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CynAxis

Traversing the Blood Brain Barrier

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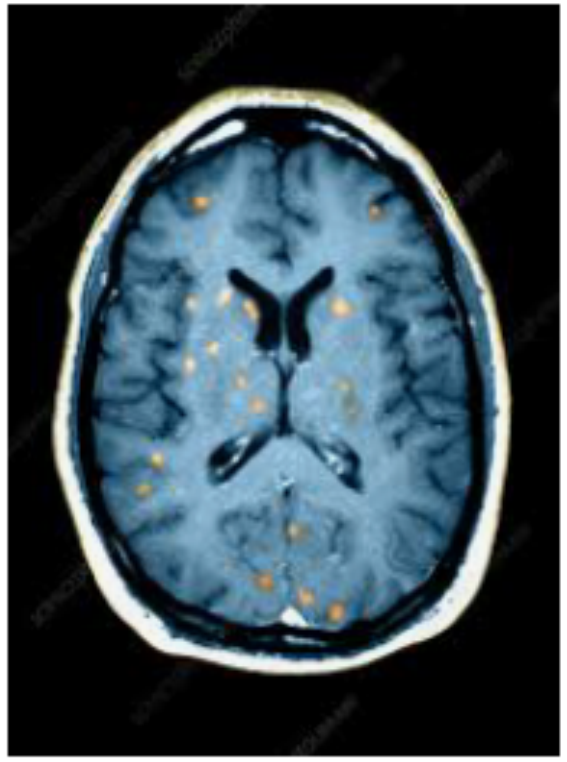
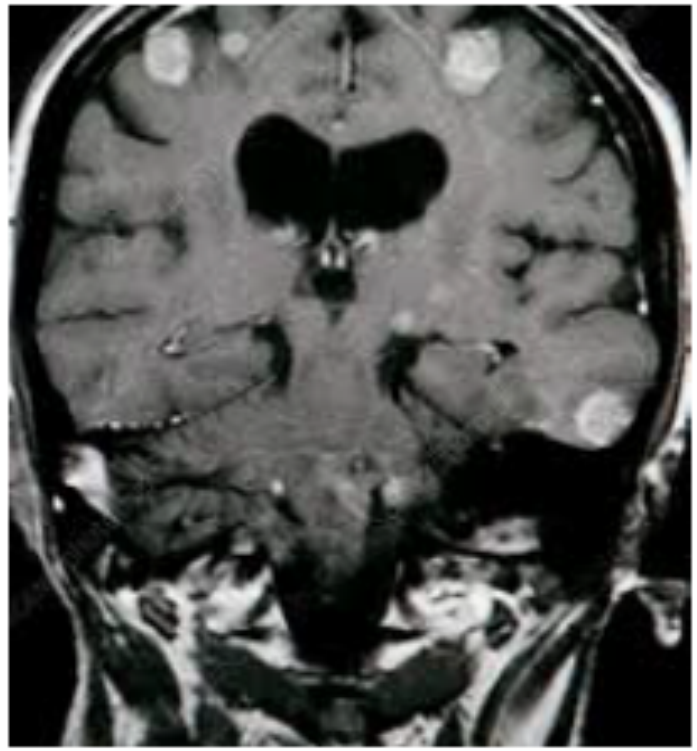
Many Effective Therapies Cannot Cross the Blood Brain Barrier (BBB)

Cancer Type	Incident Proportion of Brain Metastasis by Cancer Type
Lung	20%
Breast	5%
Melanoma	7%
Renal	7%
Colorectal	2%

- 10-20% of all patients develop brain metastasis
- Brain metastasis portends high mortality
  - 8.1% survival rate at 2 year
  - 2.4% survival rate at 5 year
- Neurosurgical excision and radiotherapy not possible or sustainable for some patients

