Philanthropy and Advocacy–Led Development of Gene Therapies and Drugs for Alpha-1 Antitrypsin Deficiency

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ALPHA-1 ANTITRYPSIN (AAT) is an antiprotease synthesized primarily by the liver and secreted into the bloodstream. Its main function is to protect the lungs from damage caused by neutrophil elastase. Alpha-1 antitrypsin deficiency (AATD) is a single-gene inherited disease that affects at least 100,000 people in the United States, about the same number in Europe, and perhaps up to 3 million worldwide.[1] AATD is a recessive condition, requiring inheritance of the mutated gene from both parents.

Most cases of severe AATD lung or liver disease are caused by homozygous inheritance of a mutation in the alpha-1 antitrypsin gene called the Z mutation (E342K). With this mutation, the alpha-1 antitrypsin Z protein is misfolded, becomes polymerized, and accumulates and aggregates in the liver, resulting in low AAT levels in the blood and lungs. The effect is progressive proteolytic destruction of the elastin in the lungs, resulting in a genetic form of emphysema. This genetic emphysema can occur relatively early in life, often in the third or fourth decade in smokers, but many individuals remain unidentified into their fifth or sixth decade of life. The accumulation of polymerized AAT in the liver can also result in cirrhosis in children and adults. The risk increases with age in adults.

There is currently no cure for AATD. For the lung disease, augmentation therapy can slow the progression of elastin destruction. Augmentation therapy, which was approved by the U.S. Food and Drug Administration (FDA) in 1987, consists of administration, by intravenous infusion, of purified AAT from pooled human plasma. The FDA's approval of augmentation therapy was based on "biochemical efficacy," after studies with patients deficient in AAT showed that intravenous administration of 60 mg of purified AAT per kilogram of body weight once per week could reestablish protective serum AAT concentrations and, importantly, raise lung alveolar AAT concentrations and antiprotease capacity. In end-stage lung disease, organ transplantation is often the only possibility.

In a study published in the *Lancet*, lead author Kenneth Chapman, M.D., and colleagues demonstrated evidence that augmentation therapy slows the progression of lung destruction in patients with AATD as measured by computed tomographic scan in a 2-year randomized placebo-controlled trial.[2] Today, four manufacturers of plasma-based augmentation therapy are active in the United States, with intravenous infusion as the only method of administration.

There is no specific therapy for AATD-related liver disease, with the only therapies being treatment of symptoms. Again, liver transplantation is the solution of last resort.

The Alpha-1 Foundation is a Miami, Florida–based not-for-profit founded in 1995 by three patients with lung disease due to AATD, with the stated mission of finding a cure for alpha-1 antitrypsin deficiency and improving the lives of people affected by alpha-1 worldwide. The Foundation has invested more than $54 million to support lung and liver AATD research and programs at 100 institutions in North America, Europe, the Middle East, and Australia.

In 2010, the Foundation announced the development of a wholly owned, for-profit subsidiary called The Alpha-1 Project (TAP). TAP is a venture philanthropy company—it uses venture capital practices from business to achieve its philanthropic

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goals. When TAP was founded, Scientific Director Adam Wanner, M.D., pointed out that basic research in alpha-1 antitrypsin deficiency, much of it funded by the Alpha-1 Foundation, has been extremely successful. He noted that the basic mechanism that results in lung damage in adults, and liver disease in children and adults, is now known and that promising drug targets have been identified.

Jean-Marc Quach was hired as the first executive director of TAP in 2011, to work on fulfilling TAP's mission: "To work with patients, academia, pharmaceutical and biotech companies, and public health organizations to relentlessly look for cures and therapies for lung and liver diseases caused by alpha-1."

TAP's *raison d'être* was and is to encourage drug development for industry by de-risking many elements. In a typical collaboration, TAP provides funding, access to AATD resources such as The Alpha-1 Foundation DNA and Tissue Bank, the Research Registry, key opinion leaders, and translational research tools. This in turn helps industry accelerate drug development and often in fundraising as well. Other patient advocacy organizations such as the National Multiple Sclerosis Society and the Cystic Fibrosis Foundation have also formed such venture philanthropy organizations.

TAP makes investments in promising therapies for AATD, the primary goal being to find new treatments and ultimately a cure for lung and liver diseases caused by AATD, with a secondary goal to use any financial returns to fund additional research.

TAP has its own governance via a separate board of directors. The board provides guidance to the executive director and approves all investments in therapies. Its Scientific and Business Advisory Council guides the company's agenda and reviews. The science advisors are world-class researchers, practitioners, and scientists in AATD and the business advisors are seasoned senior business executives, including the past chairman of the Alpha-1 Foundation Board of Directors.

