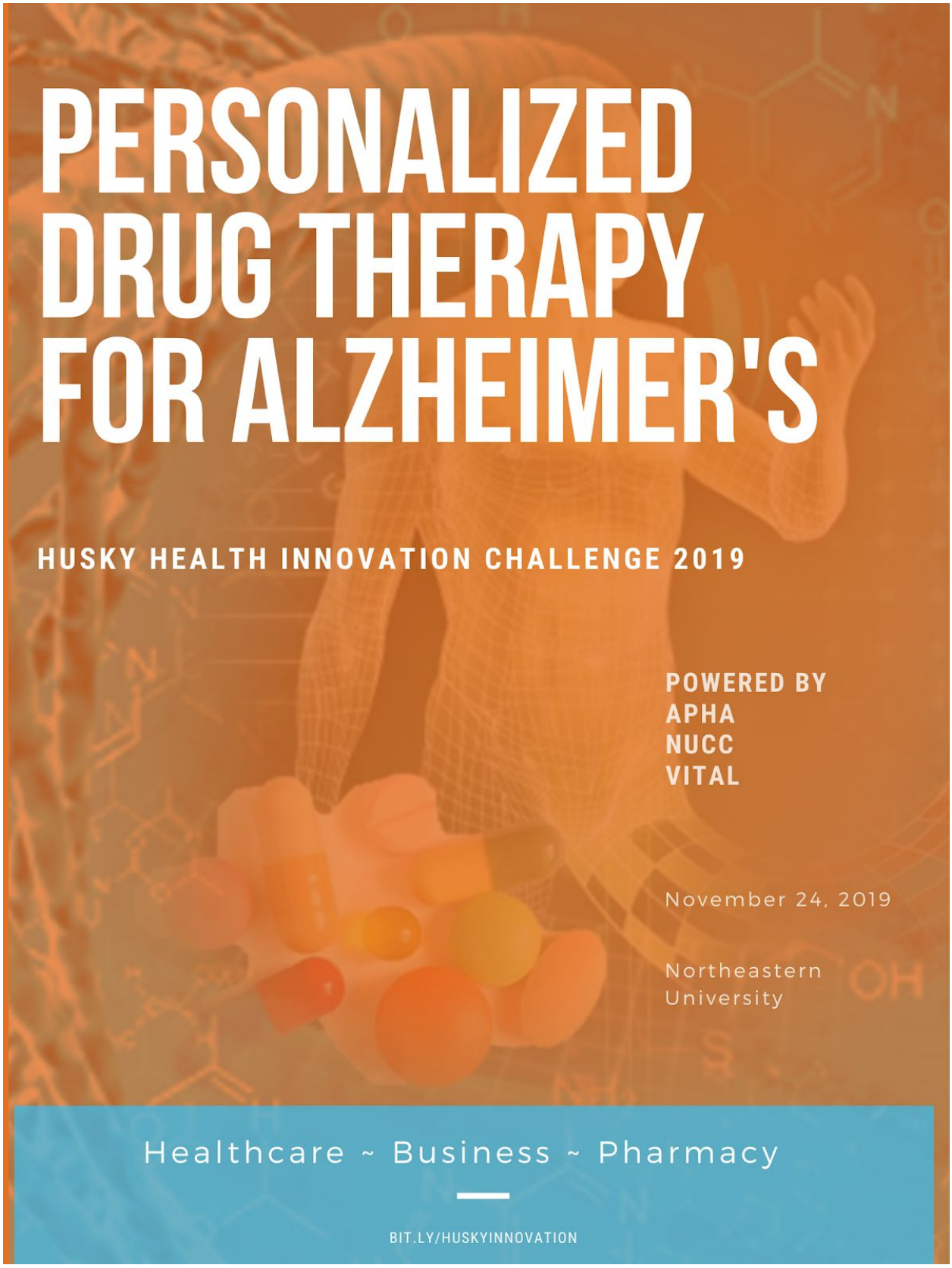

PERSONALIZED DRUG THERAPY FOR ALZHEIMER'S

HUSKY HEALTH INNOVATION CHALLENGE 2019

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Northeastern University

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Prologue

Alzheimer's disease (AD) is a subcategory of dementia associated with difficulty in behavior, memory, and thinking. Current treatments cost the nation $290 billion. Today, 5.8 million Americans have AD, and it is the 6th leading cause of death in the US[1]. Depression is common among Alzheimer's patients, with about 40% of those diagnosed with AD being clinically diagnosed[2]. Depression as a whole affects 16.1 million Americans.[3]

Specifically, a subtype of depression with high amyloid-B peptide 40 (AB40)/AB42 ratio, termed "amyloid-associated depression," has been linked with memory impairment. Elevated plasma AB40 and declining plasma AB42 levels have been both linked to pre-clinical or early stage AD[4]. Thus, it is possible that the elevated AB40/AB42 ratio seen in amyloid-associated depression may be a biomarker to determine prodromal depression of AD. Apolipoprotein E4 (ApoE4) allele contributes to this by causing high amyloid plaque buildup, primarily composed of AB40. In the past years, there has been a steady buildup of research arguing that Apolipoprotein E4 (ApoE4) plays a pivotal role in increasing the risk of developing both Alzheimer's disease and depression.

