Cancer Cell

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Voices

Translating Basic Cancer Discoveries to the Clinic

Precision Medicine for Kids

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Targeted therapies and immunotherapies have impacted the care and outcomes of adults with cancer. By contrast, pediatric and adolescent/young adult (AYA) cancer patients have not similarly benefitted. As a result, early-age cancer survivors experience significantly elevated risk of secondary cancer and a poor quality of life due to health-related sequelae. Improving this circumstance requires changes in molecular profiling, as these cancers have few point mutations and more structural alterations, gene fusions, and epigenetic drivers. Comprehensive next-generation sequencing and analysis of matched tumor:normal DNA coupled with RNA sequencing is required to identify therapeutic vulnerabilities and prognostic information. Our studies using comprehensive profiling demonstrate that over 95% of early-age patients have one or more medically meaningful results. U.S.-wide studies of this type would mirror those in Germany, Canada, and Australia and could lower barriers to access for underserved patients. In 2019, NCI convened a meeting to conceptualize a Childhood Cancer Database Initiative (CCDI) that will coalesce genomic, treatment, and outcome data from pediatric and AYA cancers generated by multiple clinical- and research-based efforts. The CCDI will allow broad data sharing, coupled with database mining tools. Increased access to clinical trials, as mandated by the RACE for Children Act, which lowers the age of eligibility and incentivizes pediatric trials of indicated new therapies, will combine with the CCDI to transform outcomes and health-related quality of life for our kids.

Curiosity Underpins Cures

Mark A. Dawson
Peter MacCallum Cancer Centre, Australia

Technological innovation over the last decade has facilitated unprecedented insights into cancer biology, and these discoveries have fueled clinical translation through the development of new diagnostic tools and cancer therapies. While this is an extraordinarily exciting time in cancer research, we also find ourselves poised at a dangerous precipice that threatens to unravel the gains made. As a clinician-scientist, simultaneously immersed in the parallel worlds of clinical care and discovery science, I am gravely concerned that the global shift to primarily fund and support translational science and clinical implementation is ironically one of the greatest impediments to improving patient outcomes.

I strongly believe that without curiosity there are no discoveries, and without discovery there will be no new cures. This interlinked pathway to cure has its origins in fundamental discovery science. All of today's curative therapies were developed through formative partnerships between scientists and clinicians, each leveraging each other's intuition, skill set, and experience. More than ever we need to continue funding discovery science to provide the scientific rationale for clinical translation; how else will we understand the implications of intra-tumor heterogeneity unveiled by studying cancer at single-cell resolution? How will we find effective strategies to tackle the pervasive genetic and non-genetic mechanisms that result in therapeutic resistance? Now is the time to invest in curious minds, the engine room that drives cutting-edge clinical care.

Computation to Translation

Christina Curtis
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Despite being a pillar of precision oncology, validated biomarkers to guide patient stratification remain few and far between. Clinically annotated molecular datasets are powerful resources for biomarker discovery using modern data science methods. Controlling for biases is crucial, as is establishing sufficiently large and representative independent cohorts for biomarker validation. Given the costs of large-scale genomic studies and clinical trials and the rapid evolution of analytic methods, data sharing is imperative for accelerating stratified medicine. Data sharing ensures the greatest value can be obtained from precious patient samples and should be enforced by funding bodies and journals.

My own research is highly interdisciplinary, drawing on computational and experimental methods and spanning basic science to predictive and prognostic biomarker development. Some of our discoveries have led to the development of clinical trials to evaluate their clinical utility. It is rewarding to pursue this initial step toward translation together with a multi-disciplinary team of clinicians, data scientists, and experimentalists, and I believe team science will be crucial for success. I also believe in the value of embedding correlative studies within therapeutic trials as a means to uncover novel resistance mechanisms and candidate biomarkers. This facilitates a new round of scientific discovery while potentially closing knowledge gaps in the path to clinical translation.

