Reimagining the Future of POC

Introducing a Novel **Alzheimer's Antigen test**

Creating a Novel Alzheimer's Antigen test leveraging Salivary Proteins

EXECUTIVE SUMMARY

Problem

The cost of diagnosing Alzheimer's per person is about $819. (1) However, 60% of patient's reside in low to middle-income countries (2) lacking access to proper diagnosis, resulting in irreversible symptoms and long-term health issues. As global life expectancy increases, the prevalence of Alzheimer's is expected to grow exponentially, underscoring the need for affordable yet effective diagnostic solutions.

Alzheimer's disease diagnosis involves a combination of methods including Cerebrospinal fluid analysis and brain imaging (via MRI, CT, or PET). Such diagnostic methods are both invasive and/or expensive. **A collective $3.4 B (3) is spent on global Alzheimer's diagnosis annually.**

Approximately **38.5 million people (4)** worldwide are currently living with Alzheimer's. Each year, about **7 million new cases (5)** of Alzheimer's are diagnosed. As global life expectancy continues to increase annually, there could be **73 million people** living with Alzheimer's by the year 2050 **(6)**.

Solution

Creating a **Novel Salivary Antigen test** capable of detecting Alzheimer's by measuring levels of plasma proteins **SVEP1, IGFBP7 & MARCKSL1**. This test is **effective** yet **affordable**, and it can be self-administered at home.

A recent study has found a connection between Alzheimer's disease and 15 plasma proteins **(7)**. Proteins such as SVEP1, IGFBP7, and MARCKSL1 were found to be elevated in concentration, with particularly high expression in the **salivary glands.**

The saliva is collected from the individual via a swab and soaked into an extraction solution, which is then applied to a test strip. It will migrate through the paper strip and interact with the specific aptamers that have been conjugated with luminescent indicators. The specific aptamers are **PEAR1, IGF1R and JNK**, which are native ligands to SVEP1, IGFBP7 and MARCKSL1 respectively. If the ligand proteins are present in the sample, coloured lines will appear on the strip test.

Upon receiving the results, the user can determine if they are in the **early stages of Alzheimer's disease**. If the test is positive, they can seek confirmation from a doctor and begin treatment early, potentially leading to a reversal of symptoms and **an improvement in the quality of life** for both the patient and their caregivers.

Impact

The Antigen test, which is sold in packs of two, is expected to generate **$60 million USD in revenue** within three years, based on a price of **$20 USD per unit** and an estimated market adoption of 14%. This cost-effective test can **significantly expedite Alzheimer's disease diagnosis,** reducing the time from several weeks to just a few days.

Switch Health has developed a cutting-edge diagnostic tool that is not only **highly effective, but also affordable and accessible** to everyone. This tool serves as a critical foundation for doctors to make a final diagnosis of Alzheimer's disease and create a treatment plan as soon as possible, thereby **minimizing the risk of long-term side effects.**

The development of this test is a significant stride towards Switch Health's **ultimate goal of offering diagnostic tests for a wide range of health conditions.** Furthermore, the technology used in this test is adaptable and can be applied to other neurological conditions that share similarities with Alzheimer's disease.

The State of Alzheimer's

The Status Quo

What is Alzheimer's?

Alzheimer's is a neurological disease leading to a decline in memory, thinking, and behaviour. Abnormal proteins build up in the brain, leading to plaques and tangles that damage brain cells. While there is no cure, treatments can help manage symptoms and improve quality of life. **38.5 million people currently suffer from this disease with 7 million new diagnoses annually.** (1)

Current Diagnosis Methods

Alzheimer's disease can be diagnosed using cognitive tests, neurological exams (such as CSF) and brain imaging techniques. **However, these tests can be expensive,** with MRI and PET scans costing an average of $819 (2) and $850 (3), respectively, in Canada. Additionally, CSF sampling is **invasive.**

