effect of target gene modulation in unpredictable ways. To clarify target:biomarker associations, the use of complementary models, such as isogenic cell pairs or tumor cells derived from inbred genetically engineered mouse models (GEMMs) are invaluable (Figure 3). For example, isogenic cell pairs with or without expression of an oncogene or loss of a tumor suppressor gene can be used to identify genes that exhibit synthetic lethality with the cancer gene of interest. These synthetic lethal genes can then be validated using models of increasing complexity including GEMMS, PDXs, and PDOs with similar genetic features to prioritize novel drug targets or to establish unforeseen activity of current drugs and their combinations (Figure 3)[65, 68–71].

Challenges

While proof of concept in the feasibility and utility of high throughput phenotyping using patient derived models has been established, several hurdles remain prior to broader adoption. Obtaining viable tumor cells from patients is not straightforward as this is not

^V<https://ocg.cancer.gov/programs/ctd2>

routine for most pathology laboratories. As each tumor type has specific growth factor or microenvironmental signaling requirements, the long-term expansion of cell lines or organoids can be difficult [42, 43]. Care must be taken to avoid selection of subclones that do not resemble the original tumor. While high-throughput drug sensitivity testing can be done in a clinically relevant time frame, the broader target discovery approach using RNAi or CRISPR methods is more complex, both in its execution and analytics. Even if promising drugs or drug combinations are identified using PDOs, there are significant challenges to use this information to guide treatment because of difficulties in obtaining off-label drugs and lack of guidelines for administering novel drug combinations [72].

Recognizing these challenges, Cure First, a not-for-profit organization, was founded to support functional genomic approaches using patient derived tumor models and to increase awareness in the biomedical and patient community^{vi}. Also, The Society of Functional Precision Medicine was founded to facilitate preservation of viable tumor cells in clinical practice^{vii}. The recent CLIA certification for high throughput drug testing of patient derived tumor cell cultures across solid tumors opens the door to deploy this type of testing in the clinic (Figure 2)^{viii}. The next step will be to determine the predictive value of *in vitro* drug testing through patient registries and clinical trials.

Demonstration of clinical utility will, in turn, pave the way for incorporation of functional assays in the practice of oncology.

Case Study: From Target Discovery in Patient Derived Tumor Cells to Successful Clinical Trial.

Head and neck squamous cell carcinoma (HNSCC), where survival is only 50%, exemplifies the type of tumor that is in need of better therapies [73]. Although DNA sequencing has revealed the mutational landscape of HNSCC in great detail, there are currently no approved targeted drugs for this disease. To determine if functional testing on patient derived tumor cells could identify candidate therapeutic gene targets, high throughput siRNA screens, drug sensitivity, and genomic analyses were performed on a tumor cell culture derived from a patient with aggressive TP53 mutant oral cancer [47]. Whole exome sequencing identified >200 protein coding mutations including TP53, hundreds of amplified genes including c-MYC, and none of these alterations pointed to obvious therapeutic choices. In contrast, siRNA profiling identified novel targets most of which were not mutated or amplified and also enabled distinction between passenger and candidate driver mutations. One of the identified non-mutated targets was WEE1, a tyrosine kinase that regulates the S and G2 cell cycle transitions [68, 74, 75]. Drug sensitivity testing with an oncology focused drug library on the same patient derived culture identified a number of effective drugs including AZD1775, a WEE1 inhibitor under clinical development. WEE1 had also emerged from a set of siRNA screens in squamous cell carcinoma cells derived from carcinogenic-induced

^{vi}www.curefirst.org/

^{vii}www.sfpmed.org/

^{viii}<https://senginemedicine.com/our-work/>

mouse models and was validated in xenograft models of HNSCC [68]. In summary, cross-species comparison as well as siRNA and drug profiling converged on same target.

The identification of WEE1 as a targetable vulnerability in TP53 mutant HNSCC cells gave rise to an investigator initiated Phase I trial with AZD1775 in the neoadjuvant setting (E.Mendez, PI)^{ix}. Stage III/IV HNSCC patients received AZD1775 orally twice a day over 2.5 days on the first week, then in combination with low doses cisplatin and docetaxel, repeated for additional 3 weeks. Remarkably, nine out of ten patients showed a partial or complete response and these responses have been durable, up to 2 years out [76].

These studies demonstrate the feasibility and utility of functionally interrogating a patient's tumor in unprecedented detail to discover novel vulnerabilities and therapeutic options. Further, the ability to perform functional studies in parallel with a clinical trial offers the possibility to ascertain the mechanism(s) underlying responders from nonresponders and to further refine biomarker associations, thereby accelerating the path to clinical approval.

Concluding Remarks

There is no doubt that combining genomics with phenotypic screening in personalized cancer models will play an important role in accelerating drug development and increasing precision in assigning effective drugs to the right patient (see Outstanding Questions). Expanding functional testing to thousands of patient derived cases will strengthen the link between complex biomarkers and therapeutic response. This data will be used to generate a functional atlas of cancer for use in precision oncology (Figure 2).

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Highlights

- In the near future, live tumor sample biopsies will be routine for use in a variety of functional assays.
- Broad functional genomic screens in patient derived cells from every cancer type will be used to generate a comprehensive phenotypic atlas of cancer.
- Combining functional data with descriptive -omics data will provide much needed translation of cancer genomics and will generate multigenic biomarkers of cancer vulnerabilities and drug sensitivities.
- As a result, cancer therapies will become more effective, personalized, and tumor type agnostic.

Outstanding Questions:

What is the predictive value of *in vitro* functional testing in a clinical trials setting?

Can we use *in vitro* functional testing to guide clinical trials; indeed can we adopt clinical trials to an N=1 format?

To what extent can *in vitro* functional testing model tumor/stroma and tumor/immune system interactions?

What is the extent of intra and inter-tumor functional heterogeneity?

Figure 1.

Every patient's tumor has a unique mosaic of genomic alterations. Shown are genomic alterations in serous ovarian cancer from TCGA taken from CBioPortal. Amplification of c-MYC MYCN and LMYC is seen in ~80 % of cases. TP53 is mutated in over 95% of cases. However, these common alterations are embedded within many additional patient-specific genomic alterations which may influence drug response. Red: amplified, Blue: deleted, Black: mutated.

Figure 2. Patient derived models for precision oncology.

Shown are key steps to enable functional drug testing on patient derived organoids and generation of a functional atlas of cancer.

Figure 3. A target discovery and validation engine.

1. A range of models can be used for target discovery. a) Isogenic cell pairs with one of the pair engineered to carry a single lesion such as a tumor suppressor deletion or oncogene mutation. This system is the cleanest to identify synthetic lethal genes. b) Tumor cells derived from GEMMs and other mouse models of cancer. Tumors can be derived from mice of the same genetic background and experimental conditions thus reducing genetic and experimental variables. c) Low passage patient derived tumor cells. The advantage of these models is their genetic and biologic relevance to actual patients. Comparing results across a set of complementary models increases confidence in target validity.² The use of arrayed siRNAs as target discovery tool enables testing one gene at a time and also can be used in primary cells from diverse models. Integration of functional screen results with genomic data also helps to prioritize targets.³ A range of tools and preclinical model systems are used to validate targets and link to candidate biomarkers. 4. The spectrum of evidence gathered can be marshalled to warrant clinical testing of candidate targeted agents.