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2025

DIAGRAM OF "KNOW YOUR MOLECULE™" REPORT

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Please note that this is a fictitious hypothesis used for illustrative purposes only.

| This format is preferred by investors seeking deal flow* |

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TABLE OF CONTENT

1. EXECUTIVE SUMMARY

High-level overview of key project findings that outlines key considerations for developing the molecule for use in a new therapeutic for a class of neurodegenerative diseases (in this example diagram, the molecule 12-O-tetradecanoylphorbol-13-acetate(TPA)), including its properties, applications, risks, and market factors.

Quality Review: Just as peer-reviewed articles represent the gold standard in scientific communication, the report provides quality assurance of the project value creation, including but not limited to methodological scrutiny, providing external and objective assessment of research hypotheses and methods planned. This identifies potential flaws or limitations in experimental design early in the process and validates statistical analysis and conclusions.

Using AI integration: Provides research reliability confirmation, which helps identify potential errors or methodological weaknesses and provides additional layers of evidence for scientific claims for reviewers or investors.

Provides Third-party validation: ensuring that scientific discoveries/hypotheses are robust, reliable, and can be trusted by investors or funding reviewers.

Critical risk assessment: Via AI integration methodology: AI platforms are used to minimize potential research investment losses.

Preliminary recommendation: Provided based on customer preferences.

2. HYPOTHESIS OVERVIEW

The sample hypothesis states that TPA can be used to transfer a phosphate group from ATP to specific amino acid residues on the target leucine protein in the 19-amino-acid Jr2R3 mutation of the Tau protein and may serve as a therapy for several related neurodegenerative diseases.

- **Target Identification:** The hypothesis clearly defines the molecular target (leucine) believed to be involved in the disease process.
- **Mechanism of Action:** Yet to be evaluated.
- **Drug Design:** The hypothesis includes a rationale.
- **Efficacy Prediction:** The hypothesis does not outline the anticipated therapeutic effects, including the magnitude and duration of the response (see suggested studies at the conclusion).
- **Safety Considerations:** The hypothesis does not address potential off-target effects.
- **Biomarkers:** The hypothesis does not propose specific biomarkers to measure the drug's engagement with the target and its therapeutic effect.
- **Resistance Mechanisms:** The hypothesis does not predict potential mechanisms of drug resistance or strategies to overcome them.
- **Combination Potential:** The hypothesis does not suggest how the therapy might synergize with existing treatments (see recommendations below).

TPA is an organic compound with the molecular formula C36H56O8 and a molecular weight of 616.83 g/mol. It belongs to the tigliane family of diterpenes and is known for its ability to activate protein kinase C (PKC).

3. INVESTIGATIVE CHEMICAL CASCADE (SAMPLE)

- The most comprehensive test to determine molecular structure is a combination of multiple analytical techniques, with Nuclear Magnetic Resonance (NMR) spectroscopy being the cornerstone using, NMR Mass Infrared spectroscopy and X-ray crystallography among other testing, however, more basic steps are taken such as searching unpublished data prior to providing a path and seeking further data.

- Literature search - The size of a literature search varies by task; in this case a specific limited task begins with an extensive published data set as this molecule is a common research staple. In order to minimize publication bias an extensive effort is made to obtain unpublished data. We incorporate AI platforms to seek this unpublished data, however, traditional approaches including Cochrane Methodology Register, MEDLINE and EMBASE and checked references in relevant reports and contact researchers who were known or who were thought likely to have carried out relevant studies are also used. We alsouse the Science Citation Index and PubMed 'related articles' feature to identify any additional studies identified by other sources.

- TPA is an organic compound with the molecular formula C36H56O8 and a molecular weight of 616.83 g/mol1. It belongs to the tigliane family of diterpenes and is known for its ability to activate protein kinase C (PKC)

- Structure - Polycyclic core with specific stereochemistry (4β, 9α, 12β, 13α, 20-Pentahydroxy configuration) A polycyclic structure derived from the natural compound phorbol. A myristate (14-carbon) fatty acid ester at the 12-position. An acetate group at the 13-position.

- The molecule contains multiple oxygen-containing functional groups, including hydroxyl groups, ester linkages, and ketone moieties.Solubility - Soluble in organic solvents (ethanol, methanol, DMSO, dimethyl formamide, acetone, ether)

- Stability - Requires storage at -20°C, protected from light

- Chirality - TPA exhibits complex stereochemistry with multiple chiral centers. The molecule has a specific optical rotation, indicating its chiral nature. The stereochemistry at key positions is as follows: 4β, 9α, 12β, 13α, 20-Pentahydroxy configuration. This specific stereochemical arrangement is crucial for its biological activity, particularly its ability to activate protein kinase C (PKC).

- Toxicity - Using AI software TPA has been docked with Imagine's proprietary panel of common human proteins and found to be in several prominent warnings alerts. Also, in the published literature TPA is highly toxic and requires careful handling.

- Its toxicity profile includes, acute toxicity: oral LD50 (Category 2), dermal LD50 (Category 1), Inhalation LC50 for dusts and mists (Category 1), corrosive properties, causes severe skin burns and eye damage, sensitization May cause allergic skin reactions and respiratory sensitization Carcinogenicity suspected carcinogen (Category 2). TPAis a potent tumor promoter in mice, particularly for skin tumors. Specific target organ toxicity: May cause respiratory irritation (single exposure, Category 3).

