Neuro-E™

Apolipoprotein E mimetic peptide for the Treatment of Stroke

Techno-Commercial Proposal

Prof. Abhay H. Pande,
Department of Biotechnology,
National Institute of Pharmaceutical Education and Research (NIPER)
Sec-67, S.A.S. Nagar (Mohali)-160062 India
(apande@niper.ac.in)

Neuro-E™ for the treatment of Stroke

Stroke is the 2nd most common cause of mortality globally and each year ~15 million people suffer from stroke worldwide. Of these, five million do not survive, and another five million are left permanently disabled, creating a significant burden on families and communities. Tissue plasminogen activator (tPA) is currently the only approved drug for stroke treatment. However, its clinical use has serious limitations - ***a narrow therapeutic window*** of 3 - 4.5 h only and ***neurotoxic & cytotoxic effects***. Furthermore, tPA can only dissolve clots (thrombolysis) and cannot heal or protect the affected tissues. Other medications used in stroke management are primarily supportive (e.g., blood thinners, anti-hypertensive agents) and serve mainly to reduce the risk of further stroke rather than address the immediate damage. Therefore, there is an urgent need to develop new agent(s) for the treatment and management of stroke.

Neuro-E™ is an engineered human apolipoprotein E mimetic peptide having neuroprotective and neuro-healing properties. Currently, it is in pre-clinical developmental stage.

Current market of Stroke medication:

According to Data Bridge Market Research analysis, the expected CAGR of the stroke drugs market is ~ 7.50% % and it will grow up to USD 58.09 billion by 2031.

Problem statement:

Stroke is a leading cause of death worldwide, and current treatments like tPA offer limited efficacy. Many patients experience poor survival rates and significant side effects, highlighting the urgent need for more effective, less toxic therapies. Therefore, novel strategies, such as NEURO-E™, are essential to improve outcomes for stroke patients.

Solution: NEURO-E™

Apolipoprotein E (ApoE), the most abundant apolipoprotein in the brain not only plays a key role in lipid metabolism but also is involved in neural repair, synapse maintenance and axonal growth. It is very crucial for various brain functions (including learning, memory formation & hippocampal neurogenesis).

NEURO-E is an engineered human Apolipoprotein E mimetic peptide. It comprises of both the LDL receptor-binding domain and lipid-binding domain of the native human ApoE. NEURO-E has demonstrated neuroprotective and neuro-healing effects in animal models of neurodegenerations including stroke.

Development of NEURO-E™

1. Identification of hApoE active region(s): Peptide walking was used to identify the active regions (anti-inflammatory & blood-brain barrier crossing region) of natural human ApoE protein.

2. Designing Drug candidate(s): Using 2 '*hit*' peptides, 07 novel drug candidates were designed and characterized. A '*lead*' candidate, NEURO-E was then finalized. This peptide contains LDL-receptor binding and lipid-binding regions of human ApoE.

3. Anti-inflammatory and neuroprotective properties of NEURO-E:

- ✓ NEURO-E has shown anti-inflammatory properties in animal model of asthma
- ✓ NEURO-E exhibits potent neurohealing properties in various animal models of neurodegeneration (in transgenic flies, mice and rat models)
- ✓ NEURO-E provided neuroprotection in focal cerebral ischemia model of stroke in rats

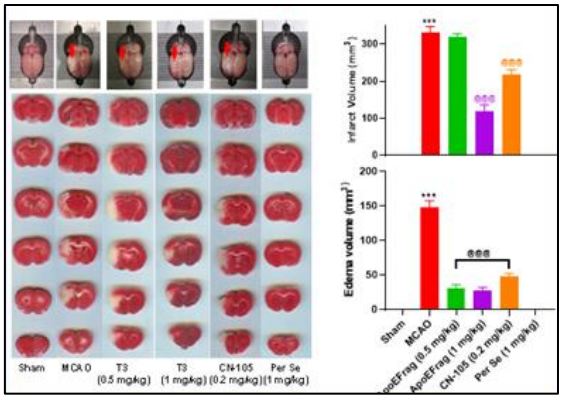


Fig Neuro-healing properties of NEURO-E was studied in the focal cerebral ischemia model of stroke (transient blockage of the left common carotid artery for 90 min after that reperfusion was performed).