ctDNA: A Close Eye on Cancer

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Our understanding of gastrointestinal (GI) cancer has rapidly evolved over the past 5 years. Gastroesophageal adenocarcinoma (GEA) exhibits considerable genetic diversity with significant intratumor, intrapatient, and interpatient heterogeneity. The "one target, one drug" rationale has proven unsuccessful for GEA because of its myriad of subtypes. Circulating tumor DNA (ctDNA) represents a promising tool to capture a broader scope of tumoral heterogeneity for both primary and metastatic diseases. Longitudinal ctDNA sequencing can provide novel insights into gene alterations underlying treatment resistance and genomic evolution in GEA. In colorectal cancer (CRC) patients, ctDNA methylation markers have emerged as a useful diagnostic and prognostic biomarker. The detection of ctDNA can identify minimal residual disease after the resection of primary tumor or liver metastases and characterize the risk stratification of adjuvant chemotherapy. ctDNA can be used for the real-time monitoring of genomic abnormalities in identifying acquired resistance to anti-EGFR or anti-HER2 therapy in mCRC patients.

In the face of this vast genomic tumoral heterogeneity, the application of ctDNA will be essential for the success of future translational clinical trials in GI cancer precision oncology. As a GI cancer oncologist, I believe that ctDNA will be broadly incorporated into future clinical trials as a biomarker for the diagnosis, surveillance, prognosis, and treatment stratification of GI cancers.

A Critical Nexus

Georgina V. Long and Richard A. Scolyer
Melanoma Institute Australia, The University of Sydney, Australia

As clinician researchers, with busy clinical loads, our greatest challenge is finding time to engage deeply in the science. But it is necessary to deliver on our research goals. The nexus between the clinician and the researcher is critical and underpins successful cancer research.

Embedded in every academic clinical cancer service there needs to be a vibrant program of research, which includes basic and translational research. Similarly, embedded in every cancer-related research laboratory, strong links to clinicians at the front line are essential. By working together, clinicians and scientists can gain insights beyond those easily achieved individually.

The clinician and scientist approach the cancer challenge from differing perspectives. Clinicians have a global perspective of the disease enabling them to identify what needs to change for maximal impact. Scientists tend to have a meticulous understanding of specific steps within complex biological systems—breaking the big picture into smaller parts, thus identifying opportunities for manipulation. Neither can successfully achieve the goal without the other.

This symbiotic relationship is well illustrated by modern cancer immunotherapy. For decades, clinicians recognized that immune manifestations correlated with good outcomes, but it was not until James Allison and Tasuko Honjo identified critical checkpoints in immune regulation that the opportunity to harness the immune system against cancer was realized. Now, checkpoint inhibitor drug therapies have transformed the cancer field, highlighting what can be achieved when clinicians and scientists build upon their respective insights.

The Forgotten Cancer Phenotype

Samuel F. Bakhoum
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The widespread adoption of genomic sequencing in oncology has galvanized the development of therapies that target drivers of tumorigenesis, with the underlying assumption that should these drivers be inhibited, the tumor can be halted in its tracks. Yet, we quickly learned that tumor cells possess a powerful weapon of resistance: randomly shuffling their chromosomes each time they divide, a process known as chromosomal instability (CIN). CIN is a widespread characteristic of metastatic cancers, and it leads to genomic heterogeneity, immune evasion, and therapeutic resistance. By using targeted therapies in advanced disease, in a way we are employing the wrong weapon in the wrong fight, and this is evidenced by these therapies' minimal impact on overall survival.

CIN remains an unresolved genomic challenge due to inadequate experimental systems, including genetically engineered mouse models, and absence of therapies that can directly target complex chromosomal alterations. Traditional drug development approaches rely on an implicit assumption of cancer as a disease of uncontrolled proliferation, overlooking the fact that the majority of disease relapse arises from cancer cells' ability to adopt a quiescent, multi-drug-resistant phenotype enabled by CIN. Accounting for CIN as an inevitable feature of metastatic cancer, developing better mouse models of genomic instability, and tailoring drug development strategies to target cellular quiescence and resistance, rather than proliferation, would enrich the drug development pipeline.

