Vertex Pharmaceuticals: Humanizing drug discovery

AUTHOR

David Altshuler, M.D. Ph.D.[1,2]

ADDRESS

50 Northern Ave

Boston, Massachusetts 02210

[1]Chief Scientific Officer, Executive Vice President, Global Research Vertex Pharmaceuticals Incorporated

[2]Senior Lecturer on Genetics and on Medicine, Harvard Medical School, Massachusetts General Hospital

Thirty-four years ago, on the day my class entered medical school, we were handed an essay from 1927 by American physician Francis Weld Peabody entitled 'The Care of the Patient'[1]. Despite being written more than 90 years ago, it remains fresh today. Peabody writes of "...the amazing progress of science in its relation to medicine during the last 30 years, and the enormous mass of scientific material which must be made available to the modern physician". He argues that in order to address human suffering, we need to combine scientific information with a dedication to understanding the patient experience. "Disease in man is never exactly the same as disease in an experimental animal," he writes, concluding "...[o]ne of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient."

Peabody's patient-focused vision informs not only the care of individuals, but also efforts to discover and develop new medicines to treat serious human diseases. First, careful study of the process and progress of drug discovery shows the centrality of causal human biology to the likelihood that a therapeutic hypothesis will translate from the laboratory to the clinic to the population. Second, a focus on the patient experience leads to serious, life-threating diseases as the most compelling targets for therapy. Addressing the human causal biology of serious diseases demands great creativity in the approach to discovering, developing and manufacturing new medicines. These dual engines of human biology and therapeutic innovation propel breakthrough progress in medicine.

This article reviews the Vertex strategy to discover, develop and manufacture breakthrough medicines for people suffering with serious diseases. We have developed a differentiated strategy to serially innovate – the virtuous cycle in which revenues and profits obtained from discovering and bringing one medicine to market are used to fuel discovery and development of the next. Our 20-year history in cystic fibrosis – a story that is still being written today – has informed the strategy and exemplifies its principles. Below, I explain the strategy, and how we are applying it not only in cystic fibrosis, but also in sickle cell disease, beta thalassemia, alpha-1-antitrypsin deficiency, APOL1-mediated kidney diseases, pain, Duchenne muscular dystrophy and type 1 diabetes.

THE CHALLENGE OF DISCOVERING NEW MEDICINES

The discovery of each new medicine starts with a therapeutic hypothesis: that modulating human biology with a given therapeutic will provide benefits to a group of patients that outweigh any potential harms. Initially, therapeutic hypotheses were based on a mixture of serendipity and observation. Hippocrates wrote that willow leaves and bark relieved pain and fevers; 2,000 years later, salicylic acid (a component of willow bark) was synthesized and commercialized as aspirin[2]. Even 100 years after the discovery of aspirin, clinical trials continue today to fully understand the uses, risks and benefits of this agent.

In the middle of the twentieth century, human biology was at the forefront of life science, including infectious diseases, clinical biochemistry and endocrinology. Accordingly, therapeutic discovery focused on anti-infectives, enzymes, hormones and their receptors, as well as chemical and radioactive agents with effects on people. For example, clinical observation of high cortisol (Cushing's disease) and cortisol deficiency (Addison's disease) defined the human biology, therapeutic potential and adverse consequences of adrenocorticoid hormones prior to the synthesis and testing of synthetic therapeutics such as the anti-inflammatory prednisone[3]. This 'golden age' of the pharmaceutical industry resulted in dramatic improvements in human health that are now widely available as generic medicines[4].

Over the past half-century, as Peabody's "amazing progress of science in its relation to medicine" has grown by leaps and bounds, therapeutic hypotheses have become more reductionist in nature: most commonly, modulation of a specific protein (or other cellular target) based on studies in laboratory models. Based on the belief that such models faithfully recapitulate important aspects of human disease, and an industrial focus on efficiency processing many 'shots on goal', convenient laboratory systems were widely adopted by the pharmaceutical industry.

Over a similar period of time the overall efficiency of pharmaceutical research and development (R&D) has declined[5]. The main reason is that an average of 15 clinical candidates are now required to enter the clinic for one new medicine to reach approval[6,7].