Company Profile

Lethe Therapeutics is a pharmaceutical startup focusing on Alzheimer's Disease (AD) research that has emerged from a joint collaboration between Northeastern University and Harvard Medical School. Their research focuses on the use of precision drug therapies to treat AD. The company was founded by passionate entrepreneurs and scientists who are determined to make a difference in the world through their innovative strategies to tackle some of the biggest unmet medical needs of the 21st century. Their first drug, referred to internally as Nucital-APhA, works by targeting the physiological effects of the Apolipoprotein E (APOE) protein. APOE is a major cholesterol carrier and is involved in the metabolism of fats around the body. In the brain, the ε4 variant has been shown to be a strong genetic risk factor for developing AD[5]. After receiving NIH funding for preclinical research, the company received $250 million in Series B funding from Polaris Partners, Staircase Ventures, and other

firms in 2016 and has conducted Phase I and II trials at the Longwood Medical Area. They signed a partnership agreement in April 2019 with Biogen to assist with clinical trial development. After accounting for startup costs, the company has $50 million left and is considering another round of private funding in the next 6 months before starting Phase III trials.

Drug Profile

Nucital-APhA has shown promise in laboratory studies and early clinical trials by chemically degrading AB40, leading to decreased levels in the plasma and thus, balancing out the ratio of AB40/AB42. Researchers hypothesize that this method of treating the disease could lead to lower incidences of AD, potentially even providing a cure. Minimal side effects are expected and no patients have yet discontinued the drug in clinical trials due to intolerable adverse events. The most common side effects reported are nausea/vomiting (20%), mood swings (13%), and insomnia (8%). In studies, the drug is administered by mouth in a 20mg tablet form once daily with a full glass of water. No other major pharmacokinetic or pharmacodynamic properties have been reported.

Executive Decision

Lethe's primary interest has been in developing the drug as a way to target the amyloid-plaque buildup that is highly characteristic of AD. Currently at the end of their Phase II trials, their results have been encouraging in eliminating the plaque buildup and they are hoping to begin recruitment for Phase III trials by the end of 2020.

Based on the continued success of Nucital-APhA in laboratory studies and early clinical trials, the company has been highly touted by industry leaders to perform well in Phase III trials and receive market approval following the submission of the NDA to the FDA. The results that have been gathered thus far have been showing some promise in the treatment of AD and are progressing to become clinically significant in practice. More recently, in Phase II trials, the study staff noticed a significant improvement in symptoms of depression in their patients.

This revelation led the principal investigator leading the clinical trials to reconsider the drug indication. Nucital-APhA showed significant promise in treating individuals who have been clinically diagnosed with amyloid-associated depression, a secondary endpoint that is being evaluated in the clinical trials. Now, he is unsure whether to keep the current primary

endpoint or change it to reflect the promising depression treatment results. The principal investigator shared his results with the executive team, each with related concerns.

Chief Medical Officer

Arindell Speare, the Chief Medical Officer, has concerns about the clinical development of Nucital-APhA.

- What is the primary endpoint we're choosing? Why?
- What types of clinical trials will we conduct?
    - Populations, safety and efficacy endpoints, timeline
- Any potential clinical development obstacles? How can we prevent them?

Chief Financial Officer

Kevin Chang, M.D., the Chief Financial Officer, oversees brand strategy with associated financial costs and benefits.

- What is the competitive landscape of the chosen indication?
    - What would be the ideal pricing scheme?
- Cost-benefit analysis between the two indications favoring the chosen indication
- Should we consider another round of private funding or go public?

Chief Ethics Officer

Ethan Mondell, the Chief Ethics Officer, prioritizes the upholding of pharmaceutical ethics at Lethe.

- How will patient confidentiality, dignity, and autonomy be upheld during the clinical trials?
- How do our chosen indication and strategies show beneficence?
- Will we be able to address unmet medical needs under our new indication?
    - Can we stay true to the vision of the company while remaining profitable?

At this point, the company sits at the end of a fork. Lethe may choose to continue to a Phase III trial and submit the NDA by the end of 2020. In the NDA, they can include data showing promise in treating amyloid associated depression, allowing physicians to potentially prescribe the drug for this off-label indication. However, the company will not be able to legally market the drug or attempt to persuade prescribers to prescribe for this indication. On the other hand, the company can choose to change the drug indication to depression, a more

prevalent disease. This may involve restarting the clinical trial from Phase I with a new sample size and will delay the 2020 goal.

You have been called in as third party consultants to advise the board. It is your role to create a presentation for the board on what they should do. Be sure to address each of the board members' concerns.

Deliverables

- PowerPoint presentation (15 minutes max)
    - Slides must be annotated and address each concern posed by the Board
    - Please bring three (3) hard copies for the judges.
- Complete citations must be included (AMA)

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