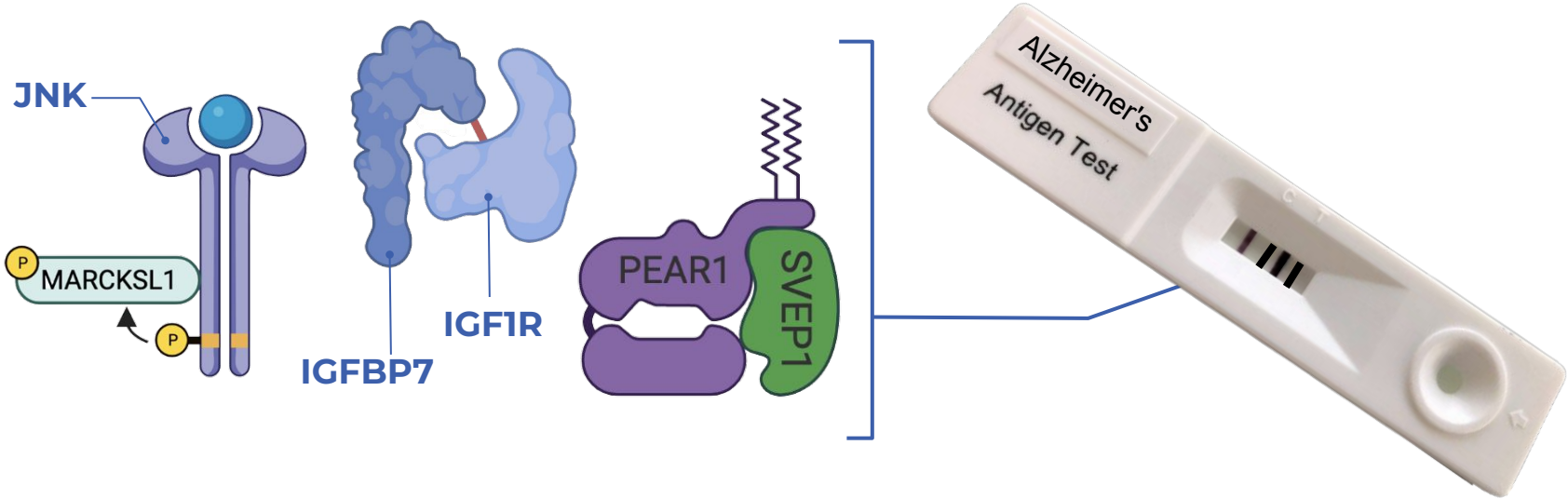
Research into Biomarkers

Pathophysiological models of Alzheimer's etiology have traditionally focused on **amyloid-β and tau proteins.** However, recent research has shown that prevention and treatment trials targeting these biomarkers have largely failed. Longitudinal studies have found that many people who are positive for amyloid-β do not develop clinical Alzheimer's. This highlights **the need to expand research on early biomarkers for Alzheimer's** beyond amyloid-β and tau.