The science agenda is determined by the science advisors, and currently includes the following therapies for AATD:

- Gene therapy and stem cell therapies
- Small-molecule chaperones and modulators
- Antiproteases and antiinflammatories
- Devices for the detection, monitoring, and treatment of AATD

In the opinion of TAP's scientific advisors, the two therapies with the highest probability for a cure are gene/stem cell therapies and small-molecule chaperones. AATD is well suited for gene correction and therapy because AATD is a monogenic condition. Newer tools such as CRISPR/Cas9 make gene correction more accessible to researchers. Gene silencing is also a strategy that, when coupled with augmentation, could bring us closer to a cure.

TAP has announced funding and partnerships with biotechnology companies seeking to develop new drugs and with academic researchers providing new tools.

When potential therapies reach the point of human testing, development companies turn to TAP and the Alpha-1 Research Registry, a confidential database of more than 4900 people diagnosed with AATD as well as carriers (who have a single mutant alpha-1 antitrypsin gene).

Our critical message to industry and academic partners is as follows:

> *TAP's investments and resources make it more attractive for manufacturers to bring a cure to market. TAP lessens their risks by reducing development costs. We fill a funding gap in the process of finding a cure. In addition to funding, we leverage all the resources and expertise that the Foundation has built to lessen the risks for companies working to take an AATD drug to market.*

TAP funded the development of translational research tools that are available to industry and the research community. One such tool is an "Open Source" stem cell bank at Boston University; it is composed of 30 clones of disease-specific induced pluripotent stem cell (iPSC) lines generated from 10 individuals with diverse AATD genotypes, including Z, S, and null AAT mutations. In addition, TAP funded the development of an antibody at the University of Massachusetts (Worcester, MA) that can detect the Z mutation.

TAP has also funded a postdoctoral fellowship at the National Center for Advancing Translational Sciences (NCATS) Division of the National Institutes of Health (NIH, Bethesda, MD), keeping AATD in the forefront at one of the world's foremost medical research centers.

TAP uses a rigorous selection process to evaluate which organizations to fund. Letters of interest are reviewed in May and November and scored by TAP's scientific advisors. Organizations with a meritorious letter of interest are invited to submit a full application, which is reviewed in depth by the full advisory council, both scientific and business. If an application is recommended for funding, TAP conducts its due diligence and negotiates the investments. A contract is finalized only after the TAP board of directors has approved it.

In the view of the Alpha-1 Foundation, TAP is a logical continuation of the excellent work by so many researchers the Foundation has funded over the years. The ultimate goal has always been to find a cure for alpha-1. The only way to accomplish this goal is to directly fund translational research—the drug development process.

TAP INVESTMENTS AS OF SEPTEMBER 2015

TAP has invested in three companies developing potential gene therapies targeted at alpha-1 lung and liver diseases. Two of those, Alnylam Pharmaceuticals (Cambridge, MA) and Arrowhead Research (Pasadena, CA), are seeking to develop injectable drugs for liver disease based on RNA interference (RNAi). The aim of these drugs is to silence the specific gene to prevent mutant AAT protein from being made and subsequently aggregating in liver cells.

- Alnylam Pharmaceuticals presented a poster at the American Association for the Study of Liver Diseases annual meeting in 2013 showing that their experimental drug reduced AAT protein by 90% in mice as well as reduced fibrosis and the incidence of liver tumors. Alnylam was granted approval by the U.K. Medicines and Healthcare products Regulatory Agency (MHRA) to initiate a phase 1/2 clinical trial with ALN-AAT. The study will be performed in normal healthy volunteers, and then in subjects with alpha-1 liver disease.
- Arrowhead Research is already conducting a phase 1 clinical trial in Australia of its gene-silencing product, ARC-AAT. In addition to the funding, TAP advised Arrowhead through the clinical trial process.
- Applied Genetic Technologies Corporation (AGTC, Alachua, FL) is a gene therapy development company. AGTC was TAP's first investment, and it will partially fund AGTC's planned phase 2b trial for gene therapy for AATD-related lung disease. Using its proprietary delivery system, AGTC can deliver a normal alpha-1 gene into muscle cells.

The Foundation had sponsored earlier basic research that established the feasibility of intramuscular gene therapy. That research led to the formation of the commercial entity, AGTC. TAP has also collaborated with two other companies:

- Carolus Therapeutics (La Jolla, CA), a biopharmaceutical company, is researching an "antiplatelet" strategy to treat chronic obstructive pulmonary disease (COPD), including COPD caused by alpha-1.
- Inhibrx (La Jolla, CA), a biopharmaceutical company, is developing a fully active recombinant AAT–IgG Fc fusion protein for augmentation therapy, engineered to eliminate inactivation by oxidation and further extend the half-life of the protein. The company believes its recombinant therapy could benefit patients by enhanced efficacy and less frequent dosing.

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