SOCIETY FOR TRANSLATIONAL ONCOLOGY®
The Oncologist IS THE SOCIETY'S OFFICIAL JOURNAL

2017 Society for Translational Oncology Fellows' Forum

Precision Medicine: A Work in Progress

Faculty Presenter
Bruce A. Chabner, MD, Allen Distinguished Investigator, Clinical Director Emeritus, Massachusetts General Hospital Cancer Center; Professor, Department of Medicine, Harvard Medical School, Boston, MA, USA

Scholars' Summaries

*Authored by **Clinton Yam, MD,** The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

Developing anti-cancer therapies that selectively destroy malignant cells while sparing normal cells has been the holy grail of cancer medicine. In this outstanding lecture, Dr. Bruce Chabner delved into the multiple challenges involved in developing new cancer drugs and provided a simple yet profound framework to help us understand the process of drug development. In 2017 alone, more than 100 new compounds entered cancer trials. Unfortunately, the success rate for new drugs in trials is less than 20%, and the cost for each new drug approval is approximately $2 billion. Thus, we have to be thoughtful and deliberate in our approach toward drug development to keep costs down and ensure that we get effective therapies to patients in the most efficient manner.

The first and most important step in the drug development process is identifying the right target. This involves meticulous validation of biologic hypotheses in preclinical and clinical studies to ensure that the candidate target is altered in human cancers and drives a critical pathway for proliferation and survival of cancer cells. Once a promising target is identified and validated in preclinical and clinical studies, a high throughput assay is needed to find suitable inhibitors. The ideal targeted agent has a high affinity for the target protein (IC_{50} in the 1-10 nM range), has high oral bioavailability (>50%), is not a substrate for multidrug resistance (MDR) transporters, and is slowly eliminated from the body.

However, the era of targeted therapies has revealed multiple challenges in identifying and developing the ideal targeted agent. First, our early experience with targeted agents was complicated by agents lacking specificity for malignant cells, leading to off-target effects and toxicity in normal tissues which has, in part, limited their effectiveness. Second, the significant pharmacokinetic variability between patients has invariably led to under- or overdosing in subsets of patients. Pharmacokinetic studies have shown that up to 30-40% of patients are under-dosed when given the recommended phase II dose, which is thought provoking given that multiple studies have shown a strong correlation between under-dosing and lack of response. Third, tumor heterogeneity and evolution results in rapid emergence of resistance to single agent targeted therapy, and while combination therapy has successfully overcome that problem in select situations (e.g. combined B-Raf and MEK inhibition in BRAF V600 mutant melanoma), drug-drug interactions, overlapping toxicity, and prohibitive costs have led to

targeted therapies have been found to work well in well-defined tumor subsets, understanding and overcoming resistance through alternate strategies is key to unlocking clinical benefit for our patients.

In summary, through this exceptional lecture, I had the privilege of learning from Dr. Chabner's vast experience in the field of drug development and gained a deeper understanding of the challenges that translational oncologists face in developing new and better therapies for our patients. While we have made great strides in the last several decades, much more needs to be done to continue to help improve outcomes for our patients.

---

*Authored by **Angel Qin, MD**, Fellow, Division of Hematology/Oncology University of Michigan, Ann Arbor, MI, USA*

We are beginning to enter the era of precision medicine in oncology whereby drugs are developed to specifically target an aberrancy that plays a central role in the pathogenesis of disease. Over 100 new chemical entities entered trial for cancer in 2017, with 200+ drugs currently being investigated in Phase I studies. As Dr. Bruce Chabner so eloquently discussed in his talk, despite the advancements we have made in targeted drug development, there remain significant challenges to overcome.

The key steps in the process of targeted drug development include identifying a high interest target, validating the target in preclinical and clinical studies, designing a high throughput assay that can identify inhibitors, thorough pharmacodynamic and pharmacokinetic evaluation of the drug in various systems, and finally taking the drug to the clinic. There have been many impressive success stories with targeted therapies that have altered the course of a disease, such as imatinib for CML (chronic myelogenous leukemia) and erlotinib for EGFR-mutated non-small cell lung cancer.

Even after the identification and validation of a specific target, there remain other road blocks in targeted drug development. These include a lack of specificity leading to off-target effects and toxicity in normal tissue and variability in drug metabolism. We also know that tumor cells are not a homogenous population, even within the same tumor, and are constantly evolving; therefore the relevance of the targeted drug may be limited or transient. Tumor cells also develop resistance mechanisms, leading to an arms race between drug development and tumor cells. Finally, one cannot discount the importance of cost when discussing drug development.

Targeted therapies have already revolutionized cancer therapy and will likely continue to define the therapeutic landscape. There is still much work to be done as we learn more about detecting and overcoming resistance and finding safe combination therapies that can enhance response.

---

*Authored by **Jia Wei, MD, PhD,** Nanjing University, Jiangsu Sheng, China*

Dr. Bruce Chabner gave an excellent talk discussing the key steps in targeted therapeutic drug development. There are a growing number of new cancer drugs entering trials with relative low success rate for each new drug in trial, indicating great challenges in the development of targeted drugs. First of all, the target should be valid. In general, mutated targets are superior to amplified or over-expressed targets. The pathway driven by selected targets should be critical for cancer proliferation or survival. In the stage of validation, patient-derived xenograft (PDX) models are relevant to demonstrate in vivo activity and drug properties (PK or toxicity).

Dr. Chabner used EGFR as an example of an ideal target. Other potential targets, such as other receptor tyrosine kinases, DNA repair genes, epigenetic targets, and genes involved in apoptosis, are also of high interest in drug development. However, there are still several problems with targeted drug development: 1) lacking of specificity for cancer, resulting in normal tissue toxicity and off-target effects; 2) Variability in PK – around 40%; 3) Limited effectiveness by toxicity; 4) Rapid emergence of resistance to single agent due to multiple mechanisms; 5) Challenges of combination therapy, especially accumulated toxicities by CYP450; 6) The cost of drug development.

A good example of anti-EGFR drug development in lung cancer has been shown to demonstrate different aspects in each key step. For instance, the third generation of anti-EGFR TKIs represent different specificity to resistant mutant EGFR genotype, resulting in a good response when patients acquired resistance to the first generation of EGFR TKIs with EGFR T790M mutation. However, other mechanisms for drug resistance need to be explored as well.

In conclusion, we should understand that targeted therapies work only in well-defined tumor subsets. It is very necessary to understand the mechanisms of acquired resistance. Needless to say, combined therapy with immunotherapy, chemotherapy, or other targeted drugs is needed in clinical settings.