

Emerging Opportunities for Target Discovery in Rare Cancers

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Rare cancers pose unique challenges to research due to their low incidence. Barriers include a scarcity of tissue and experimental models to enable basic research and insufficient patient accrual for clinical studies. Consequently, an understanding of the genetic and cellular features of many rare cancer types and their associated vulnerabilities has been lacking. However, new opportunities are emerging to facilitate discovery of therapeutic targets in rare cancers. Online platforms are allowing patients with rare cancers to organize on an unprecedented scale, tumor genome sequencing is now routinely performed in research and clinical settings, and the efficiency of patient-derived model generation has improved. New CRISPR/Cas9 and small-molecule libraries permit cancer dependency discovery in a rapid and systematic fashion. In parallel, large-scale studies of common cancers now provide reference datasets to help interpret rare cancer profiling data. Together, these advances motivate consideration of new research frameworks to accelerate rare cancer target discovery.

Introduction

A cancer type is typically designated as “common” or “rare” on the basis of its incidence. While no universally accepted cutoff exists, the National Cancer Institute (NCI) defines rare cancers as those occurring at a frequency below 15 cases per 100,000 individuals per year (National Cancer Institute, 2007). According to this definition, only 11 adult cancer types are common in the US (prostate, breast, lung, colon, uterine corpus, bladder, rectum, ovary, kidney, melanoma, and non-Hodgkin lymphoma) (Greenlee et al., 2010). The remaining adult cancer types, collectively accounting for approximately 25% of adult tumors overall, are thus considered rare (Greenlee et al., 2010). All pediatric cancers are classified as rare when the above definition is applied (Ward et al., 2014).

Despite their high collective occurrence, basic biological and clinical knowledge of many individual rare cancer types is lacking. Many of the barriers to research directly stem from the low incidence rates for rare cancer types. While tens of thousands of patients may be living with a given rare cancer (Orphanet, 2016), the geographic dispersion of rare cancer patients often limits the number of cases seen at any one institution. As a result, knowledge of rare cancers is often based on single-patient case reports (Tomich et al., 2017; Simonetti et al., 2016; Panda et al., 2016; Afani et al., 2016) or single-institution retrospective analyses that describe small cohorts of patients seen over many decades (Arikan et al., 2014; Karatayli-Ozgursoy et al., 2016; Worhunsky et al., 2015). This evidence, which can be anecdotal, is in stark contrast to the multi-institutional cancer statistics studies routinely reported for common cancer types (National Cancer Institute, 2016b). Low incidence rates also make clinical trial recruitment for rare cancers extremely challenging, stalling efforts to test emerging therapeutic hypotheses (Casali et al., 2015; Tan et al., 2003). In basic research settings, a scarcity of rare tumor tissue and patient-derived models can preclude

well-powered studies aimed at elucidating underlying biology (Boehm and Golub, 2015).

Disparities in the study and understanding of common versus rare cancers are perhaps best illustrated by the respective availability of effective therapeutic interventions. Selected examples can be drawn from the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines), an evidence-based set of guidelines for the clinical practice of adult oncology in the US (www.nccn.org). Over 20 Category 1 interventions (meaning uniform consensus that the intervention is appropriate and based on a high level of evidence) exist for breast and prostate cancer, the most common cancers affecting women and men, respectively (NCCN Guidelines, 2017b; NCCN Guidelines, 2017c; Siegel et al., 2017). By contrast, no Category 1 interventions exist for either chordoma or chondrosarcoma, bone cancer types each of which affects fewer than 1,000 individuals per year in the US (NCCN Guidelines, 2017a; McMaster et al., 2001; Orphanet, 2016).

For many patients with a rare cancer, the lack of effective treatment regimens translates to a suboptimal clinical outcome. Indeed, a study of population-based cancer registry data on European patients reported that rare cancer patients on average had worse outcomes, with estimated average 5-year relative survival rates of 47% for patients with rare cancers (defined in the study as an incidence of <6/100,000/year) versus 65% for those with common cancers (Gatta et al., 2011). In addition to a paucity of effective treatments (owing in some cases to a limited understanding of disease-modifying targets), other factors contributing to poor outcomes may include delays in obtaining a correct diagnosis, lack of treatment guidelines, fewer clinical trials dedicated to rare cancers, and less investment in drug development (Blay et al., 2016; Panageas, 2015).

With respect to knowledge of therapeutic targets in rare cancers, which is the focus herein, new advances may help

overcome historical challenges. Patients with rare cancers are increasingly interconnected online and costs of genome sequencing in both basic research and clinical settings have dropped precipitously. Indeed, it is estimated that in aggregate, nearly 3,000 tumor samples corresponding to exceedingly rare cancer types have been subjected to whole-exome, whole-genome, or other next-generation sequencing (Figure 1A). Further, the success rates of generating new organoid and cell-line models have increased substantially. These foundational advances make it possible to apply new CRISPR/Cas9 technologies and small-molecule libraries to map the dependencies for each rare cancer type in the laboratory, leading to more robust therapeutic hypotheses. Here, we describe progress in each of these areas, illustrating how the convergence of these approaches provides a framework for enabling rare cancer target discovery in an increasingly systematic fashion.

Overcoming Biospecimen Scarcity via Online Platforms

While patients with a rare tumor type may be geographically segregated, many have recently leveraged the Internet to virtually convene, organize, and engage in research. This online aggregation now facilitates rare cancer research on a scale that had once been challenging to achieve.

In some cases, the virtual organization of rare cancer patients has been mediated by consortia or foundations expressly dedicated to advancing rare disease research. Umbrella organizations such as the National Organization for Rare Disorders and the Rare Cancer Research Foundation provide online tools and infrastructure to disease-specific organizations, in turn enabling rare cancer patients to participate in clinical and basic research. This foundation-assisted engagement of rare cancer patients via online platforms has in several cases boosted study sample sizes and thereby enabled large-scale studies. For example, the Leiomyosarcoma (LMS) Direct Research Foundation (LMSDR) engaged LMS patients online in order to curate 300 archival samples, resulting in the discovery of new prognostic biomarkers and molecular subtypes (Edris et al., 2012; Beck et al., 2010; Leiomyosarcoma Direct Research Foundation, 2016). Similarly, the Multiple Myeloma Research Foundation (MMRF) has leveraged a strong online community to complete the sequencing and clinical annotation of 190 and 420 patient tumors, respectively (Multiple Myeloma Research Foundation, 2015).

In other cases, patients have self-organized online and disseminated knowledge of their own disease (Call et al., 2010; Hauber et al., 2011). Illustrative examples include the role of patients with gastrointestinal stromal tumor (GIST) or chronic myeloid leukemia (CML) in the development and application of therapies targeting the KIT and Bcr-Abl oncoproteins (see Box 1). New social media platforms, such as Facebook and Twitter, now enable such virtual patient aggregation on an even larger scale (Seltzer et al., 2014; Katz et al., 2016). For example, Facebook groups exist for the majority of rare cancer types, and these groups may currently include over 1,000 members (Figure 2). In the future, these social media platforms may accelerate clinical trial enrollment for patients with rare tumors. Today, these proof-of-concept examples demonstrate that tumor profiling and clinical studies that were once prohibitively

large for rare cancer types now can be achieved through direct engagement with patients online.

Mapping Rare Cancer Genomes

Identifying rational interventions for each rare cancer type will likely be aided by genomic and cellular characterization of these tumors. Ideally, such information might include a full map of germline and somatic variation, together with a survey of the malignant, stromal, and immune cell types and states present in each rare tumor.

Mapping the germline basis of rare cancers can provide insight into causative variants as well as therapeutic opportunities. The completion of reduced-representation haplotype maps of the human genome (International HapMap 3 Consortium et al., 2010) made large-scale genome-wide association studies (GWAS) possible. In parallel, the recognition that germline susceptibility loci in the DNA-repair pathway occur across tumor types and render tumors sensitive to PARP inhibition (Pritchard et al., 2016; Matulonis et al., 2016; Kaufman et al., 2015) provided proof of concept that mapping the germline basis of tumors may lead to new inclusion criteria for basket trials (in which patients are selected based on the molecular, as opposed to histological, features of their tumors). However, while in aggregate over 800 germline cancer-susceptibility SNPs have now been discovered (NHGRI-EBI GWAS Catalog; MacArthur et al., 2017; Burdett et al., 2017), the statistical power required to map predisposition associations initially necessitated a focus on common cancer types or familial syndromes.