THE VERTEX RESEARCH STRATEGY

Combine **transformative advances** in the **understanding of human disease** and in the **science of therapeutics** to dramatically advance human health

- Focus on **validated targets** that address causal human biology
- Create **predictive lab assays** and **clinical biomarkers**
- Identify **efficient path to registration** and approval
- Discover and develop transformative medicines **regardless of modality**

THE VERTEX APPROACH

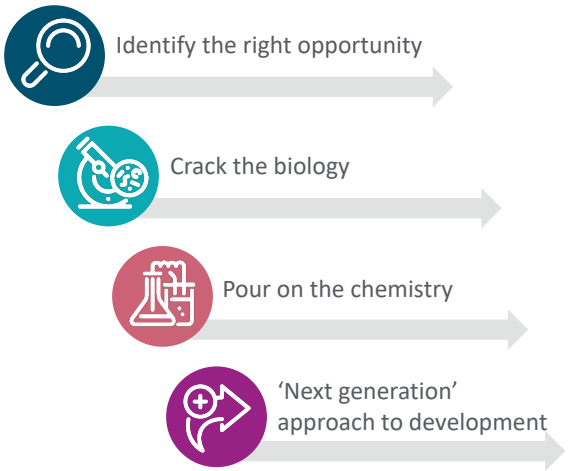

Figure 1. A summary of the Vertex strategy that guides the company's approach to creating transformative medicines.

The costs of drug discovery increase dramatically by stage: laboratory and early clinical investigation are the least expensive, and late-stage (phase III) clinical trials are the most expensive. A main driver of the investment by society to create each new and successful medicine is the cost of many failures that accumulate along the way.

Typically, the therapeutic hypothesis is first tested in phase II proof of concept studies: the initial test of the medicine in patients with disease for evidence of tolerability, safety and signals of efficacy. Systematic analysis shows that phase II is the step in clinical development with the highest attrition, with approximately 75% of all candidates failing to progress[5,6,7] to phase III Improvements in preclinical prediction have led to a decrease in the number of early failures due to safety and pharmacokinetics[7,8], which means that the majority of failures are now due to a lack of efficacy[6,9]. That is, the test of the therapeutic hypothesis failed.

The importance of successful prediction from the laboratory to proof of concept is multiplied by the time, money and effort required to translate each new therapeutic hypothesis into a clinical experiment. It takes up to one decade for a new project to discover a potential therapeutic[5,7,10] with the characteristics needed to perform a human clinical trial and then to determine the result of that clinical experiment. Unfortunately, if the underlying therapeutic hypothesis is wrong, the remainder of the effort (however expertly executed) is for naught. One analysis concluded: "When searching for rare positives (for example, candidates that will successfully complete clinical development), changes in the predictive validity of screening and disease models that many people working in drug discovery would regard as small and/or unknowable (that is, an 0.1 absolute change in correlation coefficient between model output and clinical outcomes in man) can offset large (for example, 10-fold, even 100-fold) changes in models' brute-force efficiency"[11].

Why, then, do many projects move forward without evidence for a role in causal human biology? A main reason is that only 5% or so of human proteins are 'druggable'— that is, addressable with conventional technology[12]. Faced with the tradeoff of translation risk and execution risk, many choose what can be done (use an existing technology to address a target lacking human biology) rather than what needs to be done (address the underlying cause of disease).

The perspective above highlights the challenge of discovering novel medicines, the importance of human biology and innovation in therapeutic modalities, and explains why it is rare and expensive to achieve true breakthroughs in medicine.

THE VERTEX STRATEGY

At Vertex, we have studied our own successes and failures in the 30 years since our founding, and those of others. We have learned from our experience in cystic fibrosis, and used it as a model for how we approach all our programmes. To minimize the risk of targeting the wrong biology we require targets that play a validated role in causal human disease biology as well as disease-relevant human cell assay systems. To maximize the chance of ultimate success we rapidly advance multiple clinical candidates into early clinical trials with predictive biomarkers. Only those candidates that combine causal human biology and a compelling clinical profile advance to late-stage clinical trials.

The strategy has four main steps (**Fig. 1**).