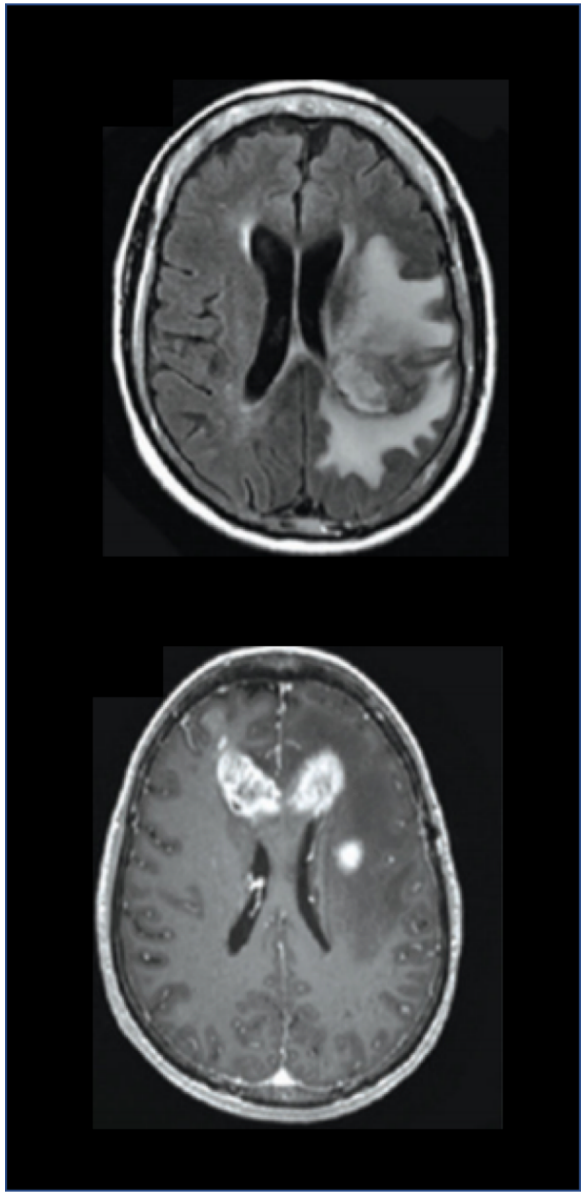
J Clin Oncol. 2004 Jul 15;22(14):2865-72.





Brain Metastases are difficult to treat because either effective therapies cannot cross the BBB or cannot reach adequate concentrations in the microtumor environment.

Glioblastoma Remains Largely Incurable



- Gliomas Grade 1-4 includes astrocytic tumors oligodendrogliomas ependymomas, and mixed glioma
- Glioblastoma multiforme (GBM) IV is malignant
- Accounts for 50% of all gliomas in all age groups; 60% of all brain tumors in adults
- Poor prognosis; 14-15 month survival after diagnosis
- Main challenges in therapy of GBM are related with the location of the disease and its complex and heterogeneous biology

Asian Pac J Cancer Prev,2017. 18 (1), 3-9
Kesari, 2011. Semin Oncol, 38, 2-10.

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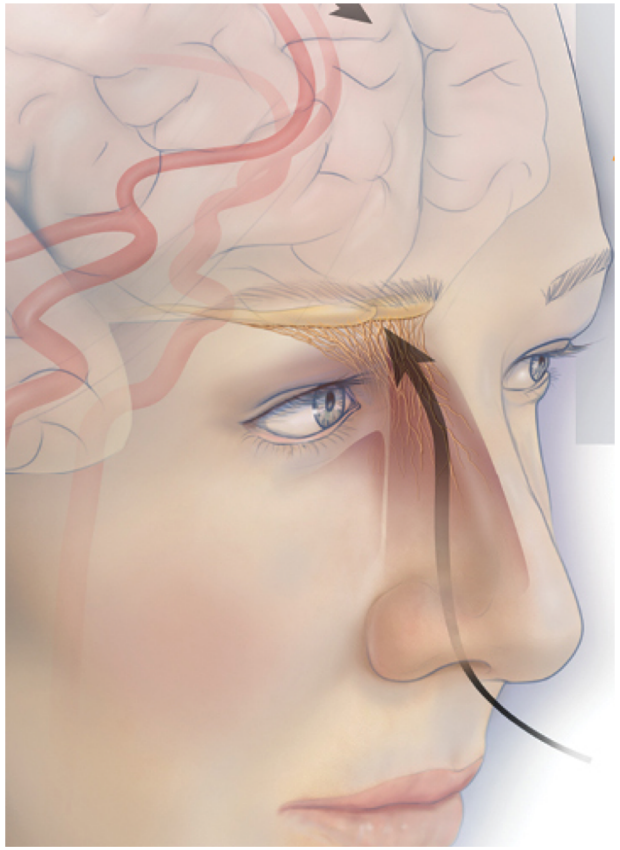
CynAxis can solve the problem



2017, LISA CLARK, The Scientist Magazine

- CynAxis can engineer patient specific peptides to activate an adaptive immune response
- This enables transient and defined access of drugs and biologics to the CNS
- This technology can allow delivery any drugs or biologics to the CNS.

