

Article

A Case Study – NeuBase Therapeutics, Inc.

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ABSTRACT

Please modify abstract to: NeuBase is a genetic medicines platform company that is developing a new type of therapy that is able to drug the human genome to increase, decrease or change gene function with single-base precision and high tolerability to resolve genetic defects that drive most diseases.

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DISCUSSION

WE ARE IN the midst of a fundamental transformation in the pharmaceutical industry. We are witnessing the shift from an analog mode of drug discovery to a digital mode, accompanied by the efficiencies that come with such shifts – increased performance, scalability and cost reductions.

Since the beginning of the era of modern medicine, drug development efforts have primarily focused on brute force approaches such as screening vast chemical libraries against a disease target to identify those which positively affect the disease process. Thereafter, often years of chemical optimization efforts ensued to maximize potency while minimizing toxicity. High-throughput screening was necessary primarily due to ambiguities in how to engage dynamic structures such as proteins within patient cells to ameliorate disease processes. The time and expense necessary to move from target selection to nominating a candidate for clinical studies essentially made each drug development effort an expensive and bespoke endeavor. As a result, most diseases remain intractable today. Consider this as an analog approach in that we use information represented by continuously variable spatial positions between, for example, a small molecule and its interaction points with proteins to optimize for potency and selectivity.

As a result of the sequencing of the human genome, more than two decades of pathogenic genetic variant discovery efforts and databasing, the establishment of global infrastructure to perform genetic testing of patients and concurrently computational infrastructure

and expertise, we have set the stage to be able to address diseases at the genetic level using a digital strategy.

New therapies have emerged as proof-points of this new digital era in the pharmaceutical industry. Gene replacement/activation, gene silencing and gene editing all target misbehaving genes directly, the true root causes of most human diseases, through Watson-Crick base-pairing for binary (at the nucleobase level) target engagement.

NeuBase Therapeutics' platform technology engages genetic targets in a sequence specific manner to increase, decrease or edit gene function to address the majority of causal mechanisms undergirding human diseases in a unifying approach with ultra-high precision of target engagement and a well-tolerated chemistry. The compounds that are produced look conceptually like single stranded short oligonucleotides, but due to the chemistry that is used, they have advantages over other genetic medicines. The "backbone" of the oligo is made of modified peptides, onto which are coupled nucleobases in a sequence that engages a nucleic acid target of interest in a sequence-specific (binary) manner. These are termed peptide-nucleic acids (PNAs). Due to a neutral charged backbone and the resultant high-affinity engagement, the oligos can invade into double-stranded DNA without being repulsed and engage the target with Watson-Crick base pairing (in addition to a variety of other binding modes to fine-tune rescuing gene function). Importantly, the backbone is also rigid which increases the precision of engagement in that even a single mismatch can cause the drug to disengage and seek a perfect match engagement. These two features allow us to drug the *genome* with *single base precision*, to increase gene

expression, decrease expression, or to edit the genome. As the backbone is a polyamide much like a nylon, it is largely biologically inert. These features form the basis for a growing pipeline of therapies at an increasing rate of output that have the cardinal features one would select for an optimal therapeutic modality: in silico design, target-specific engagement without off-target effects and a well tolerated fundamental chemistry to address a variety of single-gene Mendelian diseases, cancer targets and eventually common diseases.

Because the platform can address all three major causes of disease at the genetic level, there is broad set of targets that are under consideration. The single-base precision of engagement also allows a broadened set of therapeutics targets as many diseases are caused by small mutations (such as missense mutations in dominant diseases) that are largely not addressable by other genetic medicine technologies. This precision also has the potential to reduce off-target engagement which may result in adverse events. Finally, as the backbone appears to have minimal inherent toxicities (for example no innate or acquired immune responses seen to date), the potential for broad impact is notable. Conceptually, this has the potential to be a final generation therapeutic modality.

Related to scalability, as with any platform, the promise is that as one becomes conversant with the technology, that it becomes more efficient over time. We have seen hints of this with various first-generation genetic medicines companies. We have witnessed increasing efficiencies internally as we progress with our various programs. For example, our initial programs required manufacturing and screening hundreds of candidate compounds to identify a few hits, whereas now we are able to screen dozens of candidates to achieve high hit rates. Similarly, as the general non-sequence dependent toxicology profiles become predictable and we can focus

on off-target effects (OTES), the promise to anticipate these off-targets engagements potentially enables the Company to eliminate OTES *a priori* through careful target sequence selection, or to anticipate them in advance and monitor for them proactively to ensure efficient development.

The Company has announced several programs in areas of large unmet need. For example, in RAS-driven tumors. Approximately 30% of all cancers are caused by mutations in an oncogene named RAS. The two most common mutations in KRAS, G12D and G12V, remain “undruggable”. Investigational compounds have been developed by the Company that are able to engage the mutant copy of the KRAS gene selectively and slow tumor growth *in vivo*, in some cases illustrating tumor regression. This can be done at the DNA or at the RNA levels, and result in a lack of production of the mutant protein itself. This is a different strategy that is being used to address a less common mutation, G12C at the protein level with small molecules. Digital drug development with single base precision at the genetic levels has opened a new area of opportunity for patients suffering from a wide range of largely intractable tumor types.

NeuBase is a digital drug development company working to deliver on the promise of the Human Genome Project by outputting genetic medicines that address root causality in an ultra-precise manner across a multiplicity of diseases using a scalable platform strategy. The end result, we believe, will be to improve the lives of patients with a wide variety of diseases through moving the industry from an analog to digital mode with increased efficacy and with increased performance related to efficacy and tolerability, scalability of output to impact many more diseases and development cost reductions which may allow healthcare to become sustainable as we as an industry succeed in the coming decades.