However, new integrated strategies are shedding light on rare cancer susceptibility despite smaller cohort sizes. For instance, the initial observation that *LMO1* variation led to neuroblastoma susceptibility was bolstered by somatic copy number analysis and RNAi-based validation (Wang et al., 2011). Similarly, the insight that variation at the *NF1B* transcription factor locus predisposed to metastatic osteosarcoma was strengthened by a transposon-based genetic screen (Mirabello et al., 2015). A complementary approach leverages the divergent incidences of rare tumors across populations. For instance, while nasopharyngeal carcinoma is rare in the US, it is more common in parts of China, enabling appropriately powered association studies in this population (Cui et al., 2016; Chang and Adami, 2006).

New advances promise to further accelerate the pace of discovery of the germline basis of rare tumors. Large-scale efforts in data sharing under the auspices of The Global Alliance for Genomics and Health are aiming to create international frameworks for responsible data sharing (Global Alliance for Genomics and Health, 2016). The recognition that a large number of small, siloed rare disease datasets impede discovery propelled the launch of a Matchmaker Exchange (www.matchmakerexchange.org). This project provides a federated platform to connect rare disease genotypes and phenotypes through a common application programming interface (Philippakis et al., 2015). Remarkably, over 120,000 human exomes and 15,000 genomes have now been sequenced and aggregated (Lek et al., 2016; Genome Aggregation Database, 2017), providing an essential reference dataset for rare cancer predisposition studies to come.

In parallel to these advances in germline genomics, over the last decade there has been considerable progress in the

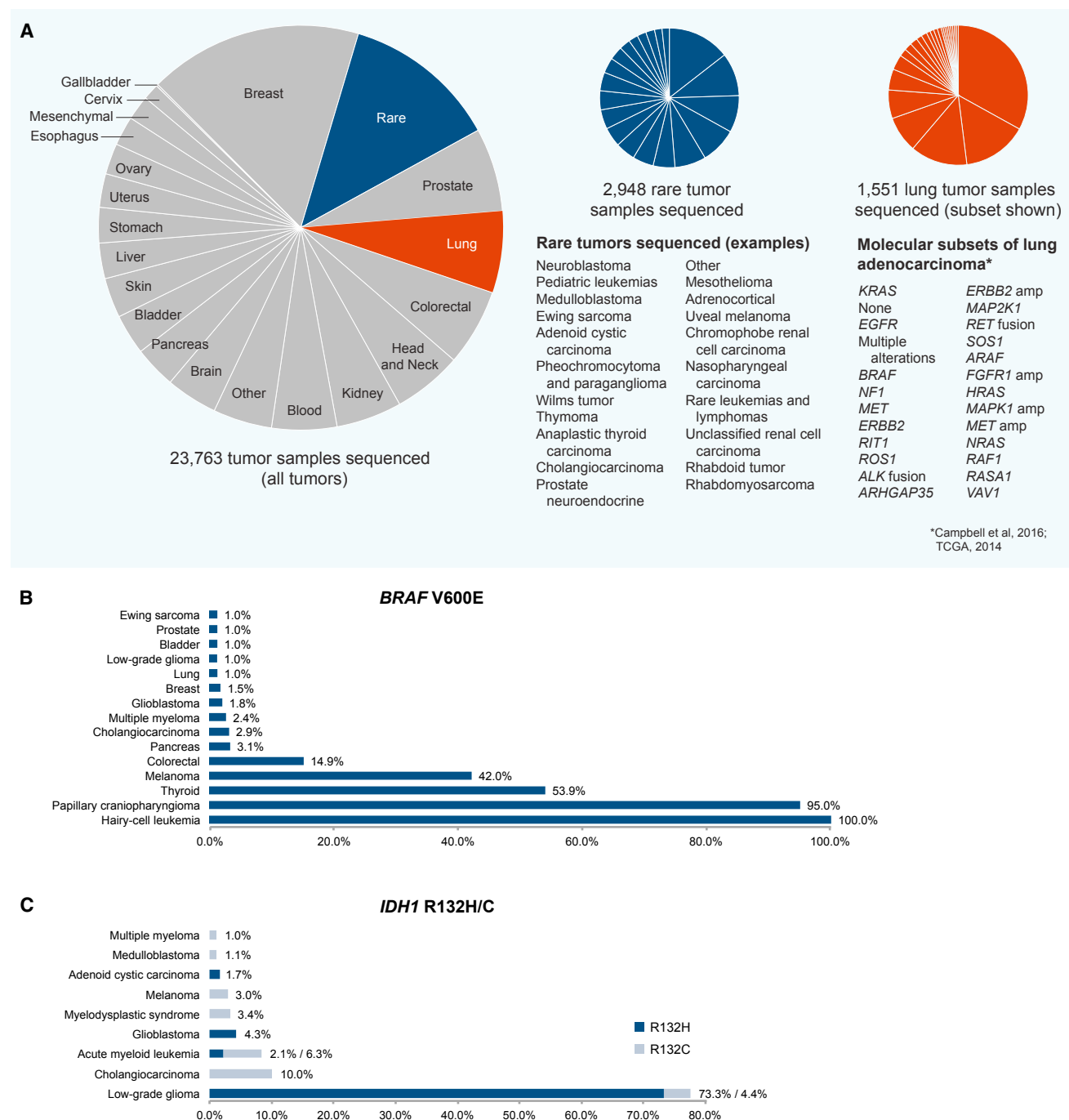


Figure 1. Progress toward the Genomic Characterization of Rare Cancers

(A) Cancer types and subtypes that have been analyzed using whole-exome, whole-genome, or other next-generation sequencing to date. Left, all tumor samples by lineage (source data: www.cbioportal.org; <https://gdc.cancer.gov/>; Brastianos et al., 2014; Tiacci et al., 2011). Center, examples of rare tumor sequencing studies performed to date; “rare” is used in the figure to describe exceedingly rare cancers with an estimated incidence below $\sim 1/100,000$ in a population. Due to the evolving taxonomy of cancers, some subjective decisions were made with respect to classifying unusual subtypes of common cancers (incidence below $\sim 1/100,000$) as “rare” in this pie chart. Rare cancer types are listed in order of decreasing study size. Right, molecular subsets of lung adenocarcinoma. Molecular subtypes were identified using a cohort of 227 lung adenocarcinoma cases with complete data and expert histological review originally reported by Cancer Genome Atlas Research Network (2014) and re-analyzed by Campbell et al. (2016). The list of known and putative receptor tyrosine kinase/Ras/Raf pathway driver genes was derived by Campbell et al. (2016). Subtypes are listed in order of decreasing frequency.

(B) Frequency of BRAF V600E mutations across rare and common tumor types (source data: www.cbioportal.org).

(C) Frequency of IDH1 R132H/C mutations across rare and common tumor types (source data: www.cbioportal.org). cBioPortal and GDC datasets were accessed Feb-March 2017.

Box 1. Leveraging the Internet to Accelerate Rare Cancer Research: The Case of Imatinib

The therapeutic development and ultimate FDA approval of imatinib for chronic myeloid leukemia (CML), a rare cancer with approximately 9,000 new cases per year in the US (Siegel et al., 2017), is an example of the successful use of the Internet to accelerate translational rare cancer research. In parallel, patients with another rare cancer in which imatinib is effective, gastrointestinal stromal tumor (GIST), successfully leveraged online resources to have an impact on the course of their disease.