Step 1: Identify the right opportunity

Our Vertex strategy is 'to invest in scientific innovation to create transformative medicines for serious diseases in specialty markets.' Each part of the strategy plays an interlocking role in selecting the problems we pursue and how we pursue them.

We invest in scientific innovation because we believe

that scientific and medical breakthroughs are the unique and lasting value created by biopharmaceutical companies. We put our money where our mouth is: approximately 60% of all Vertex employees work in R&D, and last year we dedicated 73% of our expenses to R&D.

We believe the most important medicines are those that have transformative impact for patients with serious diseases. We don't work on "me too" drugs where others have already pioneered the approach.

To focus our resources on R&D for these serious and unsolved problems, we select diseases in which we can take the medicines to patients with a relatively small investment in sales and marketing: every dollar not invested in sales and marketing is another dollar we can reinvest back into research and development.

If done correctly, this business strategy creates a virtuous cycle of serial innovation that enables us to sustainably discover and develop multiple new medicines.

This virtuous cycle requires a research engine at the cutting edge of science with demonstrated ability to discover multiple high-value innovative medicines that have the potential to positively impact people's lives. Based on the lessons described above, our research strategy is to combine transformative advances in the understanding of human disease and in the science of therapeutics. We apply this strategy with discipline and rigour, requiring all projects to have human validated targets, laboratory assays and clinical biomarkers that read out the underlying human biology of the disease, and line of sight to a medicine that may offer transformative (not incremental) benefit to patients.

In evaluating projects against these pillars we use the history of cystic fibrosis as a guiding light. In cystic fibrosis, the seminal discovery of the *CFTR* gene in 1989 and subsequent study of its mutations illuminated the central role of chloride transport[13]. Laboratory measurements in patient-derived human bronchial epithelial (HBE) cells, and clinical biomarkers measurable in early development, read out the underlying defect in chloride transport. In order to address the underlying biology of the disease, we discovered multiple CFTR modulator therapies with distinct and novel mechanisms of action. We have brought forward four medicines that have achieved regulatory approval for the treatment of cystic fibrosis, and we continue to invest in additional CFTR modulators as well as genetic therapies for patients who have mutations not amenable to CFTR modulator therapy.

We have identified and advanced a focused set of additional diseases and approaches that meet the same criteria. One such example is alpha-1 antitrypsin deficiency (AATD), which in many ways is similar to cystic fibrosis: a serious disease of the lung and the liver, it is caused by inherited mutations in a single gene. Just as the common *CFTR*-F508del mutation is present in approximately 90% of people with cystic fibrosis, the common Z-AAT allele is found in approximately 90% of people with AATD. Both mutations cause defects in protein folding. Our scientists were the first to invent small molecules that address such protein-folding defects, and for AATD they have created small molecules to address the protein folding defect caused by the Z-AAT mutation. The molecules are tested in patient-derived cells and models engineered to carry the human gene mutation, and their activity is reflected in a blood biomarker (levels of functional AAT) that reflects the underlying biology of the disease. The first two of these molecules are now in clinical development.

Step 2: Crack the biology

Tolstoy wrote that "happy families are all alike; every unhappy family is unhappy in its own way"[14]. Similarly, each disease has unique causal human biology, and cracking this biology presents a central challenge in the discovery of a novel therapeutic.

In the case of cystic fibrosis and AATD, cracking the biology required our scientists to pioneer the discovery of small molecules that address defects in protein processing and folding. In pain, our scientists had to solve a different challenge: discovery of highly selective inhibitors of the genetically validated pain target $Na_v1.8$. We have reported positive proof-of-concept data for our novel $Na_v1.8$ inhibitor VX-150 in three types of pain: acute pain, neuropathic pain and osteoarthritic pain. In the case of APOL1-mediated kidney disease, tackling a newly recognized major genetic determinant of severe kidney disease required us to determine cellular functions of APOL1 and develop multiple human-relevant assays for a precision-medicine approach to proteinuric kidney disease. The first two clinical candidates for APOL1-mediated kidney disease have been discovered in our laboratories and are now in clinical trials.