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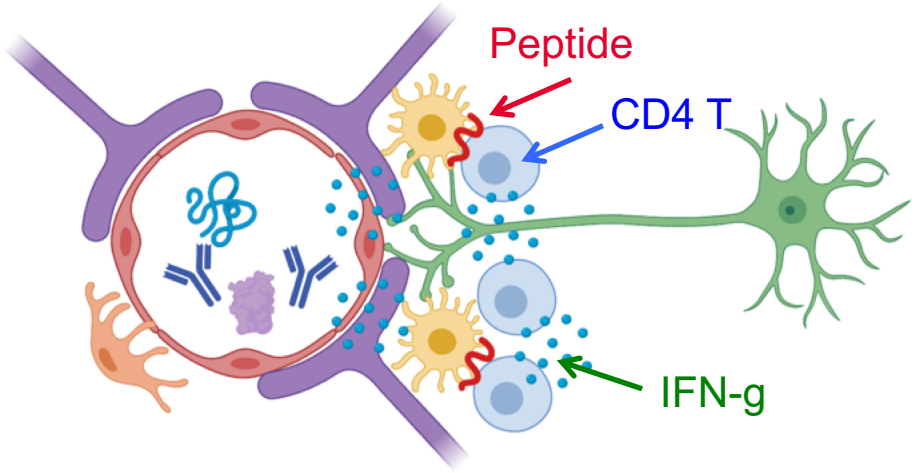
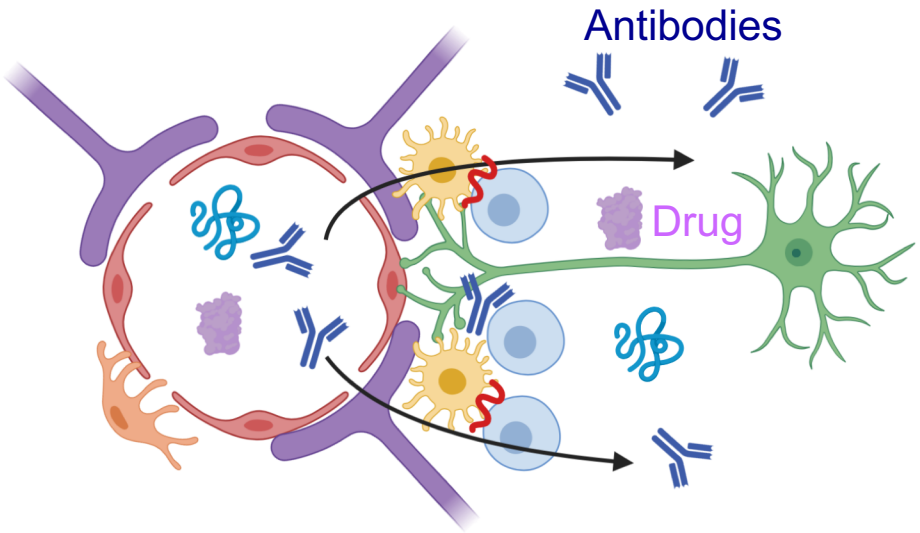
CNS antigen-specific CD4+ T Cells Could Mediate BBB opening





Step 1
Stimulate CD4 T cells with specific peptides delivered to intranasally to the CNS.

Step 2
Interferon gamma secreted by CD4 T cells enable transient permeability of the BBB, enabling drugs and biologics to access the CNS parenchyma.

Iijima N, Iwasaki A. Nature. 2016 May 26;533(7604):552-6.