Novel Alzheimer's Antigen Test

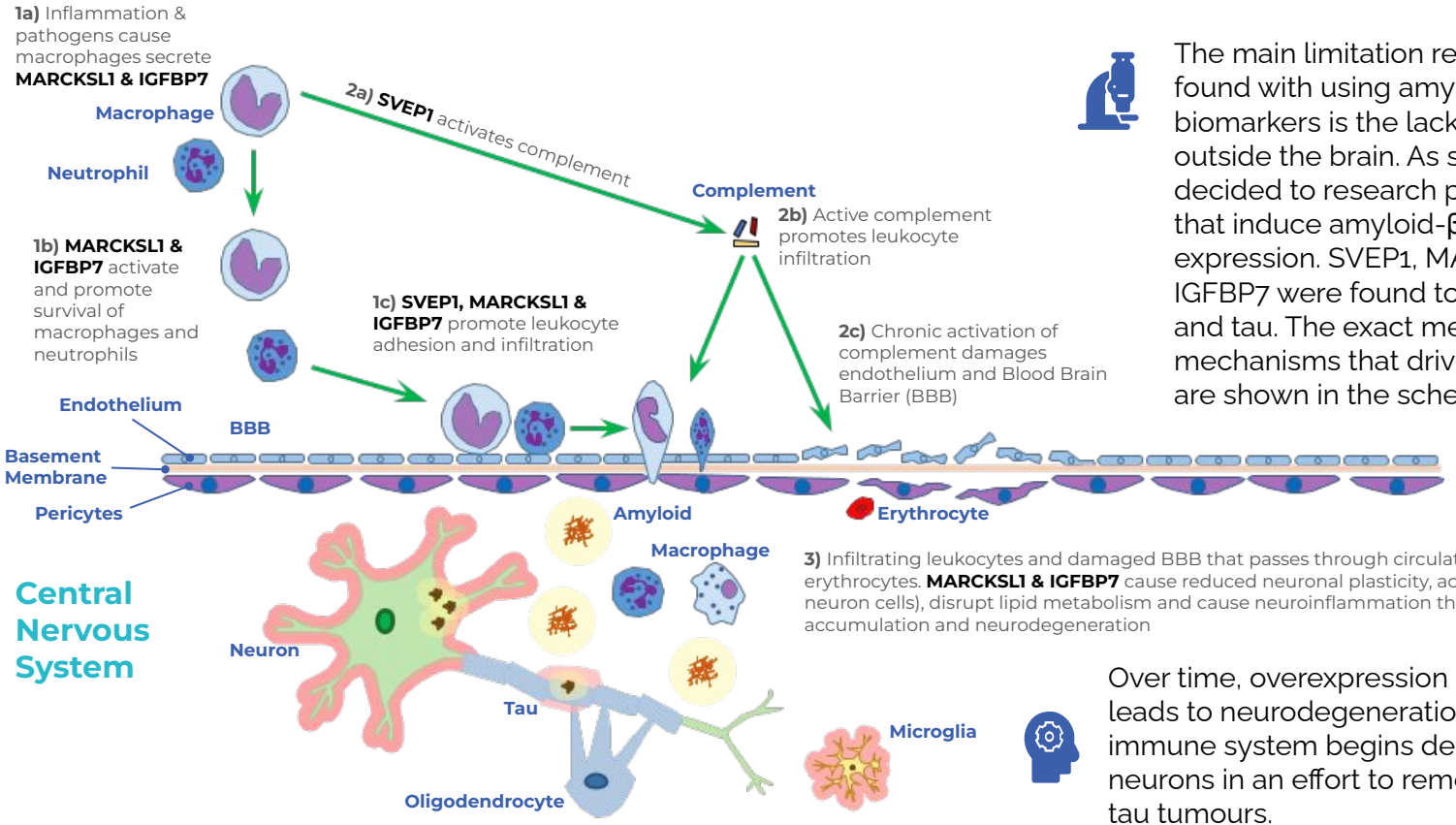
Proposed Diagnosis Method Overview

After adjusting for known Alzheimer's risk factors, new fifteen plasma proteins have been identified as being risk factors for cognitive decline rate and Alzheimer's (1). Interestingly, amyloid-beta and tau were not found to be associated with accelerated cognitive decline after FDR correction. Three of these proteins, namely **SVEP1, IGFBP7 & MARCKSL1**, are most commonly expressed by salivary glands and are specific to PEAR1, IGF1R and JNK receptors, respectively. **Switch Health can able to develop an antigen test** for the detection of these proteins from a swab sample, which will have an accuracy rate of approximately 90% based on the statistical correlation between the proteins and Alzheimer's.



Identifying the Protein Biomarkers

How does it work?



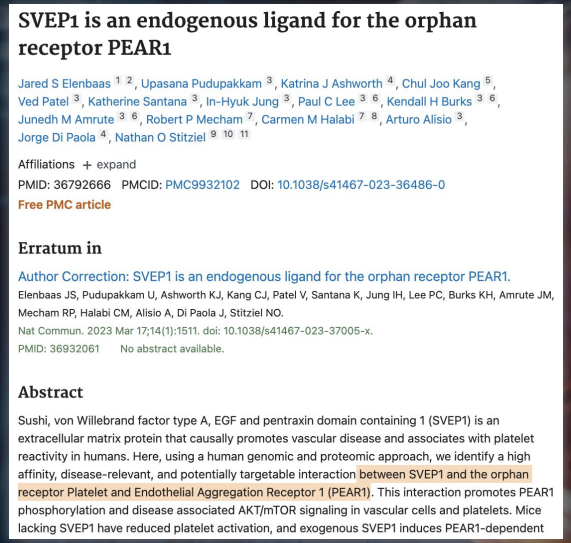
The main limitation researchers have found with using amyloid-β and tau as biomarkers is the lack of prevalence outside the brain. As such, researchers decided to research precursor proteins that induce amyloid-β and tau expression. SVEP1, MARCKSL1 and IGFBP7 were found to induce amyloid-β and tau. The exact metabolic mechanisms that drive this accumulation are shown in the schematic to the left.

3) Infiltrating leukocytes and damaged BBB that passes through circulating toxins, complement, erythrocytes. **MARCKSL1 & IGFBP7** cause reduced neuronal plasticity, activate microglia (destroys neuron cells), disrupt lipid metabolism and cause neuroinflammation that leads to amyloid and tau accumulation and neurodegeneration

Over time, overexpression of these three proteins leads to neurodegeneration as the body's immune system begins destroying its own neurons in an effort to remove the amyloid and tau tumours.