In our quest to go where the science of human causal biology demands, we have expanded our therapeutic toolkit to include cell and genetic therapies. Human genetics of sickle cell disease and beta thalassemia highlight the therapeutic potential of foetal globin (HbF). Naturally occurring human genetic variants in BCL11A found by genome-wide association studies increase HbF levels in people and to ameliorate the symptoms and consequences of both diseases[15,16]. Together with our partner CRISPR Therapeutics, a biotechnology company based in Zug, Switzerland and Cambridge, Massachusetts, we discovered and initiated the first clinical trial of a CRISPR-based therapeutic to treat human genetic disease with CRISPR-Cas9.

In some people with cystic fibrosis, rare mutations in the *CFTR* gene cause little-to-no CFTR protein to be produced, meaning there is no protein available to respond to a CFTR modulator therapy. This group of patients requires a genetic therapy approach to replace the mutated CFTR gene. We are actively working to discover and develop cystic fibrosis mRNA therapies with Moderna Therapeutics, based in Cambridge, Massachusetts, United States, gene editing of *CFTR* with CRISPR Therapeutics and Arbor Biotechnologies in Cambridge, Massachusetts, US, and novel capsids for cystic fibrosis gene delivery with Affinia Therapeutics in Waltham, Massachusetts, US.

While many examples of human causal biology are supported by human genetics[9,17] other approaches for establishing causality include human endocrinology, clinical pharmacology and human transplant data. In the case of type 1 diabetes, immune-mediated destruction of pancreatic islets leads to insulin deficiency and the hallmarks of that life-long disease. Transplantation of cadaveric islets has been shown to be curative[18], but widespread application has been hindered by two factors: the availability of human islets suitable for transplant, and well-tolerated methods to protect those islets from immune attack.

In 2019, we acquired Semma Therapeutics, a company founded by Doug Melton that has identified potential solutions to both challenges to curative therapy for type 1 diabetes: industrial-scale production of high-quality human islets[19], and protection of those islets from immune attack through

an encapsulation device. We are excited that the people, technology and programmes from Semma are now part of the foundation for Vertex Cell and Genetic Therapies, together with those from Exonics Therapeutics, a company that we acquired last year that was founded by Eric Olsen to develop gene-editing therapies for Duchenne muscular dystrophy[20]. While still preclinical, these programmes represent potential scientific breakthroughs that hold great promise for patients.

A Vertex scientist in one of the company's laboratories.

Step 3: Pour on the chemistry

Once we have identified a novel approach to crack the biology of a human validated drug target, we next 'pour on the chemistry' by focusing on rapidly discovering and developing multiple clinical candidates with potential for testing in clinical trials. While confidence in the underlying biology of the disease lowers the risk of translational failure, the properties of the candidate medicine ultimately determines its clinical profile — that is, potency, specificity, drug-like properties, delivery to the right location at needed exposures, metabolism, stability, manufacturability and, of course, safety and tolerability.

In order to 'pour on the chemistry' we invest substantially in innovative medicinal chemistry, nucleic acid and cell biology, applying resources on each project beyond what is common industry practice. Our goal in doing so is to enter the clinic with high-quality molecules in a rapid manner, identifying, exploring and advancing multiple chemical series in parallel. Rather than select one asset and wait years to receive clinical data, we drive the optimization of multiple lead molecules and invest at-risk in early manufacturing and investigative toxicology to maximize the chance that clinical candidates can move expeditiously to clinical testing. Our internal timelines for advancing a newly synthesized candidate into first-in-human clinical testing (on the order of 12 to 14 months) are less than half those described in a recent industry survey[10].

Our approach is founded on two main principles: (a) high conviction that comes from working only on human validated targets, and (b) the relatively lower cost of laboratory research and early clinical testing as compared to late-stage clinical trials. That is, we would rather test multiple compounds in our labs and in early clinical studies, selecting (based on clinical data) the one that will be most successful in later trials, rather than select one asset based on laboratory data alone. A component of this strategy is that we continue to invest at-risk in our programmes beyond the discovery of a first-in-class clinical candidate. Our goal is to continuously 'out-innovate' ourselves, delivering additional candidates that can rapidly extend and enhance the benefit we can bring to patients.

