PRECISION MEDICINE

The Exact Science of Creating A Blockbuster Drug

BattaliaWinston

By Susan Oliver, Partner

IN SPITE OF THE HEAD-SPINNING MEDICAL AND TECHNOLOGICAL PROGRESS IN EVERY ASPECT OF OUR LIVES, DR. KELVIN STOTT RECENTLY DECLARED THAT THE PHARMACEUTICAL INDUSTRY WAS "...ON THE BRINK OF TERMINAL DECLINE." DR. STOTT BELIEVES THAT THE BIG PHARMA BUSINESS MODEL IS BROKEN AND WILL NOT PRODUCE ANY SIGNIFICANT BREAKTHROUGHS IN DRUG DEVELOPMENT. (FLEMING, 2016)

This lack of confidence in future development does not take into account precision medicine and how it significantly contributes to what we think of as blockbuster drugs. It also does not take into account the expanding medical and scientific specialties—translational biomarker science, computational genomics, transcriptomics, artificial intelligence, deep machine learning, and big data that drives precision medicine programs further. Precision medicine applies specific, targeted, and more importantly, better therapeutic combinations resulting in medicines that look like the commercial successes we call blockbusters. (Jarvis, 2019).

> ***Precision medicine has placed the first footsteps on millions of acres of fertile pharmaceutical field just waiting for discovery and development. The central thesis of precise medicine is the idea that large disease categories, like type 2 diabetes, are actually a collection of multiple identifiable subtypes. Each subtype will be identified by genetic drivers and present its own distinct characteristics.***

David Shaywitz provided this explanation, "As genetics and phenotypic research advances . . . diseases like type 2 diabetes will go the way of quaint descriptive diagnoses like 'dropsy' and be replaced by more precisely defined subgroups, each ideally associated with a distinct therapy developed for that population." (Shaywitz, 2017). Each disease has specific pathways that need to be fully characterized before being used as a target. In this context, precision medicine is a scientific-driven approach aimed at bringing more specific therapy and/or diagnostic tools to help every patient.

As an example, one of the first distinct therapeutic approaches to boost immune defense to cure cancer began in the research lab of Jim Allison. Allison found a protein on the surface of T-cell called CTLA-4. This protein acts as a braking device in autoimmunity, however, Allison found the tumor cells were using this protein to mask themselves and grow. Allison's lab discovered an antibody that blocked the CTLA-4 protein to enhance native immune response and allowed T-cells to react by identifying and killing invading cancer cells. Not surprisingly, blocking this protein had some negative impacts and produced serious side and offside effects. Dr. Jedd Wolchok, a primary investigator in the clinical trials, said "...we were also seeing some remarkable things." Wolchok found it was especially successful treating metastatic melanoma patients including some in terminal stage IV.

The road to global market for Dr. Allison's drug was long and rough, but in 2011 the FDA approved anti-CTLA-4 antibody (ipilimumab), trade name Yervoy, for the treatment of melanoma. Later it was approved to treat kidney (renal cell carcinoma) and colorectal cancer and it has saved thousands of lives. (Greaber, 2018). The major contribution of Yervoy was that it proved Allison's theory that native immune response could be weaponized to fight its own cancer. Once researchers accepted this discovery they started to hunt for more and better immune checkpoints without the occasional severe side effects generated by giving CTLA-4 free reign throughout the body.

> ***One of the major discoveries in this new immuno-oncology field was made by Dr. Tasuku Honjo of Kyoto University. His checkpoint discovery, PD-1, is involved in the interaction and signaling between tumor and immune cells that keeps T-cells away from attacking the tumor. Graeber characterized this signal as a "secret handshake." Building on Allison's work, Honjo created a drug that blocked this "secret handshake." This increased the precision of the treatment and resulted in far fewer side effects than the mass assault of Allison's weaponized T-cell army. This monoclonal antibody, or anti-PD-1 drug, became Keytruda .***

The development of PD-L1 IHC was also instrumental in developing the biomarker strategy for anti-PD-1 therapy. This allowed for further patient stratification based on the percentage of tumor positive cells and consideration of complexity in biomarker approach for combination and/or second line therapy.

Keytruda was the first FDA approved cancer drug that was based on tumor biomarkers rather than the location of the tumor. The FDA originally approved Keytruda for treating metastatic melanoma, metastatic small cell lung cancer, metastatic head and neck cancer, classic Hodgkin's

lymphoma, and urothelial carcinoma. Biomarker approach and tumor immunogenicity identified other promising indications in a total of 15 types of cancer including colorectal, endometrial, gastrointestinal, breast, prostate, bladder, and thyroid as well as others. Trial results established that Keytruda achieved a complete or partial response in nearly 40% of the 149 patients in the trial studies. Of those patients who responded, 78% achieved a durable response that extended beyond five years. Using the FDA Accelerated Approval Program, Merck was permitted to market Keytruda to patients with other solid tumors. Former President Jimmy Carter presented with an aggressive brain tumor. The tumor had biomarkers that indicated Keytruda might be effective. Carter started Keytruda therapy in 2015 and was declared cancer free within four months. Keytruda is not the end of cancer but it may be the beginning of the end particularly when you consider it with combination standard of care treatment or IO combined with IO.

