Next generation gene therapy platform using Active Genetics to develop animal models and safe, non-viral, cell-based therapeutics

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Synbal is a biopharmaceutical company using a novel gene delivery platform, ***Active Genetics***, which can be harnessed to create safe, non-viral cell-based therapeutics. Active Genetics is also being used to develop novel laboratory animal models with multiple human genes inserted into the rodent genome to improve the predictability of rodent models of disease. The research tools developed during the animal projects allows Synbal to start optimizing our technology for cell-based therapies. Aiming to treat monogenic gene deficiencies, Synbal is using non-viral delivery systems and Active Genetics in autologous cells. The technology allows precise, single site, biallelic targeting to control gene dose, and allows large size DNA inserts. These features improve safety, eliminate random integration and the large cargo size allows for control elements and kill switches. Use of non-viral technology avoids both pre-existing immune responses as well viral induced immunity that may limit other approaches. The company has recently been awarded grants and contracts totaling $4.9M to develop Active Genetics in laboratory animals. We are now seeking additional seed funding of $2M to conduct cell based proof-of-concept studies. This will be followed by IND enabling studies that, in turn, will lead to solicitation of Series A funding.

Technology and Differentiator: Autologous Cell Gene Replacement

Synbal's technology uses homology directed DNA repair combined with CRISPR/Cas9, to deliver large genetic cargos at pre-determined genomic locations with a specific autocatalytic property that converts both alleles to homozygosity, increasing gene dose. Our non-viral methods and large cargo size capability avoid the safety and immunological issues hampering viral approaches. It also allows control elements and shutoff mechanism to be included with the target gene for added safety.

Technology and Differentiator: Animal Models:

Synbal's Super Mendelian inheritance technology permits the development of next-generation transgenic (humanized) laboratory animal models (rats, mice) with unprecedented genetic complexity (five or more humanized loci). Super Mendelian inheritance simultaneously reduces the number of animals by 10-fold and the number of

generations needed to obtain a product/animal by 2-fold, resulting in savings of nearly 10-fold in cost with the final product developed in half the time.

Traction - Funding:

- **September 2018:** Synbal was awarded a Small Business Innovation Research (SBIR) Fast Track award for $2.3M to develop a humanized rat model. This rat will express 9 different human Cytochrome P450 genes responsible for metabolizing 80% of small molecule drugs. This model will provide an invaluable resource for more accurate prediction of human drug metabolism in rat models of disease.
- **October 2018:** Synbal opened its laboratories in the BioLabs facility in San Diego, CA. Currently there are three scientific staff at the PhD level.
- **October 2018:** A second contract ($2.6M) was also awarded to Synbal by a Biopharmaceutical company to develop a humanized, multigene animal model in the mouse. The funds from both sources are exclusively for the development of laboratory animal models and provide the company with sufficient operating funds for approximately three years.

Human Therapeutics Focus

Synbal's efficient Active Genetics platform allows it to consider as target diseases, the majority of about 50 known lysosomal storage diseases and many other recessive single gene deficiencies. Therapy of rare diseases of these types are predicted to be 20% of the world pharmaceutical market by 2030.

Synbal's initial focus is on rare lysosomal storage diseases (LSD) which have not been targeted by other clinical stage gene therapy approaches. There is no therapy for many of the about 50 LSDs. Several (Fabray's, Gauchers, Pompe, etc.) are currently treated with enzyme replacement therapy (ERT). In 2017, global revenue of ERT is nearly $7.39 billion estimated to grow by 6.5% p.a. to $13.7billion in 2024. The US ERT market is estimated to reach $6.4 billion in 2028 accounting for 25-30% of the global market. Current therapies cost around $300K/year/patient and require that the patient endure infusions every two weeks for the rest of their lives. Solutions are needed that provide durable decades-long and lifetime therapies. The medical economic case of autologous cell-based ERT is strong. There are likely additional benefits will accrue due to the constant enzyme supply via cell therapy rather than the fluctuating levels patients experience with bi-weekly infusions.

Synbal's Therapeutic Technology Advantage:

1. Non-viral approach - less oncogenic potential and no immunological blockade to deployment
2. Unique single integration site of DNA cargo on both alleles – increasing gene dosage with no off-target integration and thus less oncogenic potential
3. New IP protected method for cell transformation and optimization techniques.
4. Focus in a therapeutically important direction and unmet need
5. Offering possibility of life-time or decades-long cure
6. Veteran team with strong product development experience

7. Risk-managed approach to treat rare diseases – HUMAN POC IN PLACE

Leadership Team

Founders: Dr. Ethan Bier and Valentino Gantz of UCSD.

Executive Team Pharma and Biotech Veterans:

CEO: Dr. David Webb, former Celgene, Syrrx, OSI, Cadus and Syntex/Roche

CSO: Dr. Kurt Jarnagin, former Pfizer, Anacor, Iconix, Syntex/Roche

David and Kurt have been involved in the development and registration of eight FDA approved drugs.

Scientific Advisory Board: Stephen Hedrick, Ph.D., Distinguished Professor, UC San Diego (Co-discoverer of the T-Cell Receptor); Rick Morrissey, Ph.D., Former VP of Development, Celgene; Kim Cooper, Ph.D., Assistant Professor at UCSD, rodent models.

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