Aeglea Biotherapeutics
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aeglea BIOTHERAPEUTICS

Enzyme engineering for rare disease and cancer

Aeglea Biotherapeutics is engineering human enzymes as replacement therapies for the treatment of both inborn errors of metabolism and cancer.

Amino acids (AAs) are fundamental building blocks of life, making up proteins, cycling nitrogen, providing energy and transmitting signals. Nine of the 21 AAs found in protein are 'essential,' meaning they must come from dietary sources in humans. Four other AAs, including arginine and cysteine, are 'semi-essential'; that is, there are biosynthetic pathways to produce them in humans, but a dietary source is required in some circumstances. Although adequate supplies of these AAs are clearly necessary for health, an oversupply of some AAs can, perhaps surprisingly, be devastating and even fatal.

Aeglea Biotherapeutics is a leader in the creation and development of novel human enzymes that act in the circulation to degrade target AAs. Aeglea's engineered proteins are designed as enzyme-replacement therapies for the treatment of rare inborn errors of metabolism (IEMs), removing excess AAs that would otherwise accumulate to toxic levels. These enzymes also hold promise as therapies for certain cancers that have become dependent on AAs in the diet to fuel their growth. Depleting key AAs in blood may selectively starve tumor cells of essential nutrients, opening a new avenue for cancer therapy.

Aeglea is focused on discovering and developing treatments for abnormalities in AA metabolism for which the biology is well understood and there is a compelling unmet medical need. IEMs are a large collection of rare genetic disorders, including disorders in AA metabolism. These rare metabolic disorders currently have limited treatment options, and no single therapy is appropriate to treat the full range of diseases. Although IEMs involving AA metabolism are rare, the biosynthetic and degradation pathways that together drive their pathology are well characterized. Aeglea has concentrated its efforts on treatments that are amenable to a blood-based mechanism of action. According to Aeglea's cofounder, president and CEO, David G. Lowe, this focus offers a high probability of success in creating effective treatments that will have a substantial impact on the course of disease. Serum AA levels are an accessible and clinically meaningful pharmacodynamic measure that provides proof of mechanism and serves as a potential surrogate marker for clinical benefit. Preclinical testing has shown that the enzymes Aeglea is developing can act in the blood to reduce AA levels.

All cells require a balance of AAs for normal function, but tumor cells can become particularly dependent on specific AAs. The energetic cost of AA production is high. In some cases, tumor cells can gain a growth advantage during oncogenesis by suppressing biosynthetic pathways, such as synthesis of the semi-essential amino acid arginine. The loss of this pathway provides a potential biomarker or companion diagnostic strategy to identify arginine-dependent tumors. This growth advantage comes at a cost, however, as it leaves the tumor vulnerable to any reduction in the supply of a necessary AA. Although two U.S. Food and Drug Administration–approved microbial enzymes targeting asparagine conceptually validate AA targeting in cancer treatment, immunogenicity is a limiting factor. For example, a mycoplasma-derived arginine-degrading enzyme elicits a neutralizing antibody response in patients.

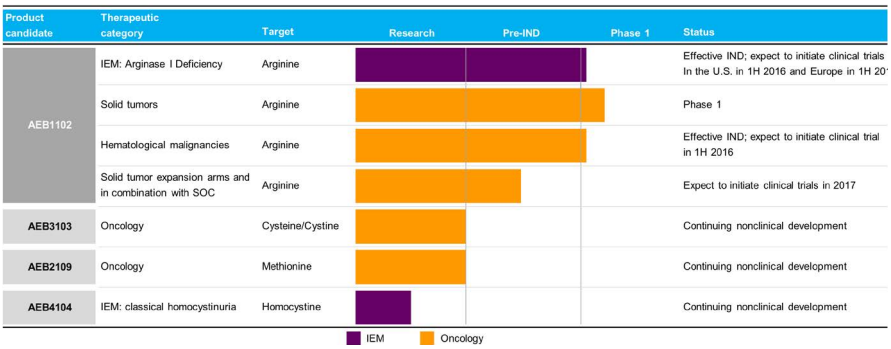

Figure 1: Aeglea's product pipeline. 1H, first half; IEM, inborn errors of metabolism; IND, investigational new drug; SOC, standard of care.

Beyond microbial enzymes, the human genome does not provide direct product candidates to more broadly exploit tumor AA dependence. Aeglea believes that its first product candidate, the arginase AEB1102, which is an engineered human enzyme, has the potential to be less immunogenic than microbe-derived enzymes. Other advantages of Aeglea's engineered-enzyme approach for AEB1102 include the potential ability to identify and select patients with AA-dependent tumors, the ease of monitoring drug activity in a blood sample and the enzyme's unique mechanism of action, which may not have overlapping toxicity with other cancer therapies.

Preclinical and clinical studies have shown that AEB1102 reduces blood arginine levels, providing proof of mechanism. As of early 2016, Aeglea has an effective investigational new drug (IND) application in the United States for patients with impaired arginine degradation caused by a mutation in the arginase 1 (*ARG1*) gene (**Fig. 1**). ARG1 deficiency is rare, occurring in an estimated 500–600 individuals in the United States and Europe combined. As early as 1–3 years of age, affected children develop neurologic symptoms, including cognitive deficits and seizures, and they may ultimately suffer from spasticity and severe intellectual disability. To date, no therapy has been approved that addresses the fundamental defect underlying the disease. To our knowledge, AEB1102 treatment is the first known attempt to create a potential enzyme-replacement therapy for ARG1 deficiency. The hope is that it may dramatically alter patients' lives if treatment is begun early in life, thereby delaying or even preventing progressive neurological impairment.

AEB1102 is also currently in phase 1 trials in cancer patients with advanced solid tumors and has an effective U.S. IND for a phase 1 trial in cancer patients with hematological malignancies, in particular acute myelogenous leukemia and myelodysplastic syndrome. Biomarkers of tumor arginine dependence have shown value as predictors of sensitivity to arginine depletion and will help guide the selection of future cancer indications to pursue in later clinical trials with AEB1102.

In addition to an ongoing trial with AEB1102, Aeglea has a robust pipeline of engineered human enzymes targeting other key AAs (**Fig. 1**). These product candidates degrade cysteine and cystine, targeting the dependence of tumors on glutathione to protect against oxidative stress, and methionine, an essential amino acid for which some cancers have an increased appetite. A third enzyme, AEB4104, degrades homocystine, which accumulates in the IEM classical homocystinuria as a result of a deficiency of the enzyme cystathionine β-synthase. Aeglea is committed to creating value by pursuing multiple clinical pathways in parallel, each tightly focused on diseases with the potential to be markedly affected by a single enzyme.

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