Our Publications:

Nankar, S.A., Bulani, Y., Sharma, S.S., Pande, A.H., 2019. ApoE-Derived Peptides Attenuated Diabetes-Induced Oxidative Stress and Inflammation. Protein Pept. Lett. 27, 193–200. https://doi.org/10.2174/0929866526666191002112655

Nankar, S.A., Ahmed, S., Sharma, S.S., Pande, A.H., 2022. Apolipoprotein-mimetic Peptides: Current and Future Prospectives. Curr. Protein Pept. Sci. 23, 757–772. https://doi.org/10.2174/1389203723666221003122624

Nankar, S.A., Bulani, Y., Sharma, S.S., Pande, A.H., 2019. ApoE-Derived Peptides Attenuated Diabetes-Induced Oxidative Stress and Inflammation. Protein Pept. Lett. 27, 193–200. https://doi.org/10.2174/0929866526666191002112655

Nankar, S.A., Pande, A.H., 2014a. Properties of apolipoprotein E derived peptide modulate their lipid-binding capacity and influence their anti-inflammatory function. Biochim. Biophys. Acta - Mol. Cell Biol. Lipids 1841, 620–629. https://doi.org/10.1016/j.bbalip.2014.01.006

A Nankar, S., S Prajapati, J. and H Pande, A., 2014b. Apolipoprotein E derived peptides inhibit the pro-inflammatory effect of lysophosphatidylcholine. Protein Pept. Lett. 21(2), 101-107.

Nankar, S.A., Bajaj, P., Sravanthi, R., Pande, A.H., 2013a. Differential interaction of peptides derived from C-terminal domain of human apolipoprotein E with platelet-activating factor analogs. Biochimie 95, 1196–1207. https://doi.org/10.1016/j.biochi.2013.01.011

Nankar, S.A. and Pande, A.H., 2013b. Physicochemical properties of bacterial pro-inflammatory lipids influence their interaction with apolipoprotein-derived peptides. Biochim. Biophys. Acta (BBA). 1831(4), 853-862. https://doi.org/10.1016/j.bbalip.2013.01.006

Pande, AH, Tripathy, RK, 2009a. Preferential binding of apolipoprotein E-derived peptides with oxidized phospholipid. Biochem. Biophys. Res. Commun. 380, 71–75. https://doi.org/10.1016/j.bbrc.2009.01.029

Pande, A.H., Tripathy, R.K. and Nankar, S.A., 2009b. Membrane surface charge modulates lipoprotein complex forming capability of peptides derived from the C-terminal domain of apolipoprotein E. Biochim. Biophys. Acta (BBA). 1788(6), 1366-1376. https://doi.org/10.1016/j.bbamem.2009.03.020

Ahmed, S., Pande, A.H. and Sharma, S.S., 2022. Therapeutic potential of ApoE-mimetic peptides in CNS disorders: Current perspective. Exp. Neuro. 353, p.114051. https://doi.org/10.1016/j.expneurol.2022.114051

Ahmed, S., Pande, A.H. and Sharma, S.S., 2024. ApoE Potential in CNS Drugs Targeting and as CNS Therapeutic. Targeted Therapy for Central Nervous System, Elsevier, 2024.

Indian Patent # 327385 Abhay H Pande, Sunil A. Nankar. Anti-inflammatory peptides

Indian patent application # 202311067164 Abhay H Pande, Sakeel Ahmad, Shyam S. Sharma. Anti-inflammatory peptides.