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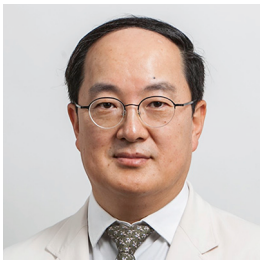
Precision Neuro-oncology



Do-Hyun Nam
Samsung Medical Center, South Korea

Despite many recent successes in solid tumor treatment, effective therapies for brain malignancies remain limited. The rarity and intrinsic tumor heterogeneity of brain malignancies contribute to the infeasibility of large-scale clinical validation of various therapeutics. Molecular profiling of tumors has offered only minor improvements in treatments in the field of neuro-oncology, necessitating an alternative approach that consists of the integration of multi-layered datasets.

Recent advances in artificial intelligence and big-data analyses have the potential to guide the medical decision-making process and to significantly improve neuro-oncology treatment. Data-driven approaches could potentially enable virtual-based clinical trials and provide timely and targeted solutions for brain tumor patients. To realize the clinical potential of these approaches in neuro-oncology will require further generation of "big data" for brain malignancies, including drug response evaluation. Developing drug response datasets will require clinically relevant models. As brain tumors often show a rapidly progressive clinical course, xenograft models and organoids may not be ideal proxies for the clinical context of brain malignancies. Patient-derived cells (PDCs) could represent a suitable model to evaluate compound efficacy, and PDC-derived preclinical results could even potentially be utilized as surrogates for real patients and aid in prioritization of known drug targets. More data and better models could substantially help identify successful therapeutic strategies for brain malignancies.

Experimental Models Are Key

Mathew Garnett
Wellcome Sanger Institute, United Kingdom

When considering the gap between discoveries and clinical translation, I've focused on a foundation that underpins much of research—namely, the use of experimental cancer models. There are a range of models available—from cell lines and engineered mouse models to patient-derived organoids and xenografts—and their use for research is ubiquitous. Yet concerns about how well models reflect patient tumors, and the clinical translatability of findings, create uncertainty undermining their utility. In reality, no model is perfect, but most have strengths, and smartly exploiting these strengths is key.

We need to get the basics right, like avoiding prolonged model propagation to minimize adaptation and being vigilant for cross-contamination. To reflect diversity, more models of different tissue and molecular sub-types, disease stages, and ethnicities are needed. We should develop tools so scientists can identify models suitable for their research from molecularly annotated collections, ideally accessible from repositories. Patient-derived models should be benchmarked against clinical samples and be available in numbers sufficient for cohort analyses to power statistical methods. Better models are needed to study tumor interactions with their microenvironment, including the immune system. Achieving these advances is realistic, given the accessibility of DNA and RNA sequencing, new methods for model generation, and technologies such as gene editing and single-cell analysis. In an era of precision oncology, improving cancer models will yield important dividends for the clinical translation of new discoveries.

Something Old, Something New

Annie Huang
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Recent technological innovations have enabled rapid developments in cancer biology, with increased recognition of molecular classes and subclasses of cancers. While such discoveries have yielded refined clinical paradigms and new targeted molecules, translation to bedside applications has become more complex. With increased selection of patients based on tumor molecular features, traditional trial design and methods of evaluation may not be practical or appropriate.

Trials, particularly those evaluating targeted agents in multi-modal regimens, could be significantly enhanced by fundamental clinical information on disease phenotypes and response to conventional modalities. Clinical and treatment data are, however, often limited or outdated, particularly for uncommon and newer molecular categories of cancers. Pediatric oncologists who have long faced small patient populations have relied on retrospective and prospective clinical registries with phenotypic, treatment, and outcome data linked to cancer molecular annotation to inform parsimonious and efficient clinical trials. Thus, future efforts to integrate molecular and clinical informatics will be critical for defining the bedside context in which biological information and intervention are most relevant. Depending on the disease phenotypes, associated biology, and nature of targeted therapies, more specific molecular assays, in addition to cytoreduction, will be needed to measure drug activity and efficacy.

Together with next-generation tools to evaluate tumor response, resurgence, and evolution on treatment, clinicians will be poised to deliver real-time individualized cancer therapy.