Identifying the Diagnostic Method

How does it work? (cont'd)



SVEP1 is an endogenous ligand for the orphan receptor PEAR1

Jared S Elenbaas [1 2], Upasana Pudupakkam [3], Katrina J Ashworth [4], Chul Joo Kang [5], Ved Patel [3], Katherine Santana [3], In-Hyuk Jung [3], Paul C Lee [3 6], Kendall H Burks [3 6], Junedh M Amrute [3 6], Robert P Mecham [7], Carmen M Halabi [7 8], Arturo Alisio [3], Jorge Di Paola [4], Nathan O Stitziel [9 10 11]

Affiliations + expand

PMID: 36792666 PMCID: PMC9932102 DOI: 10.1038/s41467-023-36486-0

Free PMC article

Erratum in

Author Correction: SVEP1 is an endogenous ligand for the orphan receptor PEAR1.

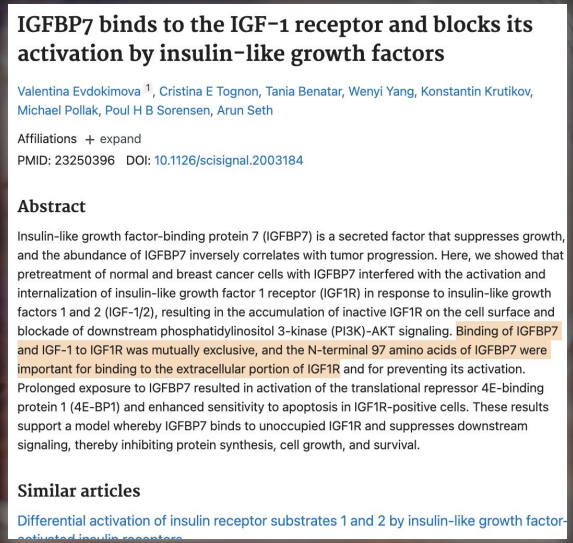
Elenbaas JS, Pudupakkam U, Ashworth KJ, Kang CJ, Patel V, Santana K, Jung IH, Lee PC, Burks KH, Amrute JM, Mecham RP, Halabi CM, Alisio A, Di Paola J, Stitziel NO.

Nat Commun. 2023 Mar 17;14(1):1511. doi: 10.1038/s41467-023-37005-x.

PMID: 36932061 No abstract available.

Abstract

Sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1 (SVEP1) is an extracellular matrix protein that causally promotes vascular disease and associates with platelet reactivity in humans. Here, using a human genomic and proteomic approach, we identify a high affinity, disease-relevant, and potentially targetable interaction between SVEP1 and the orphan receptor Platelet and Endothelial Aggregation Receptor 1 (PEAR1). This interaction promotes PEAR1 phosphorylation and disease associated AKT/mTOR signaling in vascular cells and platelets. Mice lacking SVEP1 have reduced platelet activation, and exogenous SVEP1 induces PEAR1-dependent



IGFBP7 binds to the IGF-1 receptor and blocks its activation by insulin-like growth factors

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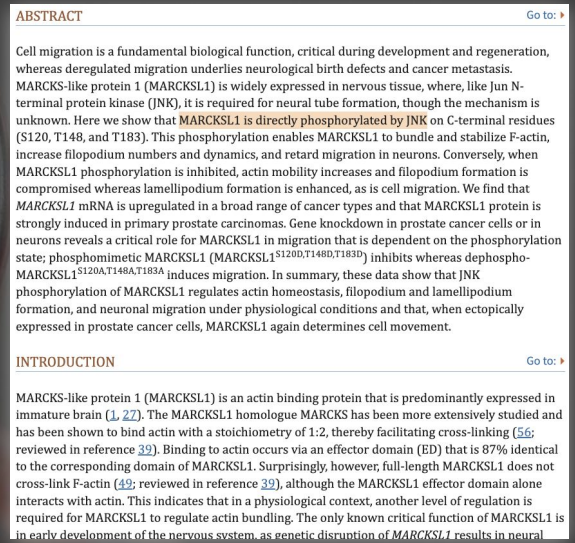
Abstract

Insulin-like growth factor-binding protein 7 (IGFBP7) is a secreted factor that suppresses growth, and the abundance of IGFBP7 inversely correlates with tumor progression. Here, we showed that pretreatment of normal and breast cancer cells with IGFBP7 interfered with the activation and internalization of insulin-like growth factor 1 receptor (IGF1R) in response to insulin-like growth factors 1 and 2 (IGF-1/2), resulting in the accumulation of inactive IGF1R on the cell surface and blockade of downstream phosphatidylinositol 3-kinase (PI3K)-AKT signaling. Binding of IGFBP7 and IGF-1 to IGF1R was mutually exclusive, and the N-terminal 97 amino acids of IGFBP7 were important for binding to the extracellular portion of IGF1R and for preventing its activation. Prolonged exposure to IGFBP7 resulted in activation of the translational repressor 4E-binding protein 1 (4E-BP1) and enhanced sensitivity to apoptosis in IGF1R-positive cells. These results support a model whereby IGFBP7 binds to unoccupied IGF1R and suppresses downstream signaling, thereby inhibiting protein synthesis, cell growth, and survival.