In 1999, CML patients who were enrolled in a phase I study testing the targeted inhibition of the oncogenic Bcr-Abl fusion protein in CML were experiencing disease remission following treatment with the Bcr-Abl inhibitor STI571 (later named imatinib) (Druker et al., 2001; The New York Times, 2009). Prior to publication of the study findings, patients treated with this drug as part of the clinical trial began disseminating news of their responses in online patient chat rooms. While knowledge of these anecdotal clinical responses motivated other CML patients to seek inclusion in a trial, the pharmaceutical company Novartis had not made sufficient quantities of imatinib to enable a large-scale phase II trial. Consequently, a patient with CML drafted a petition, addressed to the then-CEO of Novartis, requesting that Novartis scale production of the drug. Using the Internet, this patient identified at least 2,000 additional patients to sign the petition. In response, Novartis increased production of imatinib, permitting the enrollment of many additional patients as part of a phase II trial (The New York Times, 2001). Imatinib was approved for CML shortly thereafter (Cohen et al., 2002).

In addition to its use for the treatment of CML, imatinib was approved for the treatment of GIST in 2001 (Dagher et al., 2002). In this cancer type, the anticancer activity of imatinib is mediated through inhibition of another protein target, KIT, which is commonly activated by gene mutation in GIST tumors (Demetri, 2001). Historically, a subset of GIST patients have been misdiagnosed with leiomyosarcoma (LMS), which is typically treated with chemotherapies largely ineffective against GIST (Price et al., 2007). From 1998 to 2000, prior to the approval of imatinib for GIST, hundreds of patients misdiagnosed with LMS joined an active LMS online community, part of the Association of Cancer Online Resources website, and were advised by other group members to request testing for the *KIT* mutation. These patients were told that their physicians might not have been familiar with this new test. Through these online exchanges, hundreds of misdiagnosed patients requested testing for the *KIT* mutation, and those who were KIT positive were ultimately diagnosed with GIST. Obtaining a correct diagnosis and thus qualifying for treatment with imatinib is expected to have dramatically improved clinical outcomes for many of these patients (Frydman, 2009).

Furthermore, an online support group, the Life Raft Group (LRG) (www.liferaftgroup.org), emerged in 2000 from these engaged GIST patients. Using online resources, GIST patients receiving imatinib as part of a trial shared symptoms and side effects of treatment (The Life Raft Group, 2000). The patient-driven database maintained by LRG has enabled long-term retrospective analyses on KIT-positive GIST patients treated with imatinib (Call et al., 2012).

development and implementation of new technologies to characterize somatic alterations in tumor genomes. New second-generation sequencing technologies and applications (reviewed in Meyerson et al., 2010) have permitted investigators to detect somatic genomic and epigenomic variation from individual tumors with increased efficiency and resolution. In 2008, the report of the application of whole-genome sequencing to a single acute myeloid leukemia tumor sample (Ley et al., 2008) and the first report from The Cancer Genome Atlas (TCGA) project, focused on glioblastoma (Cancer Genome Atlas Research Network, 2008), launched the era of somatic cancer genomics in earnest.

The progress over the last decade has propelled our understanding of the somatic genomic basis of both common and rare cancers. Over 140 such sequencing studies have now been reported and deposited into the NCI's Genomic Data Commons (GDC) and/or other public databases (<https://gdc.cancer.gov/>; dcc.icgc.org/; www.cbioportal.org), totaling over 23,000 tumor samples subjected to whole-exome, whole-genome, or other next-generation sequencing (Figure 1A). It is estimated that nearly 3,000 of these tumor samples represent exceedingly rare cancer types (Figure 1A).

The pursuit of a genomic understanding of common and rare cancers has been mutually beneficial. In one direction, a suite of technological advances, initially developed and applied to common cancers, has now enabled genomic analysis of rare cancers. Reciprocally, in some cases, rare tumors exhibit

striking genomic homogeneity (for instance, near universal *SMARCB1* loss in malignant rhabdoid tumors [Lee et al., 2012]; *BRAF* mutations in papillary craniopharyngiomas [Brastianos et al., 2014] and hairy-cell leukemia [Tiacci et al., 2011]; and *IDH1* mutations in low-grade gliomas [Yan et al., 2009]), enabling genomic discoveries with small sample cohort sizes that are pertinent to common and rare cancers alike (Figure 1B–1C). In this regard, rare cancer types have the potential to provide disproportionate insight into tumor biology in spite of their low incidence. Still, for many rare cancer types, a genomic understanding remains incomplete or absent.

Excitingly, building on the success of the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative for pediatric cancers (Mullighan et al., 2009; Pugh et al., 2013; Chun et al., 2016), a series of ten rare adult tumor types is now being analyzed as part of TCGA, leading to new insights into these diseases. For example, despite an extremely low incidence, 173 cases of neuroendocrine-based pheochromocytoma (PCC) and paraganglioma (PGL) tumors have been collected and analyzed, leading to the discovery of novel WNT-activating *MAML3* and *CSDE1* alterations and the convergence of germline and somatic alterations in the *RET*, *NF1*, and *VHL* genes (Fishbein et al., 2017). Sequencing of chromophobe renal cell carcinoma (ChRCC) revealed novel structural rearrangements at the *TERT* promoter and novel mtDNA mutations (Davis et al., 2014). As another example, a relationship between whole-genome doubling and aggressive disease was

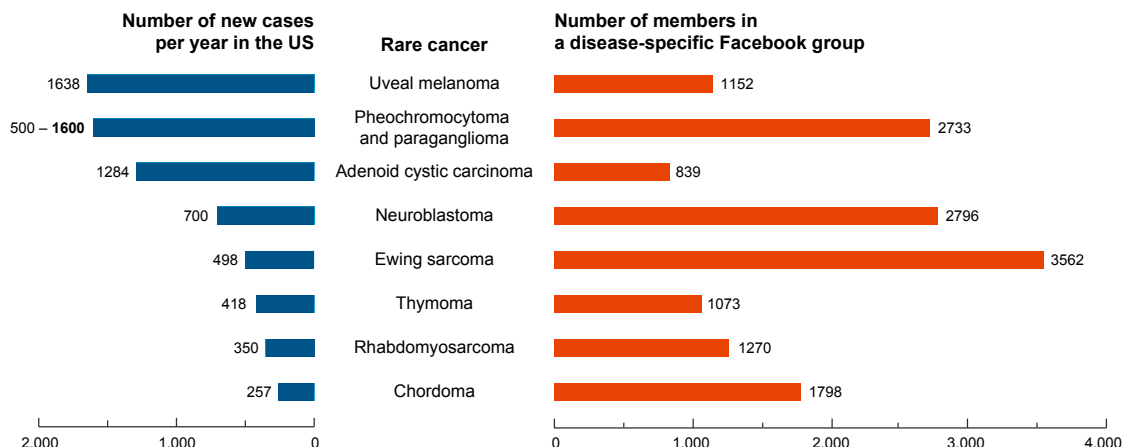


Figure 2. Aggregating Patients with Rare Cancers via Social Media Platforms

Social media platforms, such as Facebook, are a vehicle to connect patients with rare cancers. Depicted are eight cancer types that are exceedingly rare, typically precluding well-powered studies at any one institution. However, there now exists at least one Facebook group relevant to each cancer type (right, in orange). Membership in these Facebook groups sometimes exceeds the number of new cases of the disease per year in the US (left, in blue). While members may not all be patients living with disease, these groups reflect disease-specific communities that are coalescing via online platforms and may translate to increased access to patients for research studies. Number of new cases per year in the US is based on the current estimated US population (321 million). Facebook data were accessed on July 2, 2017; group numbers are subject to change.

discovered in adrenocortical carcinoma (Zheng et al., 2016), pointing to the importance of genome structure in the etiology of certain rare tumors. In pediatric cancers, the discovery of novel fusion proteins is providing clear mechanistic hypotheses, such as the discovery of the MYB-QKI protein driving pediatric angiocentric gliomas (Bandopadhyay et al., 2016).