Ahmed S, Tripathy RK, Pande AH and Sharma SS, Neuroprotective Potential of ApoE-mimetic peptide (ApoEFrag) in Stroke Models: Neurobehavioural and Mechanistic Study. Communicated

Market Opportunity:

There is a growing need for the development of more effective treatment(s) for Stroke. The stroke medication market size is projected to grow up to USD 58.09 billion by 2031 with CAGR of ~ 7.50%. There is a very-high chance that NEURO-E™ can turn out to be potential blockbusters in the treatment of stroke in coming years!!!

So, there is a HUGE market potential for is NEURO-E™ as it possesses both neuroprotective and neuro healing properties.

Development Plan: Long term (2025-2035)

Long-term (2025-2035) and immediate short-term (2025-2027) plans for the development of NEURO-E™ is given as **Annexure 1**

Financial Projections:

- Cost of non-GLP studies is tabulated in **Annexure 2**

- Further cost will require in-depth discussion with the partner company

Why NEURO-E is ideal for stroke?

NEURO-E™ is ideal for stroke treatment due to its unique design and mechanism of action that directly target brain repair and neuroprotection

- ✓ NEURO-E is specifically designed to contain both LDL-R binding domain and the lipid-binding domain of native human ApoE, making it a ***highly efficacious*** to cross the blood-brain barrier, target brain cells, and promote repair.

- ✓ Neuro-E possess both ***Neuroprotective*** *and* ***Neuro-healing*** Properties:

- ✓ ***Cost-effectiveness*** and potential for ***affordability,*** compared to existing treatments, makes NEURO-E an ideal candidate for stroke patients, particularly in regions like India.

- ✓ NEURO-E offers ***broad therapeutic window***, making it accessible to more patients, particularly in acute and subacute phases of stroke.

Annexure 1
NEURO-E Development Plan -1 (Long term, 2025-2035)

Developmental Stages	Time-line	Milestones
Stage 1: Discovery & Early Development (Already Done) Engineering, *in vitro* testing and efficacy assessment in relevant animal models is completed. Prototype of product and proof-of-concept is ready.	2007-2024	Prototype, process of production & PoC READY
Stage 2: Non-GLP studies-1 i) Development of stable formulation of NEURO-E and stability studies ii) Toxicology studies of NEURO-E formulation iii) Safety pharmacology studies of NEURO-E formulation iv) PK studies of NEURO-E formulation	2025-2027	
Stage 3: Non-GLP studies-2 i) Re-validation of stage-2 studies in higher animals ii) Efficacy studies (dose, route, combination etc) of NEURO-E formulation in relevant animal model ii) Re-validation of efficacy of NEURO-E formulation in relevant animal model	2027-2028	
Stage 4: GLP studies i) GLP-studies for IND application filing ii) IND application filing iii) Rebuttal	2028-2029	
Stage 5: Manufacturing process for clinical studies i) Preparation of NEURO-E batch in GMP facility for clinical studies	---	
Stage 6: Clinical studies i) Phase I Clinical Trials	---	

ii) Phase II Clinical Trials iii) Phase III Clinical Trials		
Stage 7: Regulatory Review and Approval i) NDA / BLA filing ii) Rebuttal iii) Product labelling and marketing approvals iv) Post approval preparation and preparation of product launch	2035	
Stage 8: Commercialization and Post-Market Activities i) Product launch ii) Expansion and Scaling iii) Post-Market Surveillance & Lifecycle Management	---	

Annexure 2

NEURO-E Development Plan-2 (Jan 2025-Dec 2027)

(Stage 2: Non-GLP studies-1)

Target: to generate data for Stage 3 and 4 studies!