Similar articles

Differential activation of insulin receptor substrates 1 and 2 by insulin-like growth factor-activated insulin receptors



ABSTRACT Go to:

Cell migration is a fundamental biological function, critical during development and regeneration, whereas deregulated migration underlies neurological birth defects and cancer metastasis. MARCKS-like protein 1 (MARCKSL1) is widely expressed in nervous tissue, where, like Jun N-terminal protein kinase (JNK), it is required for neural tube formation, though the mechanism is unknown. Here we show that MARCKSL1 is directly phosphorylated by JNK on C-terminal residues (S120, T148, and T183). This phosphorylation enables MARCKSL1 to bundle and stabilize F-actin, increase filopodium numbers and dynamics, and retard migration in neurons. Conversely, when MARCKSL1 phosphorylation is inhibited, actin mobility increases and filopodium formation is compromised whereas lamellipodium formation is enhanced, as is cell migration. We find that *MARCKSL1* mRNA is upregulated in a broad range of cancer types and that MARCKSL1 protein is strongly induced in primary prostate carcinomas. Gene knockdown in prostate cancer cells or in neurons reveals a critical role for MARCKSL1 in migration that is dependent on the phosphorylation state; phosphomimetic MARCKSL1 ($MARCKSL1^{S120D,T148D,T183D}$) inhibits whereas dephospho-MARCKSL1 ($MARCKSL1^{S120A,T148A,T183A}$ induces migration. In summary, these data show that JNK phosphorylation of MARCKSL1 regulates actin homeostasis, filopodium and lamellipodium formation, and neuronal migration under physiological conditions and that, when ectopically expressed in prostate cancer cells, MARCKSL1 again determines cell movement.

INTRODUCTION Go to:

MARCKS-like protein 1 (MARCKSL1) is an actin binding protein that is predominantly expressed in immature brain (1, 27). The MARCKSL1 homologue MARCKS has been more extensively studied and has been shown to bind actin with a stoichiometry of 1:2, thereby facilitating cross-linking (56; reviewed in reference 39). Binding to actin occurs via an effector domain (ED) that is 87% identical to the corresponding domain of MARCKSL1. Surprisingly, however, full-length MARCKSL1 does not cross-link F-actin (49; reviewed in reference 39), although the MARCKSL1 effector domain alone interacts with actin. This indicates that in a physiological context, another level of regulation is required for MARCKSL1 to regulate actin bundling. The only known critical function of MARCKSL1 is in early development of the nervous system, as genetic disruption of *MARCKSL1* results in neural

"SVEP1 is a endogenous ligand for the receptor PEAR1" (1)