In many cases, these rare cancer genome studies point directly to new cancer targets that had previously been overlooked. For instance, the observation that mutations in chromatin-regulating genes occur across cancer types (Garraway and Lander, 2013) has now been extended to a series of rare tumor types. Examples include *BAP1* mutations in uveal melanoma and cholangiocarcinoma (Harbour et al., 2010; Jiao et al., 2013); *MLL3* mutations in cholangiocarcinoma (Ong et al., 2012); and *SMARCA2*, *KDM6A*, and *ARID1A* mutations in adenoid cystic carcinoma (Stephens et al., 2013; Ho et al., 2013; Ross et al., 2014). Further, potentially targetable mutations in the G-protein alpha subunit are characteristic of uveal melanoma (Van Raamsdonk et al., 2009). In some cases, direct possibilities for therapeutic intervention have emerged, such as the discovery that PCC/PGL tumors can harbor mutations in genes (including *BRAF* and *FGFR1*) for which approved therapies already exist (Fishbein et al., 2017). Similarly, mutations in the FGF-IGF-PI3K pathway, including in the *FGFR2* gene itself, were found to be harbored by up to 30% of adenoid cystic carcinomas (Stephens et al., 2013; Ho et al., 2013).

Looking ahead, in addition to bulk tumor measurements, recent advances in plate- and droplet-based single-cell sequencing have now made it possible to profile tumors at unprecedented cellular resolution (Tirosh et al., 2016a, 2016b). In these studies, the malignant, stromal, and immune composition of each tumor can be resolved. As single-cell genomic studies increasingly point toward causative mechanisms (Tanay and Regev, 2017), the implementation of such advanced technology may soon be routine in clinical settings and applied to rare tumors.

More generally, these and other cancer genome studies point to eroding distinctions between rare and common tumors and to their complementarity. For example, genomic analysis of common cancer types, such as lung adenocarcinoma, suggests that molecular subcategorization into collections of rare, molecularly distinct “tumor types” (sharing a common etiology or histology) has high clinical relevance (Figure 1A). Reciprocally, now that sample collection bottlenecks are beginning to be overcome for rare cancers, in some cases it may be possible to further leverage their homogeneity to power the analysis of cancer genomes and discover genes and variants inducing tumor fitness, with smaller sample numbers than might otherwise be needed.

Finally, alongside the generation of cancer genome data by individual laboratories and centers, infrastructure to support data sharing, controlled access, and advanced analysis across cancer genome studies may further enable appropriately powered studies of rare tumors. The recent launch of the NCI’s GDC (<https://gdc.cancer.gov/>) establishes a unified data repository that harmonizes existing cancer genome data and thereby permits direct comparison of datasets generated by different large-scale research programs. Further, the GDC supports submission of data from other community- and investigator-led sequencing projects, including those studying rare tumor types. For example, the MMRF is depositing its genomic and clinical data on multiple myeloma in the GDC (National Cancer Institute, 2016a). In the future, a shift to cloud-based data platforms may increase the flexibility, reliability, and security of genomic analyses, as well as reduce costs, through harnessing the elastic compute capacity of commercial clouds such as Google, Amazon, or Microsoft (Stein et al., 2015). The NCI’s Cancer Genomics Cloud Pilots program is helping to hasten this transition and democratize access to cancer genome data.

Advances in Clinical Tumor Sequencing

In parallel to the cohort-based research studies described above, tumor sequencing is increasingly being used in clinical

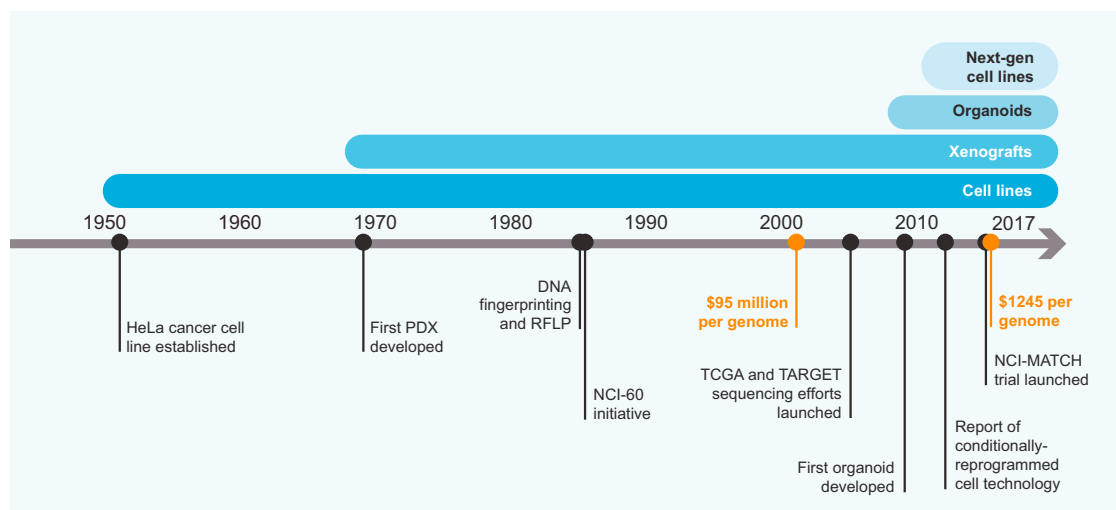


Figure 3. Advances in the Development of Patient-Derived Models

Timeline describing key developments in the generation of patient-derived models. Declines in sequencing costs (orange points); and the emergence of model types, including cell lines, xenografts, organoids, and “next-generation” cell lines, are highlighted (source data: [Rygaard and Povlsen, 1969](#); [Jeffreys et al., 1985](#); [The Cancer Genome Atlas, 2005](#); [Wetterstrand, 2016](#); and references cited in the main text).

settings to guide therapeutic decision making for individual patients ([Abrams et al., 2014](#)). Historically, pathologists relied primarily on the histology of tumor tissue to subcategorize cancers. Over the last several decades, the clinical implementation of flow cytometry, multiplex ligation-dependent probe amplification, reverse transcription (RT)-PCR, and fluorescence *in situ* hybridization allowed pathologists to further subcategorize cancers, leading to changes in clinical management. As one illustrative example, the pediatric tumor type formerly treated uniformly as “small-round-blue-cell” tumor is now subclassified according to the presence of specific fusion transcripts (e.g., *EWS-FLI1* versus *PAX3-FKHR*), leading to distinct treatment regimens ([Lewis et al., 2007](#)).

In more recent years, the somatic sequencing of individual rare cancer types, driven largely by cost reductions ([Figure 3](#)), has revealed additional key diagnostic classifications that are likely to inform prognosis and targeting strategies. For instance, analysis of ChRCC confirmed that this rare tumor is a distinct disease entity from the more common clear cell renal carcinoma, suggesting against the direct implementation of clear cell RCC therapies for such tumors ([Davis et al., 2014](#)). As another example, adenoid cystic carcinomas of the breast were found to lack mutations and copy number alterations characteristic of other triple-negative breast cancers ([Martelotto et al., 2015](#)). The genomics-based subclassification of pediatric medulloblastoma or leukemia facilitates risk stratification ([Jones et al., 2012](#); [Mullighan, 2013](#)). Finally, cholangiocarcinoma genomics revealed distinct mutational patterns between cases induced (versus those not induced) by intrahepatic *Opisthorchis viverrini* infection, suggesting distinct therapeutic approaches might be needed within the same rare tumor type based on the causative etiology ([Chan-On et al., 2013](#)).

In some instances, technologies have made it possible to identify novel oncogenic drivers in rare cancers with potential benefits to current patients. To provide several illustrative exam-

ples, as outlined above, improved outcomes with imatinib treatment in gastrointestinal stromal tumor (GIST) were achieved based on the discovery of mutations in the *KIT* tyrosine kinase gene (see [Box 1](#); [Heinrich et al., 2008](#); [Tuveson et al., 2001](#)). In addition, the discovery of *NTRK* fusions across adult and pediatric cancers (e.g., thyroid cancers and infantile fibrosarcoma) has led to clinical trials with NTRK-targeted agents in adults and children ([Stransky et al., 2014](#); [Knezevich et al., 1998](#); NCT02576431).

The cohort-based genomic discoveries made as part of the TCGA, International Cancer Genome Consortium, and TARGET initiatives have aided the design of more cost-effective sequencing panels, facilitating the testing of larger numbers of rare cancer samples in clinical settings. Individual hospitals ([Wagle et al., 2012](#); [Cheng et al., 2015](#); [Roychowdhury et al., 2011](#)), for-profit companies ([www.foundationmedicine.com](#)), or consortia ([www.rarecancergenome.org](#)) now routinely offer such panel tests to patients and clinicians to guide individual treatment options or in certain cases have performed extensive sequencing (e.g., whole-genome, whole-exome, and transcriptome) on patient tumors.