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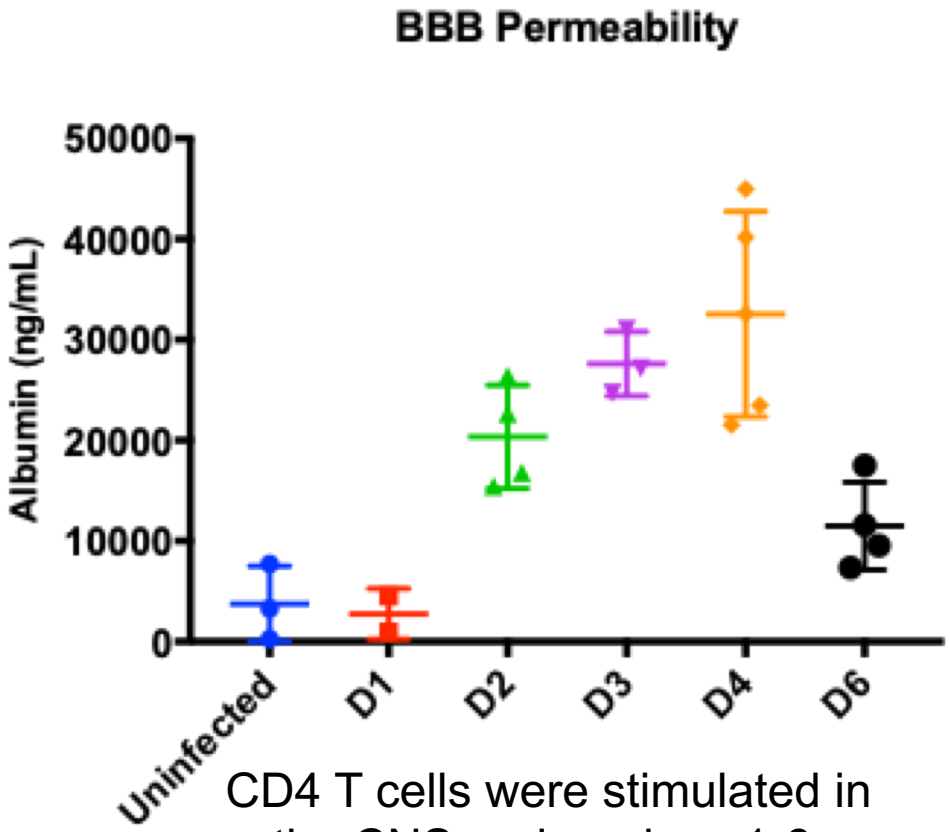
CynAxis Intranasally Delivers MHC Class II Peptides to Open Up BBB



CD4 T cells were stimulated in the CNS and on days 1-6, BBB permeability was measured by albumin access to the CNS

- MHC class II peptide will be delivered intranasally using a spray.
- Peptide will follow olfactory nerves to enter the CNS to stimulate CD4 T cells.
- CD4 T cells produce interferon gamma to open up the BBB for a few days.