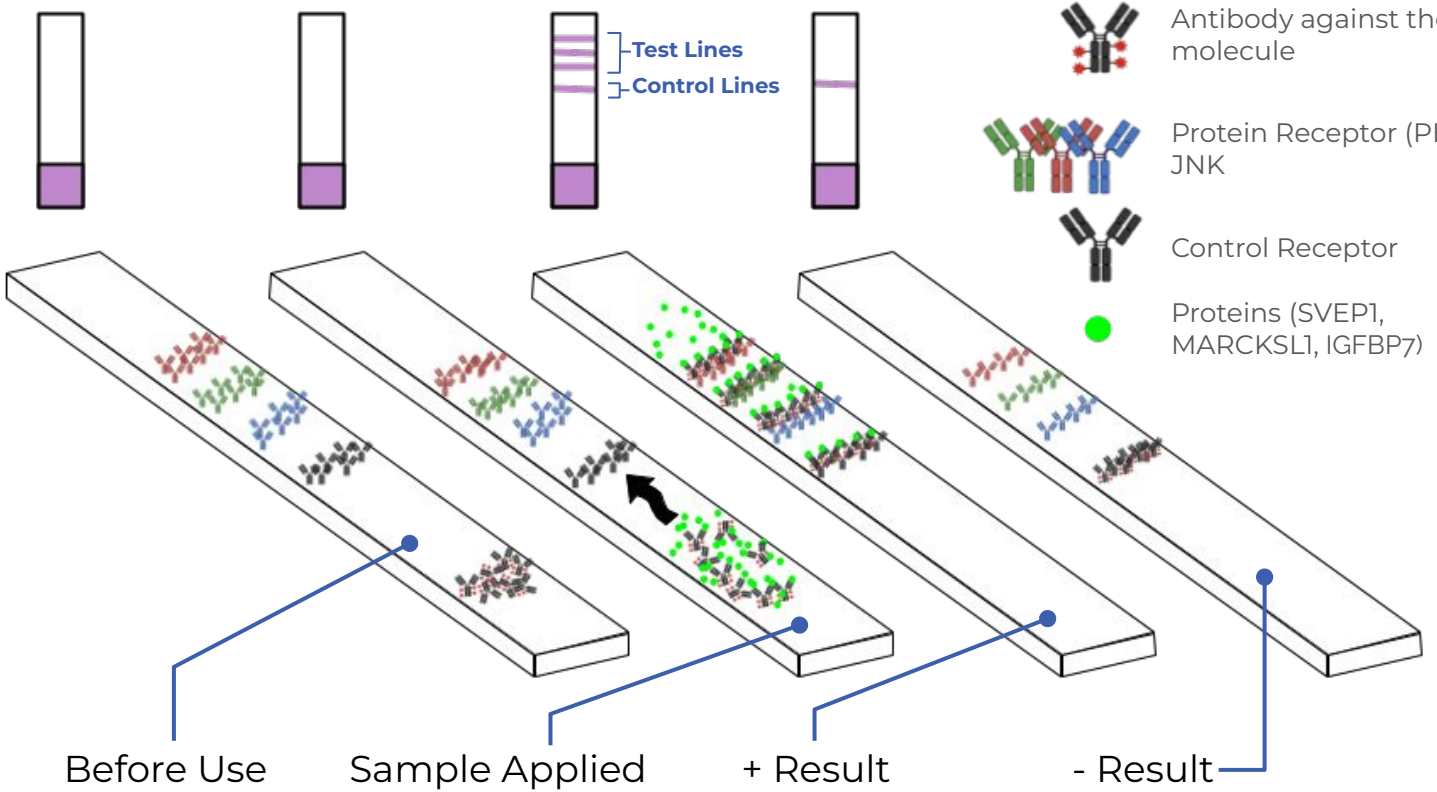
"Binding of IGFBP7 and IGF-1 are **mutually exclusive**" (2)

"MARCKSL1 is directly **phosphorylated** by JNK" (3)

Each of the proteins binds to one receptor, making it possible to determine the presence of a protein (via a lock and key mechanism).

Schematic of Test Kit

Rapid Antigen Test



Antibody against the proteins linked to detector molecule

Protein Receptor (PEAR1, IGF1R and JNK

Control Receptor

Proteins (SVEP1, MARCKSL1, IGFBP7)

The proteins will be mixed with an aqueous solution (assay buffer) which will separate the proteins. This solution will be applied on a paper strip where the solution will mitigate through the strip. As the proteins come in contact with their respective receptor, they will bind, releasing a fluorescent dye. If no proteins come in contact with the receptor (or the lines are very faint in colour), then the patient does not have Alzheimer's. If 1 or 2 of the proteins are detected, then only 1 or 2 lines will be shown. In this case, it is not conclusive enough to determine Alzheimer's. **Only if all 3 test lines are present can the diagnosis be considered 90% accurate.** (1)

Procedures to use test kit

Rapid Antigen Test (cont'd)