Proof-of-concept studies determining the feasibility of such studies are now complete. For example, for rare pediatric tumors, initial CLIA sequencing efforts confirmed that many parents and children wish to have such testing performed, results could be returned over a clinically practical time frame, and that “actionable” gene mutations with matched therapies could be identified in a subset of patients ([Harris et al., 2016](#); [Parsons et al., 2016](#); [Mody et al., 2015](#)). These initial feasibility studies provided rationale for the NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) trial and the NCI-Children’s Oncology Group (NCI-COG) Pediatric MATCH trial, nationwide trials to test the hypothesis that matching a tumor’s genomic profile with potential targeted agents will improve outcomes in adults and children, respectively (NCT02465060; NCT03155620).

Accordingly, large-scale precision oncology data-sharing projects are emerging, such as the AACR Project Genomics Evidence Neoplasia Information Exchange (GENIE), which is coordinating the aggregation and release of clinical cancer sequencing and patient outcome datasets across multiple institutions. Similarly, in support of the National Cancer Moonshot initiative, Foundation Medicine, Inc. has now made approximately 18,000 clinical sequencing results available, including many from rare tumors (Foundation Medicine, 2016). Together, these technologies, datasets, and sharing initiatives should accelerate the path toward precision oncology for both common and rare cancers (reviewed in Hyman et al., 2017).

Advances in Generating Patient-Derived Models from Rare Cancers

While clinical trials provide one path to confirm relationships between the genetic basis of rare tumors and their associated therapeutic vulnerabilities, a complementary approach relies on the generation and application of laboratory-based models so as to inform future clinical testing. Historically, few or zero models existed for most rare cancer types (Barretina et al., 2012). Now, a diversity of model types, including patient-derived xenografts (PDXs), organoid cultures, and “next-generation” cell-line models (as defined below), coupled with clinical information, is being developed for many rare cancers (Figure 3).

Cancer cell lines have been used for nearly three-quarters of a century to identify biological mechanisms and test novel therapeutic agents. In 1951, the first human cancer cell line, HeLa, was established from a cervical tumor (Scherer et al., 1953), and this proof-of-concept demonstration laid the groundwork for the development of additional cell lines. Over the next four decades, efforts to establish additional cancer cell lines from patients achieved modest success, culminating with the aggregation of a panel of 60 common cancer cell models representing nine tumor types as part of the National Cancer Institute-60 (NCI-60) collection in the late 1980s (Shoemaker, 2006) and approximately 1,000 cell-line models by 2012 (Barretina et al., 2012; Garnett et al., 2012).

In aggregate, these efforts yielded approximately 10–20 cell lines annually. Several key bottlenecks prevented progress for most cancer types, including rare cancers, including suboptimal *ex vivo* propagation technologies (<1% success rates overall), undetected mycoplasma contamination (Callaway, 2014), and extensive cross-contamination that was later detected (Yu et al., 2015) (reviewed in American Type Culture Collection Standards Development Organization Workgroup ASN-0002, 2010). Furthermore, the lack of clinical annotation and heterogeneity retained by even the successful models remained suboptimal. Despite these limitations, recent work suggests that some findings in cell lines have indeed been recapitulated in patient tumors and vice versa (Sharifnia et al., 2014; Gazdar et al., 2010; Masters, 2000).

Technological advances are now facilitating the generation of high-quality laboratory models representing many rare tumor types. In particular, new technologies now make it possible to generate patient-derived cancer cell lines with substantially higher success rates than historical approaches (Ince et al., 2015; Liu et al., 2012; Oie et al., 1996) (Figure 3). For example, the use of a Rho kinase inhibitor (Y-27632) along with condi-

tioned media from 3T3-J2 murine feeder cells has enabled the generation of models from tumor epithelial cells (Liu et al., 2012). While traditional cell lines have been passaged for many decades, do not have coupled clinical annotation, and tend to lack the ability to recapitulate tumor histology when implanted into animals, many of these “next-generation” cell lines overcome these barriers. As one example of the utility of such cell lines, the aforementioned Rho kinase inhibitor-based approach facilitated the generation of the first model of a recurrent respiratory papillomatosis, together with matched normal tissue. This advance led to the discovery of an effective therapeutic intervention for the same patient (Yuan et al., 2012).

Other applications demonstrate new opportunities to model rare tumor types or subtypes. Soon after the discovery of the *DNAJB1-PRKACA* fusion transcript driving fibrolamellar hepatocellular carcinoma (Honeyman et al., 2014), a transplantable tumor line of this rare cancer was developed (Oikawa et al., 2015). The recent development of a cell-line model from a rare undifferentiated pediatric sarcoma demonstrated how the derivation of a single rare cancer model can be used in high-throughput screens to drive new therapeutic discoveries (Hong et al., 2016). In other applications, cell culture models were generated from individual lung cancer patients that had progressed after EGFR- or ALK-targeted therapies, or from the circulating tumor cells of advanced breast cancer patients, and were subjected to drug testing (Crystal et al., 2014; Yu et al., 2014). As the genomic and clinical annotation of patient tumors and derived models is now cost-effective and feasible, the quality and utility of each successful cell-line model is improved. Overall, the use of such models to nominate effective therapeutic options for relapsed patients in real time represents an exciting, but challenging future direction (recently reviewed in Friedman et al., 2015). Validating the clinical utility of such *ex vivo* precision functional genomic diagnostic tests remains a high priority for the field.

Importantly, some aspects of cellular physiology and heterogeneity may be inadequately retained in cell-line cultures. The recent development and application of “organoid” technology (Sato et al., 2009) provide a new opportunity to model cancer *ex vivo* while retaining some important physiology (Figure 3). Briefly, a cocktail of cytokines and growth factors is used in conjunction with Matrigel to propagate tumor cells in a three-dimensional matrix, retaining aspects of tissue architecture (reviewed in Clevers, 2016). Some cancers and cell types for which establishing standard cell-line models has been challenging, including prostate cancers and nonneoplastic pancreatic cells, can instead be propagated as organoids (Gao et al., 2014; Boj et al., 2015). The use of patient-derived tumor organoid cultures for drug screening has enabled researchers to identify personalized therapeutic hypotheses (van de Wetering et al., 2015).

A complementary approach involves the derivation of PDXs from rare tumors, which may preserve aspects of tumor heterogeneity and microenvironmental influences that are lacking in organoid or cell-line cultures (Izumchenko et al., 2016; Morelli et al., 2012). In this approach, patient-derived tumor specimens are subcutaneously or orthotopically injected into mouse models. PDXs are providing researchers with tools to develop human randomized clinical trials in mice (Gao et al., 2015; Townsend et al., 2016; Bruna et al., 2016), with an ultimate goal to

connect genotypes to dependencies in models with intact micro-environments. In recent years, several initiatives have scaled the development of such PDXs for both common and rare tumors, and these include the EurOPDX Consortium (www.europdx.eu), the NCI's Pediatric Preclinical Testing Program (PPTP), or focused efforts in specific tumor types (Houghton et al., 2007; Pavia-Jimenez et al., 2014; Weroha et al., 2014). After testing over 80 agents in numerous models of childhood cancer, in 2015, the PPTP evolved to the Pediatric Preclinical Testing Consortium (www.ncipptc.org), which now uses genomically characterized pediatric cancer xenograft lines to generate robust preclinical datasets. Furthermore, for-profit companies now exist (www.championsoncology.com) that provide patients with rare cancers the opportunity to develop a PDX model directly from their tumors (Brait et al., 2017). Indeed, over 70 PDX models derived from rare cancers are now in the Champions Oncology biorepository (D. Ciznadija, Champions Oncology, Inc., personal communication).