> ***Keytruda and other new cancer drugs have been proven more effective when combined with one or more traditional cancer treatments including surgery, radiation, or chemotherapy. This area invites more investigation, development, and evaluation to consider combination therapy approaches. These combinations take what would be $300 million a year drugs to billions of dollars a year platforms.***

Additional precise methods based on Allison's research include Adoptive T-cell transfer. Chimeric T-cell therapy (CAR-T) extracts T-Cells and reengineers them into Robo Cancer Killers. Prior to CAR-T, many forms of childhood leukemia were often fatal. Novartis' Kymriah was the first FDA approved drug for pediatric and young ALL patients and opened a new chapter in immuno-oncology. CAR-T has almost eliminated some forms of this type of leukemia. (Graeber, 2018). This precise immunotherapy caused Dr. Axel Hoos, the former Global Medical Lead at BMS Immuno-Oncology to announce, "The word cure can now be used in oncology. It's no longer a fantasy or a cruel promise that you can't fulfill. We don't yet know who will be the lucky patients who will be cured, but we have seen cures already." (Graeber, 2018).

Even in this announcement of victory, Dr. Hoos identified a critical new area for precision medicine to be more scientific-driven that can never depend upon luck. Targeted medicine demands that diagnostic tests identify precisely which patients or patient populations will respond and, indeed, be cured. Targeted medicine is too expensive to use in a shotgun method hoping to hit something vulnerable. This is a place for blockbuster drug discovery.

We have discussed only four areas of immunotherapies focused solely on cancer, but the field of targeted therapy is not just oncology.

> *Targeted therapy is the bright promise for the future and there are many diseases in addition to cancer that have and will respond to new precision treatments. The recently approved drug, Onpattro, enhances targeted therapies by intercepting RNA before it delivers instructions to build an unwanted protein in the treatment of hereditary transthyretin-mediated amyloidosis.*

In general, targeted diagnostics offer promise to autoimmune disease patients. People with chronic autoimmune disorders such as multiple sclerosis, lupus, and rheumatoid arthritis require a lifetime of care. These diseases are complex and frequent testing is challenging, but without testing data disease management is less effective. DxTerity delivers a home-based diagnostics method to permit routine monitoring of disease activity and response to specific treatments. This should be a complex approach, including genomic data, as well as protein-based technology. Testing at local clinic sites has some limitations due to available diagnostics platforms. Longitudinal gene expression data from biological samples provides a more complete picture of the disease and offers specific data to determine the appropriate use of costly medications. (Kilmer, 2019).

The future of precise therapy is bright. In 2017 Allied Market Research valued the precise therapy market at $3.5 trillion. With a compound annual growth rate of 11.9% from 2017-2023 the projected market by 2023 will be $7.7 trillion. Precision therapy improves treatment, achieves cures, and holds the hope of preventing disease. (Helwande, 2018)

Targeted therapy is not without its critics. Some scientists argue that the impact of targeted therapy on overall public health has been very small while the costs have been very high. Critics argue that the model of targeted therapy comes at the expense of all other approaches to disease including molecular, cellular, physiological, and epidemiological strategies. While some of these concerns are very real, they do not constitute sufficient reasons to abandon targeted therapy. The ultimate promise of targeted therapy is that it will unite medical research in pursuit of improved health for all people. (Joyner, 2019).

Precision medicine requires contributions from the broadest scientific, medical, clinical, and technological experts at the same table at the same time. It is the industry's recognition and commitment to these functionally diverse teams that prevents Dr. Stott's prediction from coming true. Precision medicine holds the same promise of treating millions of people as do medicines we traditionally think of as blockbuster drugs. The difference is the promise of how much better the outcomes are and will be.

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About the contributor

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In the life sciences industry, Susan has placed numerous clinical, regulatory, commercial and operations executives in biotech, medical device and pharmaceutical companies.

Susan has an excellent understanding of specialties that are of critical importance to life sciences companies, including regulatory and clinical affairs, clinical development in specialty pharma and the growing arena of drug/device combination therapies.

Prior to joining Battalia Winston, Susan was a Senior Partner with NGS Global, where she earned a reputation for delighting both clients and candidates with her high-quality search process. Prior to her time at NGS, Susan was a Founding Partner and Senior Executive Search Consultant at Oliver John Partners, where she conducted numerous senior-level assignments for pharmaceutical, biotech, retail and consumer packaged goods companies.

Susan has served on the board of the Atlanta Downtown Neighborhood Association, a non-profit organization founded to promote downtown Atlanta and improve the quality of life for Atlanta's businesses and residents.