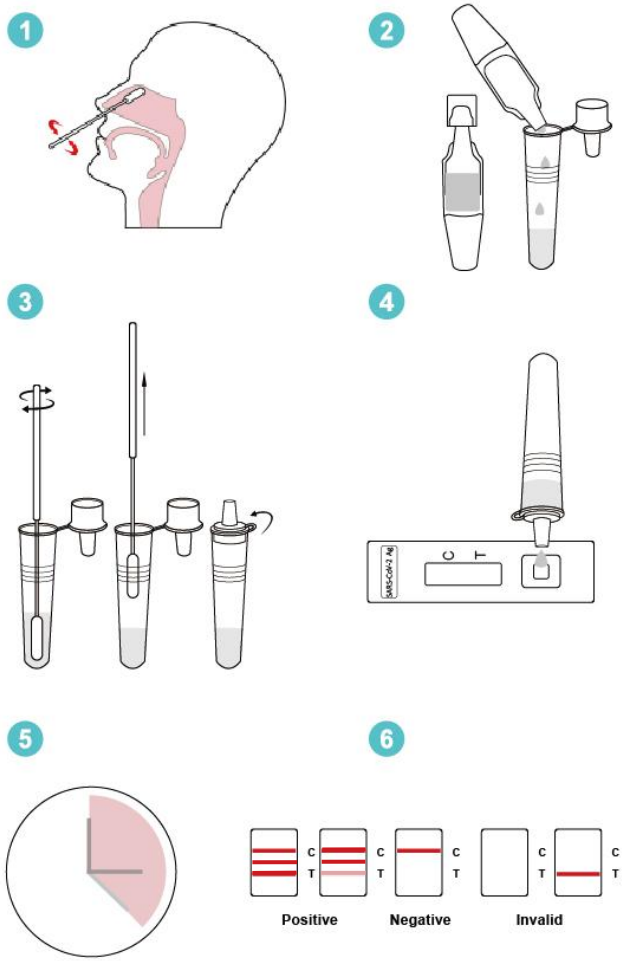
(1) A swab of the nasal and oral cavity is taken.

(2) User will pour the packaged vial of assay buffer into the capsule.

(3) The user will then place the swab into the tube and swirl the swab around in the fluid capsule 5 times. The fluid will break down the quaternary protein complexes into tertiary protein structures.

(4) Several drops of the solution will be applied to the antigen test.

(5 & 6) After some while, the user will be able to determine the diagnosis. Depending on the severity of Alzheimer's (whether the patient is in the early-stage or middle-stage), 3 dark or 3 faint lines will appear. 2 or fewer lines are considered not conclusive enough to determine Alzheimer's, although two lines would indicate a potential doctor's visit is necessary.



Financial Analysis

Cost Breakdown of Antigen Test

Components	Notes	Cost (USD)
Total BOM Cost		$10.50
Manufacturing cost		$0.30
BOM + Manufacturing		**$10.80**
Major Cost Drivers		
Test strip	Contains the receptors needed to detect the presence of the SVEP1, MARCKSL1, & IGFBP7	$0.50
Assay Buffer solution		$2
Swab		$0.30
Extraction tube		$0.70
Plastic components	Plastic housings, caps	$5
Label and packaging materials	Instruction manuals, labeling	$2

Final cost derived from the bill of materials of Covid-19 Rapid Antigen Tests. Selling at **$20 USD**, the product would have roughly 50% profit margin. (1)

The receptors would have a large initial cost as it would require creating a **plasmid** to insert inside of a bacterium (***Lactobacillus plantarum*** is a suitable candidate for its genetic plasticity). The bacterium would then express the receptor which would be harvested. Replicating/Maintaining a bacterium colony would not require significant cost once a colony has been established.

Why is it better than current solutions?