Further enabling the application of these approaches to rare tumors, an evolution toward “living biorepositories” has occurred over the past decade (Chalfin et al., 2016; Vaughn et al., 2009; Somiari and Somiari, 2015). Historically, archival samples were frozen or stored in fixatives such as paraffin, precluding the generation of live patient-derived models (ISBER, 2012). Now, new biorepository protocols include the routine, viable freezing of patient samples, such as in DMSO (Rasmussen et al., 2015). In addition, more robust Institutional Review Board consent protocols are being used to properly inform patients of the opportunity to participate in research projects in which patient-derived models are being generated. While some of these advances are focused on common cancers, once such infrastructure is established, the barriers for rare cancer samples to be similarly processed are expected to lower.

This confluence of new technologies promises to usher in a new era for the development of high-quality models from multiple rare tumor types. Looking ahead, it will be of great interest whether new online patient engagement strategies can facilitate the acquisition of fresh tumor samples for rare cancer types to further accelerate model generation.

New Functional Screening Tools to Map Rare Cancer Dependencies

Functional experiments using patient-derived models represent an important approach to help interpret the cancer genome with respect to dependencies. In some cases, individual tumors harbor large numbers of somatic mutations (Lawrence et al., 2013), rendering it difficult to determine which mutations enhance fitness during tumor initiation or maintenance. In addition, some mutations are presently challenging to modulate with small molecules, such as those in transcription factor genes or those that have loss-of-function effects. As such, the sequencing of rare cancers may be insufficient to nominate tractable therapeutic targets.

Mapping relationships between the features of rare tumors and their associated dependencies (defined here as genes or proteins required for the viability and/or proliferation of cancer cells) facilitates the identification of candidate therapeutic targets. New technological advances in genetic and small-molecule screening approaches, applied to patient-derived cellular

models from rare and common cancers, now enable the generation of such “dependency maps” in a systematic fashion.

Cancer dependency discovery relies on loss-of-function methodologies, which aim to elucidate gene function by means of reducing or eliminating gene expression or protein activity. The development and application of small interfering RNA (siRNA)- and short hairpin RNA (shRNA)-based reagent libraries have permitted transient or stable RNAi in cancer cells at genome scale (Aza-Blanc et al., 2003; Moffat et al., 2006; Root et al., 2006). The recent emergence of clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9-based technologies, which mediate gene inactivation (reviewed in Howard et al., 2016), now provide an exciting complementary approach (Wang et al., 2015). The joint application of both RNAi-based and CRISPR/Cas9-based technologies to discover rare cancer dependencies that are technology agnostic is now possible (Hong et al., 2016).

New libraries of small molecules are also facilitating the mapping of cancer dependencies. Pioneering efforts to produce small-molecule probes with novel mechanisms of action, such as those mobilized by the launch of the Molecular Libraries Program by the NIH in 2005, have expanded the repertoire of biologically active small molecules available for screening (Austin et al., 2004). In addition, new libraries have been assembled that include thousands of existing, approved drugs, with the potential to be repurposed for a new therapeutic indication (Huang et al., 2011; Corsello et al., 2017). Focused screening libraries may also include small-molecule probes that collectively cover a wide range of targets and cellular processes (Basu et al., 2013; Seashore-Ludlow et al., 2015; Yang et al., 2013).

Notably, small-molecule sensitivity profiling can provide therapeutic and biological insights not achievable with genetic perturbation studies alone. For example, because most small-molecule drugs modulate protein activity, the effects of which may not perfectly mirror those resulting from perturbation of nucleic acids, identifying a cancer dependency via a small-molecule probe can be an important proof of concept for ultimate therapeutic development (Schreiber, 2011). In addition, small molecules enable exploration of protein-protein interactions, alterations in protein stability, and inhibition of protein dimerization (Schreiber et al., 2015).

The mapping of cancer dependencies is now proceeding swiftly with these new small-molecule and genetic perturbation tools in hand. Earlier efforts such as the NCI-60 anticancer drug screen (Shoemaker, 2006) and focused profiling of breast cancer cell lines (Daemen et al., 2013) provided essential proof of concept. In recent years, small-molecule sensitivity datasets have been generated using much larger cancer-cell-line panels, which have the potential to better represent the diversity of patient tumors and permit the identification of context-specific dependencies. These newer datasets include pharmacological profiles of ~500 cancer cell lines tested with 24 anticancer drugs, generated as part of the Cancer Cell Line Encyclopedia project (Barretina et al., 2012); and an independent study in which 130 preclinical or clinical agents were tested across a range of 275–507 cancer cell lines (Garnett et al., 2012). Some concerns were initially raised about the reproducibility of such large-scale studies (Haibe-Kains et al., 2013). However, a recent confirmatory study (Haverty et al.,

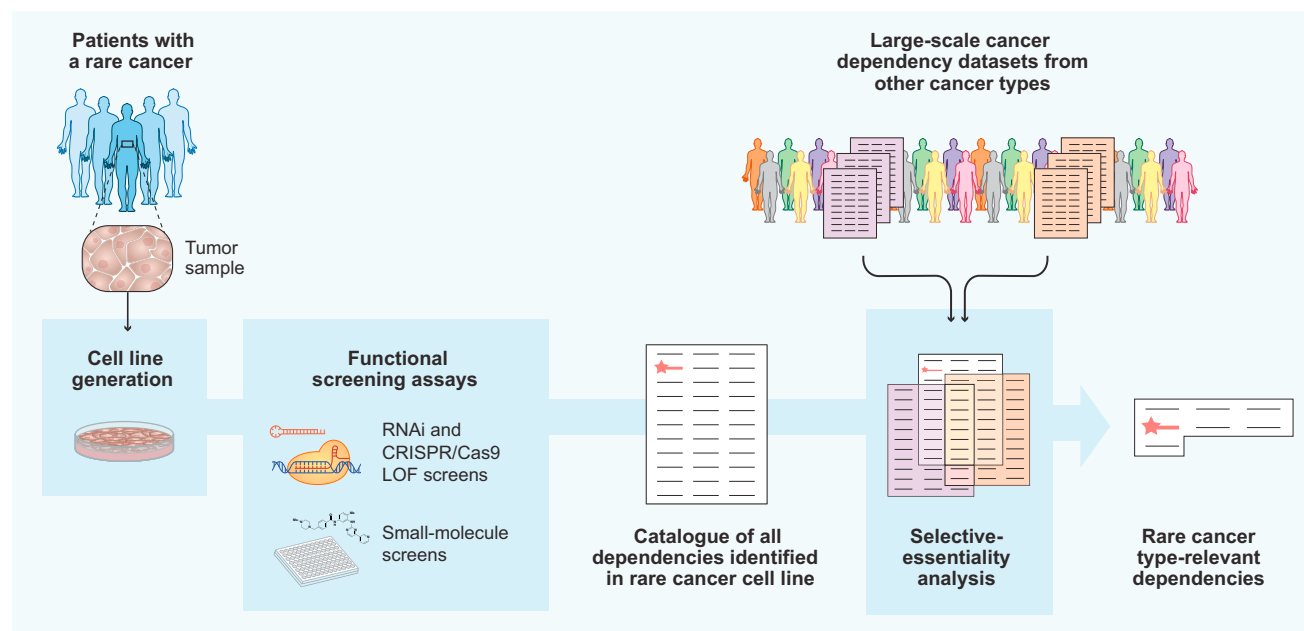


Figure 4. Large-Scale Cancer Dependency Datasets Enable the Identification of Rare Cancer Type-Relevant Vulnerabilities

Workflow of cancer dependency discovery in rare cancers. Patient-derived cell lines are subjected to loss-of-function (LOF) screening approaches to identify a catalogue of all dependencies in a given rare tumor model. To distinguish key rare cancer type-relevant dependencies (red star) from commonly essential genes or pan-lethal small molecules, large-scale cancer dependency datasets generated using other cancer types can then be used to compare and filter screening results. A list of rare cancer type-relevant dependencies, including key targets, is thus obtained.

2016) as well as new integrated analysis of the two initial reports (Cancer Cell Line Encyclopedia Consortium and Genomics of Drug Sensitivity in Cancer Consortium, 2015) now point to reasonable agreement and biological consilience between the studies.