- Energy State - Bind to the C1a and C1b domains of PKC with high affinity (Ki = 2.6 nM). Induce membrane translocation of PKC, leading to its activation. Activate specific PKC isoforms, including α, β, γ, δ, ε, η, and θ, but not ζ or ι/λ. The energy state of TPA is relatively stable, allowing it to persistently activate PKC. This prolonged activation is key to its biological effects, including its tumor-promoting activity.

- PKC activation: TPA mimics the natural PKC activator diacylglycerol (DAG), binding to and activating PKC. Calcium binding enhancement: It increases PKC's affinity for calcium in the presence of phosphatidylserine.

- Signaling cascade initiation: TPA stimulates various downstream signaling pathways, including the ERK/MAPK cascade. Tumor promotion: It is widely used in research as a tumor promoter in two-stage carcinogenesis models.

Cellular effects:

- TPA can induce cell proliferation, differentiation, and gene expression changes in various cell types.

- Indirect phosphorylation: While TPA doesn't directly phosphorylate proteins, it indirectly leads to the phosphorylation of many cellular proteins through PKC activation.

- While TPA can indirectly lead to the phosphorylation of many proteins through its activation of PKC and other signaling pathways**, it does not cause the direct phosphorylation of leucine**, which is not a phosphorylation target amino acid in cellular proteins. (see recommendations below for new formulation suggestions and affirming data sets).

4. MARKET ANALYSIS

- The market for neurodegenerative disease therapeutics is substantial, given the increasing prevalence of conditions like Alzheimer's disease, Parkinson's disease, and other related disorders in aging populations worldwide.

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- The total market value encompasses various treatment modalities, including small molecule drugs, biologics, and potentially emerging gene and cell therapies targeting neurodegenerative conditions.

- Factors such as the aging global population, increased diagnosis rates, and advancements in understanding disease mechanisms are driving market expansion.

- The market size reflects the high costs associated with treating chronic neurodegenerative conditions, which often require long-term care and multiple interventions.

- To provide a specific validated and up-to-date figure for the total world market value, it would be necessary to consult recent market research reports from various companies including but not limited to; Grand View Research, Mordor Intelligence, Globa Data ,Transparency Market Research BCC Research Frost & Sullivan, Research and Markets. (Special pricing is available thru Imagine).

- **Competition:** The general categories of current treatments commonly used include cholinesterase inhibitors, NMDA receptor antagonists, dopaminergic medications, MAO-B inhibitors, and COMT inhibitors.

- Dementia costs exceed other diseases: In the last five years of life, total healthcare spending for people with dementia was $287,000 per person.

- Alzheimer's and related dementias (ADRDs) are particularly expensive: The estimated per-patient cost of formal care for **ADRDs in 2016 was $28,078, with total per-patient costs, including informal care, reaching $64,745.**

- **Parkinson's disease:** The total economic burden of PD in the U.S. was estimated at $51.9 billion in 2017, with direct medical costs of $25.4 billion and indirect and non-medical costs of $26.5 billion.

- Neurodegenerative diseases collectively impose a massive economic burden: **The annual cost for Alzheimer's, Parkinson's, and motor neuron diseases in the U.S. was $655 billion in 2020, including direct medical, non-medical, and indirect costs.**

- **Pricing:** High value (see recommendations below, valued through phase 3).

5. PRODUCTION CONSIDERATIONS

- **Manufacturing scale-up:** Transitioning from small-scale production for clinical trials to large-scale commercial manufacturing costs will be determined based on final formulation.
- **Regulatory compliance:** Predictive costs of adhering to Good Manufacturing Practices (GMP) and meeting regulatory requirements set by agencies like the FDA and EMA. (see recommendations below which is dependent on status, biologicals, small/large molecules, antivirals etc.).
- **Supply chain management:** determined to be reliable at this formulation .
- **Synthesis:** Complex process requiring specialized equipment and expertise.
- **Quality Control:** High purity (≥98% HPLC) essential
- **Packaging:** Per dosage route.

6. RECOMMENDATIONS

Dependent on Hypothesis Complexity (Specific Recommendation #1)

- Based on the literature research and the findings in the unpublished dataset, it does not cause the direct phosphorylation of leucine. A new formulation is advised.

Dependent on Hypothesis Complexity (Specific Recommendation #2)

- Direct phosphorylation of leucine in proteins is not possible through conventional biological mechanisms. Leucine is not one of the amino acids that can be phosphorylated by protein kinases in living cells.

Dependent on Hypothesis Complexity (Specific Recommendation #3)

- The project might consider the following approaches: **Chemical Modification**: Synthetic chemistry techniques could potentially be used to add a phosphate group to leucine in vitro, but this would not occur naturally in biological systems.

Dependent on Hypothesis Complexity (Specific Recommendation #4)

- **Mimicking Phosphorylation:** Instead of direct phosphorylation, the project might use leucine analogs that mimic the effects of phosphorylation, such as glutamic acid substitutions, which can sometimes simulate the negative charge of a phosphate group.

7. CONCLUSION

As cost of finding new drug formulations for diseases can be in the billions of dollars per successful drug this hypothesis requires a higher level of de-risking activity. Using our recommendations below may reduce development costs considerably.

Careful consideration of regulatory requirements, safety measures, and market dynamics is essential before proceeding with further funding plans.

THANK YOU

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