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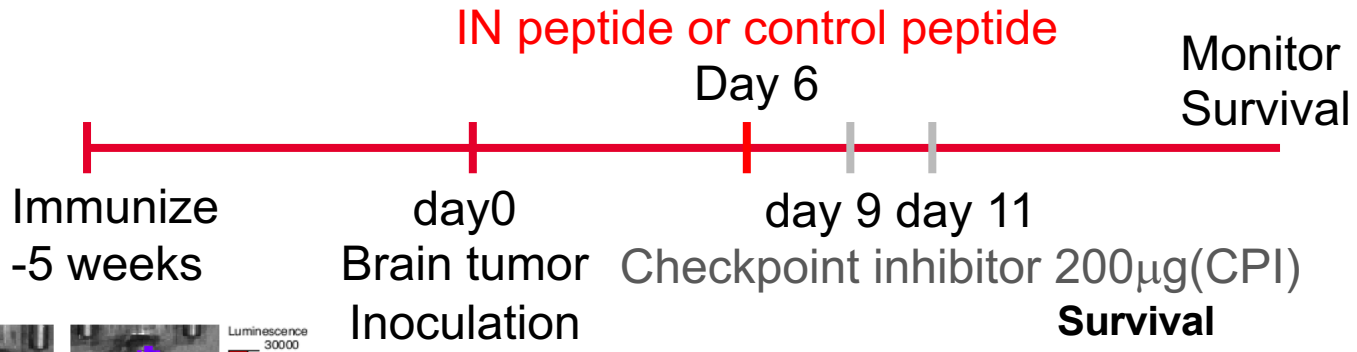
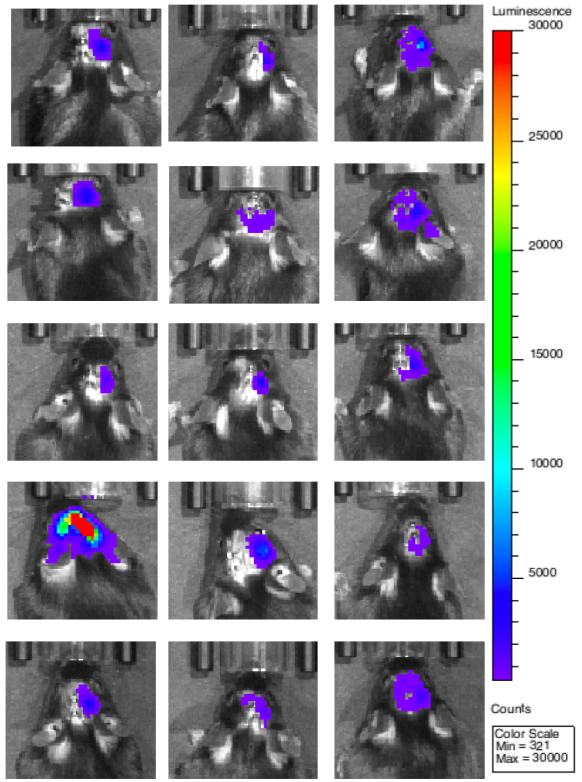
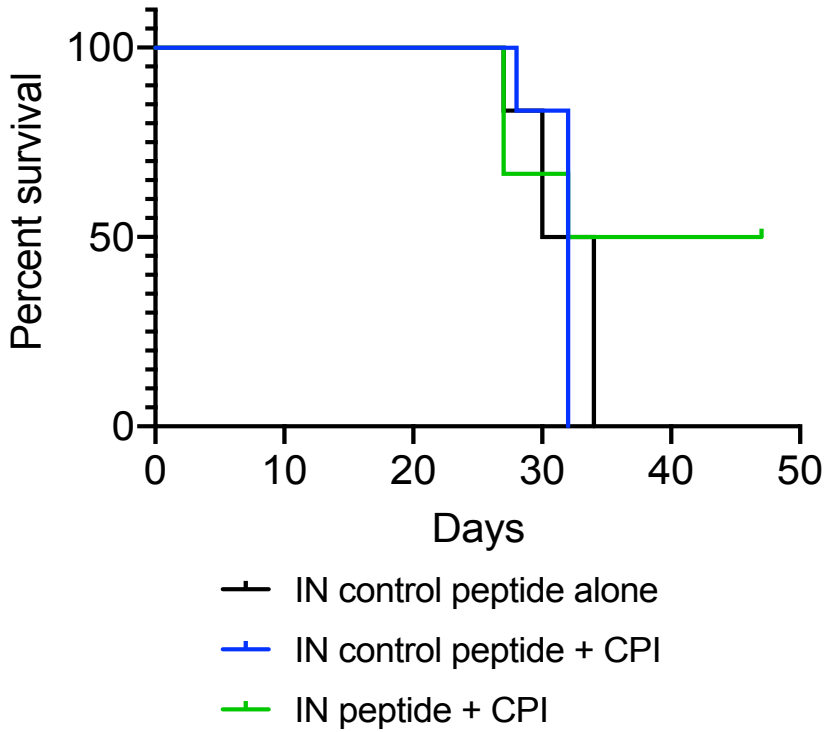
Stimulation of T cells by Intranasal Peptide (IN) Enables Checkpoint Inhibitor Biologics to Access Brain Tissue and Treat Tumor



Day 7
Tumor burden
prior to
treatment





Competitive Landscape

Intervention	Technology	Limitations
Convection-enhanced delivery **Nanoparticles**	Catheters placed to infuse into a specified area of the brain Various classes of particles types engineered to enhance delivery across BBB	• Larger molecules have low Vd, hence limited efficacy • Relies on endocytosis so trafficking drug of interest to correct cellular compartments challenging • Rapid particle clearance in systemic circulation
Focused Ultrasound and Microbubbles	Microbubbles are injected peripherally and ultrasound causes the bubbles to swell and contract.	• Effects on endothelial tissue integrity unknown and may increase risk of leaky endothelium, • Increased risk thrombosis, infection
Chemical Disruption	Non-Ionic Amphiphilic compounds can traverse BBB via endothelial cells.	• Clinical trials to date have shown no efficacy
Utilizing specific receptors or transporters	Leverage a specific receptor or transporter that gates BBB access.	• Achieving sufficient concentrations in CNS via transport mechanism variable and unpredictable
Osmotic diuretics	Temporary dehydration of BBB endothelial cells, grants small and large molecules indiscriminate access to the brain for limited time	• Technology developed in 1970s • Osmotic BBB disruption results in transient cerebral edema