New efforts are expanding this approach even further. As one example, an effort as part of the NCI-sponsored Cancer Target Discovery and Development (CTD²) initiative has led to small-molecule sensitivity profiling of over 800 genomically characterized cancer cell lines, using a panel of 481 US Food and Drug Administration (FDA)-approved drugs, clinical candidates, and small-molecule probes (Seashore-Ludlow et al., 2015). A more recent study correlated molecular features of a larger panel of ~1,000 cancer cell lines to sensitivity to 265 anticancer drugs (Genomics of Drug Sensitivity in Cancer [GDSC] database; Iorio et al., 2016). Finally, a new cellular barcoding method called PRISM enabled the high-throughput viability assessment of 8,400 small molecules against 102 cell lines (Yu et al., 2016). Now, each rare cancer small-molecule dependency assessment can be compared against these large reference datasets (Figure 4) to prioritize dependencies that share a common cellular feature or are highly specific to the rare cancer under study, thereby deprioritizing compounds whose effects are pan-lethal. For example, these types of comparative analyses have recently been used to identify small-molecule dependencies in models of medulloblastoma (Hanaford et al., 2016) and pediatric undifferentiated sarcoma (Hong et al., 2016).

In parallel, the application of genome-scale RNAi and CRISPR/Cas9 libraries to large genomically characterized panels of can-

cer cell lines provides a critical reference dataset for identifying rare tumor dependencies. Earlier work as part of Project Achilles demonstrated basic feasibility using RNAi and mapped dependencies at genome scale to 102 or 216 cell lines (Cheung et al., 2011; Cowley et al., 2014). In parallel, other efforts focused on individual tumor types, such as breast, pancreatic, and ovarian cancers (Marcotte et al., 2012, 2016). Recent proof-of-concept studies demonstrating the potential for large-scale application of CRISPR/Cas9 technology (Wang et al., 2015) have now been extended to 5 (Munoz et al., 2016), 14 (Wang et al., 2017), or 33 (Aguirre et al., 2016) cancer cell lines, leading to the discovery of *PREX1* as an activator of MAPK signaling in Ras-driven acute myeloid leukemia cells, among other discoveries.

Several key principles have emerged from these studies that are relevant to rare tumors. Firstly, many clinically validated dependencies that arise from activated oncogenes (Weinstein, 2002) are readily recapitulated in these studies (Cheung et al., 2011). Thus, if a novel rare cancer model is found to be exquisitely dependent on a mutated oncogene, there may be strong rationale for therapeutic targeting of such oncogene. Second, expression-driven dependencies are prominent and include lineage-specifying transcription factors such as *PAX8* and other master regulator genes (Marcotte et al., 2016; Cheung et al., 2011), suggesting potential to target the underlying tissue lineage for rare tumors in which such lineage is expendable. Also, partial copy number loss of certain genes renders cancer cells highly sensitive to further depletion (Nijhawani et al., 2012), suggesting therapeutic opportunities for rare tumors with hemizygous deletions.

Table 1. Advances in Chordoma Research Assets

	2007	2017	Interventions
Researcher community	Small, disconnected	>300 active researchers; robust collaboration	International Chordoma Research Workshops; networking events
Patient community	None	>1,800 patients	Facebook group; website; online advertising and search engine optimization; educational materials; Chordoma Community Conferences
Tumor tissue	Scarce, no centralized source	Centralized repository with tissue from >200 cases	Tumor donation program allows patients to donate tumor from any US hospital; CF Biobank stores and distributes tumor samples
Genome characterization	None	35 cases sequenced	Chordoma Genome Project, in partnership with academic labs
Cell lines	1	17	Cell line prize; cell line validation pipeline; genomic characterization; publicly accessible cell-line repository
Patient-derived xenografts (PDX)	None	5	Tumor donation program coupled with rapid implantation <i>in vivo</i> ; PDX prize; PDX validation pipeline; publicly accessible PDX repository
Small-molecule screening	None	>10,000 compounds screened, including all FDA-approved drugs	Collaboration with NIH Chemical Genomics Center; grants to academic investigators; collaborations with industry
Functional genomic screening	None	Genome-wide CRISPR/Cas9 screens; targeted shRNA screen	Grants to academic investigators
<i>In vivo</i> evaluation	None	>20 drugs evaluated	CF drug screening pipeline provides <i>in vivo</i> evaluation as a service to academic and industry collaborators
Clinical trials	1 completed clinical trial	Pipeline of 7 new clinical trials	Clinical trials program supports trials with: funding, trial design, patient education, and outreach

Source material: Chordoma Foundation (J. Sommer, personal communication) and www.chordomafoundation.org.

Lastly, these studies point to opportunities to target previously challenging loss-of-function events in cancer, by exploiting the concept of synthetic lethality (Kaelin, 2005). One example relates to *CDKN2A* deletion, which is a common alteration in multiple cancer lineages. The co-deletion of the enzyme methylthioadenosine phosphorylase (MTAP), which frequently co-occurs with *CDKN2A* loss due to their genomic proximity, confers selective dependence on the protein arginine methyltransferase 5 (*PRMT5*) gene (Kryukov et al., 2016; Mavrakis et al., 2016). Other examples include paralog dependencies (also called “collateral vulnerabilities”) in which the loss of one paralogous protein is associated with a dependency on another. Examples include the ARID1B dependency in *ARID1A*-mutant cancers (Helming et al., 2014), the SMARCA2 vulnerability in *SMARCA4*-mutant cancers (Wilson et al., 2014), and the ENO2 vulnerability in glioblastomas with *ENO1* deletion (Muller et al., 2012).

Now, demonstration efforts have shown basic feasibility of using these technologies to assess cancer dependencies in novel patient-derived cell lines (Hong et al., 2016; Crystal et al., 2014; Yu et al., 2014), organoids (van de Wetering et al., 2015), and xenografts (Bruna et al., 2016; Townsend et al., 2016; Gao et al., 2015; Bossi et al., 2016). Leveraging multiple technologies in unison, it should soon become increasingly feasible to assess dependencies of a given rare cancer type (even with a limited number of models), compare results to large reference datasets, and home in on therapeutically actionable dependencies that are induced by specific, shared cellular features (Figure 4).

Accelerating Research on Chordoma

One example of the convergence of the advances described in the above sections can be found in chordoma research. For this rare cancer type, an important event was the founding, in 2007, of the Chordoma Foundation (CF), which over the last decade has mobilized the chordoma research field and played key roles in several areas, described in detail below and summarized in Table 1.

First, a key advance was the physical and virtual unification of the scientific, medical, and patient communities, which had previously been siloed and geographically dispersed. To accomplish this, the CF established International Chordoma Research Workshops and Chordoma Community Conferences, allowing researchers, patients, and caregivers to physically gather and collaborate. Social media was used extensively to enable the virtual interaction and engagement of patients. Second, a centralized tumor biorepository, the “CF Biobank,” was established in 2012 to collect and provide access to tumor tissue, blood, and clinical data; this permitted any chordoma patient at any hospital in the US to contribute material. In addition to being banked for future use, when possible, samples are engrafted in mice to create PDX models. Third, the CF implemented a system of monetary prizes that have incentivized the development of new chordoma cell-line and PDX models, which are subsequently validated and deposited in publicly accessible repositories. Together, these efforts effectively lower the barriers to research for new and existing investigators.