	Experiments	Deliverables	Time-line	Cost
1	**Formulation & Stability studies**: (as per NDCT-2019 rules) i) Formulation ii) Stability studies iii) Data of final formulation	- 2 final formulations; - stability data; - analytical data of formulation; - data for further pre-clinical/clinical studies as well as for scale-up of formulation	**03 - 18 Mo**	**29.0 lakh**
2	**Toxicological studies**: (as per NDCT-2019 rules) i) *Systemic Toxicity studies* (Single dose / dose ranging toxicity studies; *Repeated-dose systemic toxicity studies* (14/28/90/180 days); ii) *Immunogenicity / Hypersensitivity* studies iii) *Local toxicity studies* with proposed route of application? iv) *Genotoxicity studies* v) *Reproductive toxicology studies* (Male fertility, other studies)	- toxicological profile of formulation - therapeutic index of formulation - data for Stage-3/4 studies	**09 - 33 Mo**	**51.0 lakh**
3	**Safety Pharmacological studies**: (as per NDCT-2019 rules) i) Cardiovascular system ii) Central nervous system iii) Respiratory system	- safety profile of formulation - data for Stage-3 experiments	**12 - 18 Mo**	**19.0 lakh**
4	**Pharmacokinetic studies**: i) All ADME parameters	- Pharmacokinetic data / metabolic profile of formulation - data for Stage-3/4/6	**12 - 18 Mo**	**44.0 lakh**
5	**Administrative cost**			**22.0 lakh**

*Tentative, based on the estimates received.

Funding:

1. Partner company shall fund 100% of these studies, or
2. Partner company & NIPER SAS Nagar together shall arrange funding from various schemes of GoI (ex, BIRAC, ICMR, DST, Others).

SWOT Analysis

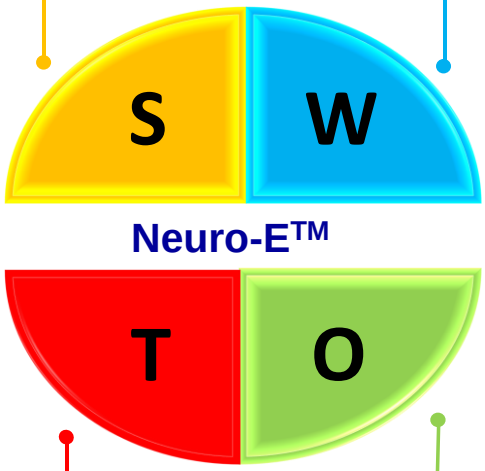
Neuro-E™

STRENGTHS

- Neuroprotective and Neurohealing properties
- Can be useful in numerous Neurodegenerative conditions

WEAKNESS

- Production system
- Detailed toxicity, safety and efficacy studies NOT completed yet



THREATS

- IND filing and clinical studies may take substantial time
- Competitors may GO ahead

OPPORTUNITIES

- Novel neuro-protective and neuro-healing biologics for numerous Neurodegenerative conditions
- Made in India

NEURO-E™: Engineered Human Apolipoprotein E mimetic peptide for the Treatment of Stroke

1. Field: Stroke is the 2nd most common cause of mortality globally. Each year, approximately 15 million people worldwide suffer from stroke. Of these, five million do not survive, and another five million are left permanently disabled, creating a significant burden on families and communities..

2. Problem: Currently tissue plasminogen activator (tPA) is the only approved drug for stroke treatment. However, its clinical use has serious limitations - ***a narrow therapeutic window*** of 3 - 4.5 h only and ***neurotoxic & cytotoxic effects***. Furthermore, tPA can only dissolve clots (thrombolysis) and cannot heal or protect the affected tissues. Other medications used in stroke management are primarily supportive (e.g., blood thinners, anti-hypertensive agents) and serve mainly to reduce the risk of further stroke rather than address the immediate damage. Therefore, there is an urgent need to develop new agent(s) for the treatment and management of stroke.

3. Need of the hour: The urgent need for safer, more effective treatments for stroke is critical due to the high mortality and severe side effects of current therapies.