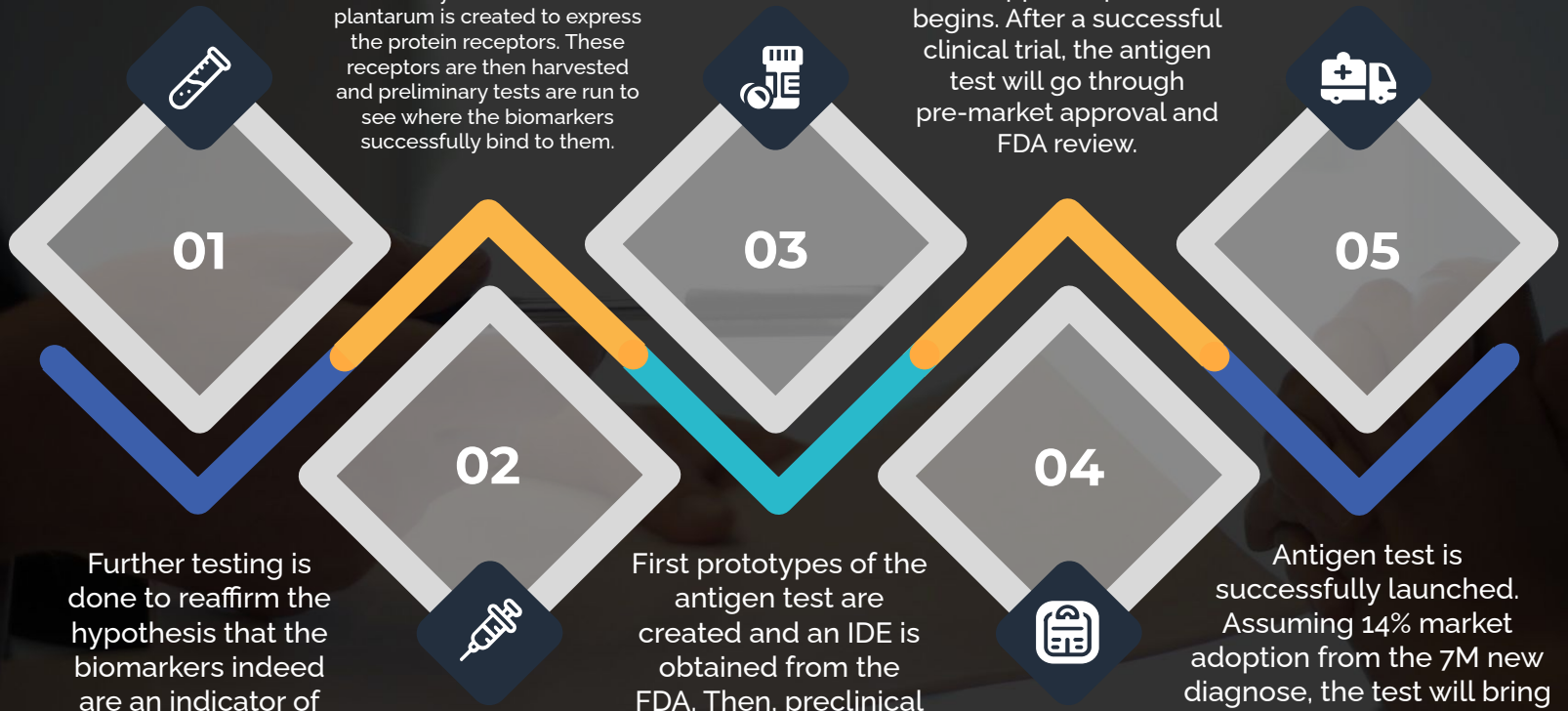
Market Advantage

More **cost-effective and financially accessible** for 60% of Alzheimer's patients from low-medium income countries [1]. It is important to note that a doctor's appointment might still be necessary to confirm the diagnosis, although this is often covered by government-funded healthcare.

Less invasive than existing diagnostic methods that require biomarkers (i.e CSF).

The **diagnosis time** has been **significantly reduced** from weeks or months (due to follow-up appointments with doctors and waiting for MRI scans) to just a few minutes.

Implementation Plan



The Patient Experience

A step by step process from the customer buying the product to getting a diagnosis to aftercare

Purchase

The patient will walk into the store to pick up the diagnostic kit OR have the diagnostic kit shipped to their house.

Pre-Test

The detailed yet simple instructions will guide the patient through the self-diagnosis process. The process will be designed while considering the cognitive capabilities of seniors.

Diagnosis

Within several minutes of performing the test, the patient will have a diagnosis. Depending on the result, the patient will be instructed to follow-up with a doctor.

Checkup

The patient will book an appointment with the doctor as soon as possible to confirm the diagnosis (via a cognitive test).

Aftercare

The patient will be prescribed a treatment model early in the pre-clinical phase of Alzheimer's. As such, many of the patient's symptoms will be reversible and the patient will be able to live a longer, happy life.

Expert Validation

Suvendrini Lena

Neurologist at CAMH

"I can tell that you've done profound research to understand the science and the current gaps in the field. You understand that the largest impact will be made by building upon current research. You have a commendable grasp on your proposal and have created a diagnostic tool that is both efficient and simplistic."

Jason Lazarou

Neurologist at Mt. Sinai Hospital

"Your proposal is not only backed in research but also offers insights as to why past research into biomarkers has been unfruitful. The use of biomarkers and an antigen test for diagnosis is sensible and thoughtfully curated. Well done"

On a More Personal Note

THANK YOU

“The past five weeks has allowed for me to be exposed to new learnings and experiences and I’m so eternally grateful for Switch Health for providing me with this opportunity. Your commitment to innovation in the medical field is truly inspiring, and I am honoured to be a part of it. The process of developing a new solution using current research has given me tremendous insights on the processes behind new medical innovations for specific diseases, and these learnings and skills will forever stick with me as I continue to pursue a career in medicine. This sprint has challenged my time management and reinforced that I am capable of creating an impact at this age; I hold so much gratitude for it all.”

Krish Mendapara