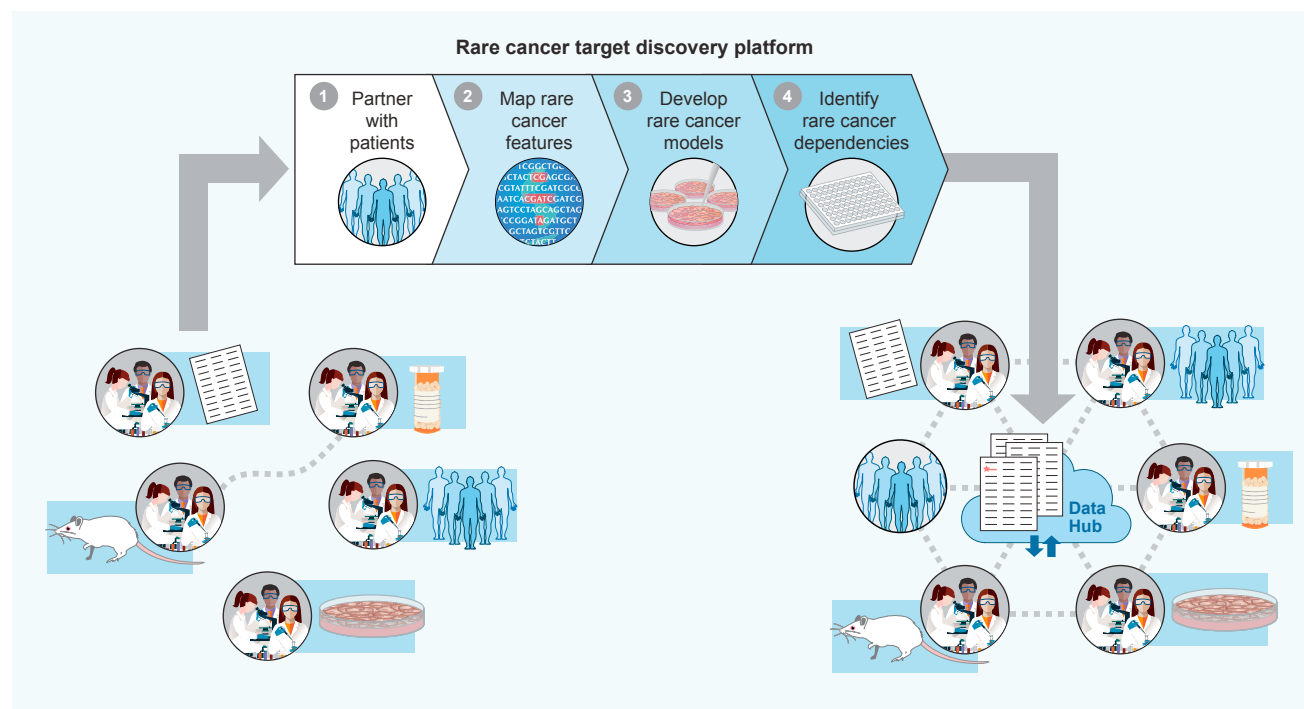


Figure 5. Toward a Platform for Target Discovery in Rare Cancers

Historically, research on rare cancers has been carried out by small numbers of independent laboratories. The emergence of new technologies permits the potential implementation of new research frameworks to (1) leverage online platforms and social media to partner with patients, (2) perform genomic and cellular characterization of samples that such patients contribute, (3) create cell line, organoid, and/or PDX models from such samples, and (4) use small-molecule and CRISPR/Cas9 libraries to create “dependency maps” for each rare cancer type. Resulting target discovery findings, stored in cloud-based “data hubs,” can help further coalesce rare cancer research communities, with each laboratory contributing specific areas of expertise to the larger community.

Building on this new convergence of researchers and scientific resources, the Foundation initiated several projects to identify possible therapeutic targets in chordoma. In 2007, little was known of the molecular basis of chordoma. To address this gap, the Chordoma Genome Project was launched to perform whole-genome, whole-exome, and transcriptome sequencing of chordoma tumors, leading to the discovery of a common variant in the *T* (brachyury) gene (Pillay et al., 2012), as well as several other known cancer genes. With these genomic data now available, large-scale functional genomic and small-molecule screening efforts are underway in industry and academia to uncover dependencies linked to these underlying features (J. Sommer, Chordoma Foundation, personal communication).

Finally, to facilitate translation of novel discoveries, the CF launched additional programs. These included a centralized pipeline for conducting *in vivo* efficacy studies in a contract lab that continually maintains tumor-bearing animals, permitting chordoma investigators to rapidly test candidate therapies with no upfront investment in personnel or laboratory setup. In addition, a formal process for providing grant support for clinical trials was established in 2015, and a patient navigation service was created to connect patients to available trials, among other programs intended to speed clinical impact.

As a result of these efforts, foundational datasets and resources have been established, and several clinical trials have now been launched, in contrast to a single phase II trial that had been completed by 2007. Overall, the current pace of prog-

ress in chordoma research demonstrates how new structures to facilitate rare cancer target discovery and translation can have major impact.

Toward a Platform for Rare Cancer Target Discovery

As described above, important biological and translational discoveries have been made for specific rare cancer types, often by individual laboratories or institutions with disease-specific expertise (Figure 5). In recent years, this work has been advanced considerably by research consortia and disease-specific research foundations, which have coalesced communities comprising patients, scientists, and clinicians for specific rare tumor types, such as chordoma.

However, despite these successes, each rare cancer community is often charged with independently establishing components that are needed (to perform genomic analysis, develop organoid models, or assemble small-molecule libraries, for example), often with extremely limited funds. As a result, there may be missed opportunities to benefit from existing expertise or to capture cost reductions that might come from scale.

Looking ahead, given the remarkable technological and social advances that have recently emerged, it is worth considering whether additional research structures might now accelerate progress. One possible framework includes technology-focused “rare cancer target discovery” platforms, acting as close partners with biology-focused rare cancer research laboratories. These platforms could support the four essential components

of rare cancer target discovery described here: (1) leveraging on-line platforms and social media to establish meaningful partnerships with patients (providing remote opportunities to provide consent for specific research projects), (2) performing genomic and cellular characterization of samples that such patients contribute, (3) creating cell-line, organoid, and/or PDX models from such samples, and (4) using small-molecule and CRISPR/Cas9 libraries to create “dependency maps” for each rare cancer type (Figure 5). Resulting target discovery findings can help further coalesce rare cancer research communities (Figure 5).

The potential for such platforms to be transformative will rely on commitments at each step to share reagents, cell models, and data broadly. In the case of data, cloud-based rare cancer “data hubs” (Figure 5) could permit each lab to have access to aggregated rare cancer data in an environment that maintains patient privacy while flexibly and cost-effectively supporting data sharing and analysis. By sharing data and resources, each stakeholder in the rare cancer research enterprise stands to benefit: target discovery could be enabled in a more cost-effective fashion, individual laboratories and clinicians could translate key findings toward the clinic, and patients could become further empowered as important partners in the research process.

Future Directions

Here, we have presented a status update on overarching progress to target rare cancers, describing new advances in social media, genomics, *ex vivo* patient-derived model propagation, and cancer dependency screening with CRISPR/Cas9 reagents and small molecules. Important additional topics, not reviewed herein, include challenges in funding rare cancer research and opportunities to accelerate the drug development process, including drug development incentives and redesign of clinical trial protocols (Panageas, 2015; Casali et al., 2015).

In the case of clinical trials for rare cancers, for example, innovative approaches are emerging that may speed progress. Historically, relatively low rates of patient accrual have impeded clinical testing of therapies for rare cancers. In addition, conventional trial design based on histological subtype challenges the testing of emerging (or approved) therapies in patients whose tumors do harbor the relevant mutation, but in a distinct histology. One potential solution involves the phasing of trials to first demonstrate proof of concept using small trials that focus on homogeneous rare tumor types; indications can later be expanded to subsets of patients with common cancers (Fishman, 2013). Another approach includes the broad implementation of basket trials based on molecular criteria, such as the NCI-MATCH or NCI-COG Pediatric MATCH, as described above (NCT02465060; NCT03155620). Finally, the recent FDA approval of the immune checkpoint inhibitor pembrolizumab for solid tumors with microsatellite instability-high or mismatch repair deficient status (US Food and Drug Administration, 2017) is a key harbinger of genetic-based, tissue/site-agnostic approvals. Removing limitations based on tissue or site in this way can mitigate the difficulties associated with using (rare) histological criteria to accrue, or treat, cancer patients.

As reviewed herein, each rare cancer type is distinct, but different rare cancer types can pose similar impediments to research progress. New preclinical research frameworks, such

as those discussed here, may accelerate rare cancer research and draw research communities together to benefit patients. Looking forward, we anticipate that target discovery approaches successfully employed in rare cancer test cases may be broadly applicable to common cancer types, many of which are increasingly viewed as heterogeneous collections of “rare” diseases that require tailored treatment approaches (Figure 1A). In this way, the rapidly evolving field of rare cancer research may provide a learning system for the treatment of more common cancer types, whose increasing fragmentation according to molecular criteria may soon classify them, too, as “rare.”

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