4. Our solution: NEURO-E™, an engineered human apolipoprotein E mimetic peptide addresses these challenges

PATENT STATUS:

Granted

TRL STATUS: TRL3/4

NEURO-E

SPECIFICATIONS OF TECHNOLOGY:

1.**Unique structural design** NEURO-E is specifically designed to contain both LDL-R binding domain and the lipid-binding domain of native human ApoE, making it a highly efficacious to cross the blood-brain barrier, target brain cells, and promote repair.

2.**Neuroprotective Properties:** By mimicking ApoE natural role, NEURO-E™ protects neurons from damage caused by ischemia, oxidative stress, and inflammation, which are major contributors to stroke injury.

3.**Enhanced Neural Repair:** NEURO-E™ supports synapse formation, axonal growth, and neurogenesis in the hippocampus, all essential for cognitive recovery and motor function post-stroke.

4. **Protected intellectual property**: Indian patent filed.

5. **Made In India !!!**

Please Contact:

Dr. Abhay H. Pande,

Professor (Department of Biotechnology)
National Institute of Pharmaceutical Edu. Res. (NIPER)
Sector-67, S.A.S. Nagar, Mohali-160062, Punjab (India)
Telephone: 0172-2214682-85, Extn: 2068
E-mail: apande@niper.ac.in;
IPR cell: iprcell@niper.ac.in;
Technical cell: technicalcell@niper.ac.in

SCAN QR TO SEE THE LAB TECHNOLOGIES

Business Model Canvas for NEURO-E™

<table>
<tr>
<td>Problem:
- Stroke is a leading cause of death and disability worldwide. Globally, 1 in 4 adults over the age of 25 will have a stroke in their lifetime.

- Rates of stroke are growing fastest in low- and middle-income countries, often where healthcare providers find it more challenging to provide the care.

- There is no effective way to prevent, or treatment of stroke.

Shortcomings:
- Current treatments are inadequate
- A dire need to develop more efficacious treatment</td>
<td>Solution:

- Apolipoprotein E (ApoE), the most abundant apolipoprotein in the brain, plays a key role in lipid metabolism, neural repair mechanisms, synapse formation and remodelling, and axonal growth.

- NEURO-E is an engineered human apolipoprotein E mimetic peptide involved in neural repair mechanism and manage stroke effectively</td>
<td>Unique Value Prop:

Enhanced Efficacy
Neuro-E possess both Neuroprotective and Neuro-healing Properties

Reduced Adverse Reaction
(potential for lower doses & fewer side effects compared to existing treatments)

Cost-Effective
(potentially lower production costs, more accessible and more affordable for Indian patients; Made in India)

Versatility
(Potential applicability to a range of neurodegenerative disorders</td>
<td>Unfair Advantage:

Reduced Adverse Reaction
Potential for lower doses and reduced side effects

Versatility:
Potential applicability for the treatment and management of multiple neurodegenerative disorders

Affordable-n-accessible:
Potential low cost and made in India</td>
<td>Customer Segments:

Disease segments:
Multiple CNS disorders

Partners:
National and international Start-ups & Pharmaceutical companies for co-development</td>
</tr>
<tr>
<td>Existing Alternatives:

- Tissue plasminogen activator (tPA) is currently the only approved drug available for stroke treatment but has its own limitations.</td>
<td>Key Metrics:

- Efficacy in multiple pre-clinical models

- Cost of GLP mode proof</td>
<td>High-level Concept:

- Unique design features of NEURO-E™ make it as both Neuroprotective and Neurohealer.</td>
<td>Channels:

National & international
- Start-ups
- Pharmaceutical companies</td>
<td>Early Adopters:

National & international
- Start-ups</td>
</tr>
<tr>
<td colspan="3">Cost Structure:
- Cost of non-GLP studies is tabulated in Annexure 2
- Further cost will require in-depth discussion with the partner company</td>
<td colspan="2">Revenue Streams:
- Funding from government/non-government research grants</td>
</tr>
</table>