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CynAxis IP Estate

Patent Title	Country	Application Type	Status	Application No.	Patent No.	Expiration Date
Composition and Methods	US		Issued			2036
Utility and Formulation	US		Issued			2038

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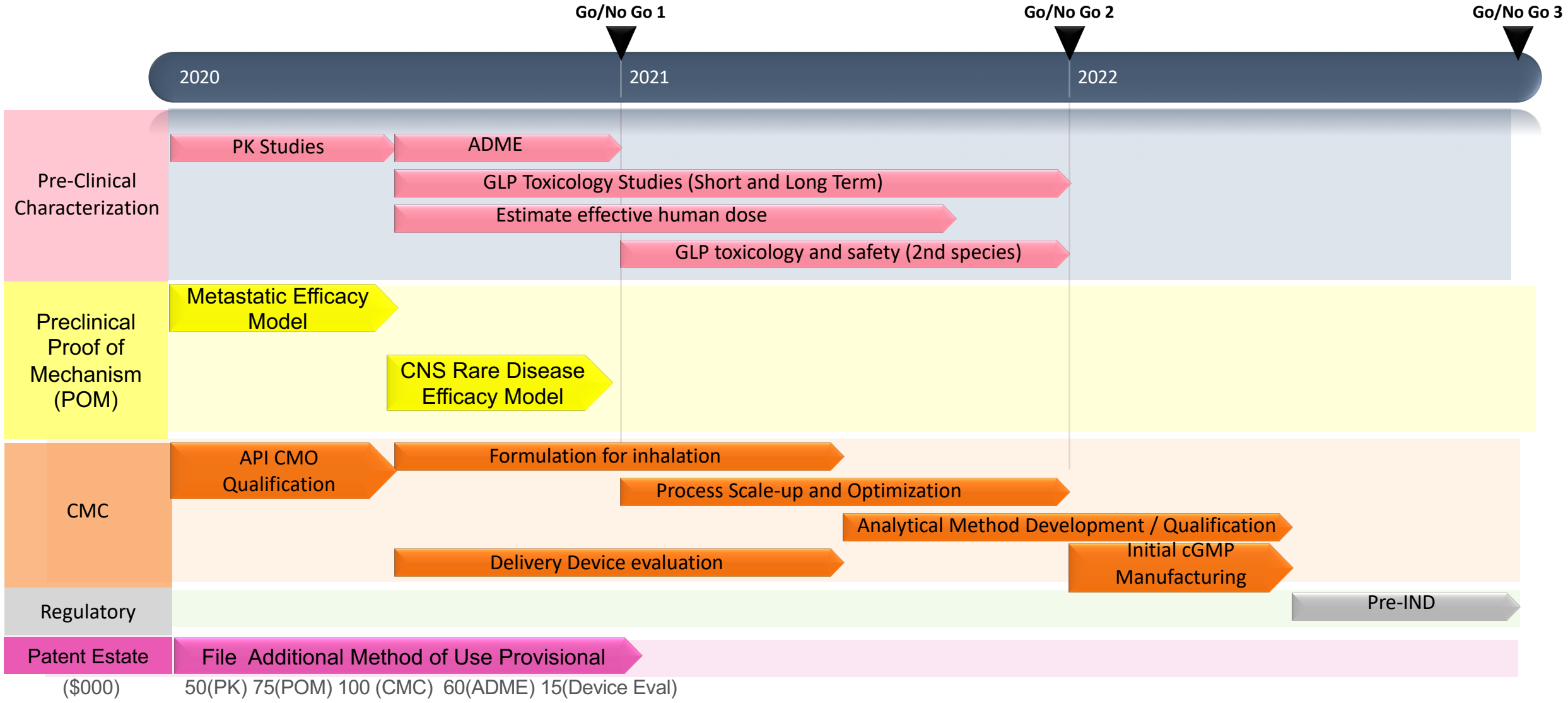
Cynaxis Timeline and Use of Proceeds



Budget reflects development costs only and excludes personnel, G&A