Many of the targets with the strongest human biology validation are also some of the most challenging to tackle in conventional, so-called 'drug-like', chemical space. While we strive to deliver candidates in classical drug space wherever possible, we are guided by, but don't rigidly adhere to, medicinal chemistry 'rules', and are prepared to advance creative and unprecedented molecules. A core aspect of our chemistry culture is a healthy tension between credentialing of a target, rigorous molecular design and expansion into uncharted territory.

Although the phrase 'pour on the chemistry' suggests small molecule programmes, the same mindset applies to all our programmes regardless of modality. The underlying principle remains the same: when we have picked the right projects and cracked the biology, we then resource our projects heavily to ensure we rapidly deliver the best possible therapy for patients.

In the case of cystic fibrosis, we have screened libraries of more than one million molecules, designed and synthesized more than 30,000 molecules in medicinal chemistry, and brought forward into clinical development ten different candidates discovered in our labs. We have performed in excess of 150 clinical trials, enrolling more than 10,000 subjects. For our four medicines that have been approved by a health authority, we continue to collect data on clinical outcomes through real world evidence and long-term follow-up. In addition to characterizing the properties of each individual candidate, such information has built a strong understanding of how laboratory assays translate to the clinic, and the relationship of shorter-term and longer-term outcomes in patients.

As we move forward additional programmes, we take a similar approach of developing multiple candidates, moving them into early clinical development to assess their profile, and learning iteratively from the laboratory to the clinic and back again.

Step 4: The 'next generation' approach to development

As described above, once a compelling clinical candidate has been identified, our strategy is to move with great urgency to characterize the potential medicine's full profile in patients, to establish manufacturing at the scale and quality needed, and to work with regulators and payors to provide access to patients. Each of these challenges is an opportunity for creativity, and inventing novel solutions has made it possible for Vertex to

Vertex employees collaborate on a project.

advance five medicines from discovery in our laboratories to first regulatory approval with average timelines approximately one-third shorter than a recently reported industry average[10].

One example is our parallel approach to clinical development. Across our research programmes, our strategy is to bring multiple therapeutic candidates into the clinic and investigate them in phase I and phase II studies at the same time, when possible. Performing multiple development activities at the same time provides efficiencies and further mitigates risk of compound-specific failure and enables us to select the best possible candidate based on clinical data. In this way, the compound selected to advance into large, phase III trials is intended to have the best profile we can achieve. This approach requires greater upfront investment but enables more rapid progress and lower risk of expensive late-stage attrition — all with the goal of rapidly bringing the best medicines to patients.

Another example is the use of novel manufacturing technologies that enable faster, more agile production of potential medicines. In 2015, Vertex became one of the first companies to implement drug product continuous manufacturing technology in the development and production of our investigational and commercial medicines. This results in faster, more streamlined manufacturing process development and scale-up with quality control taking place throughout the production process. We've successfully integrated this technology into our process development, clinical and commercial supply production processes across our cystic fibrosis programme and other disease areas.

As we add cell and genetic therapies to our portfolio, we are investing in the science of discovering, developing and manufacturing these new modalities. In June 2019, Vertex announced the establishment of a new research site in the Boston Seaport, Massachusetts, US, where research, development and clinical manufacturing for cell and genetic therapies will be primarily based. At Vertex Cell and Genetic Therapies (VCGT) our teams will bring together the best biology, technologies and enhanced manufacturing capabilities to ensure we bring these cutting-edge and potentially transformative therapies to patients as quickly as possible.

HUMANIZING DRUG DISCOVERY

Many important advances in medicine come from the discovery, development and widespread use of therapeutics that address the underlying biology of human disease. Success is extremely challenging and built upon a combination of deep insight into human biology and novel therapeutic approaches. Cystic fibrosis is an example where human biology and therapeutic innovation have come together with potential to substantially impact human health. At Vertex, we're applying what we've learned from internally discovering and developing the first CFTR modulators to address a number of other serious diseases in which causal human biology illuminates validated drug targets and biomarkers provide high fidelity from bench to bedside. In each case, we bring whatever therapeutic modality is needed to address the underlying human biology. By taking this disciplined scientific approach to some of the most serious diseases in medicine, and by bringing rigour and creativity to how we address them, we strive to improve the health of patients, their families and the communities in which we live.

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