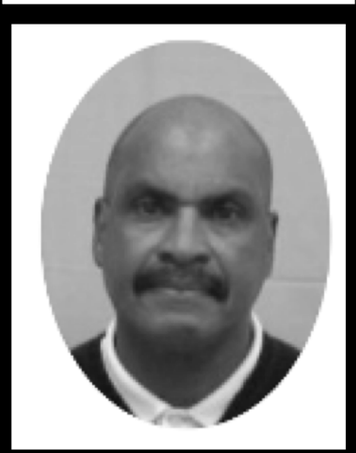
# Targeting NETs in human disease

Demetrios Braddock

# Team

**Reinaldo M. Diaz, MBA:** Lead investor and Board of Directors, Inozyme Pharma, Venture partner at Longitude Capitol Management, LLC; Managing director of DA Advisors LLC; co-founder of Diaz & Altschul Capital Management, LLC.



**Gene Griffin, D.V.M., M.S:** Senior Director at Alexion Pharma (Solaris, Strensiq, ENPP1-Fc in collaboration with Braddock Lab), VP Therapeutic Head at CureVac, 30 years of drug development experience in pharmaceutical and biotechnology companies including Biogen, Sandoz, Bristol-Myers Squibb, and Warner lambert-Parke-Davis

**Demetrios Braddock MD/PhD:** Assoc. Prof. Yale; Expertise in enzyme therapeutics and biologic development; Scientific Founder of Inozyme (Series A Jan 2017, IPO July 2020); Scientific Founder of Petragen (Series A Oct 2020); Founder and Medical Director of Precipio (2011-2017).

**David Lewin PhD:** Sr. Assoc. Dir. Bus. Dev. Yale, OCR; David and Demetrios have worked closely together for over 15 years; collaborations include the founding of Inzoyme, Precipio, and Petrogen.

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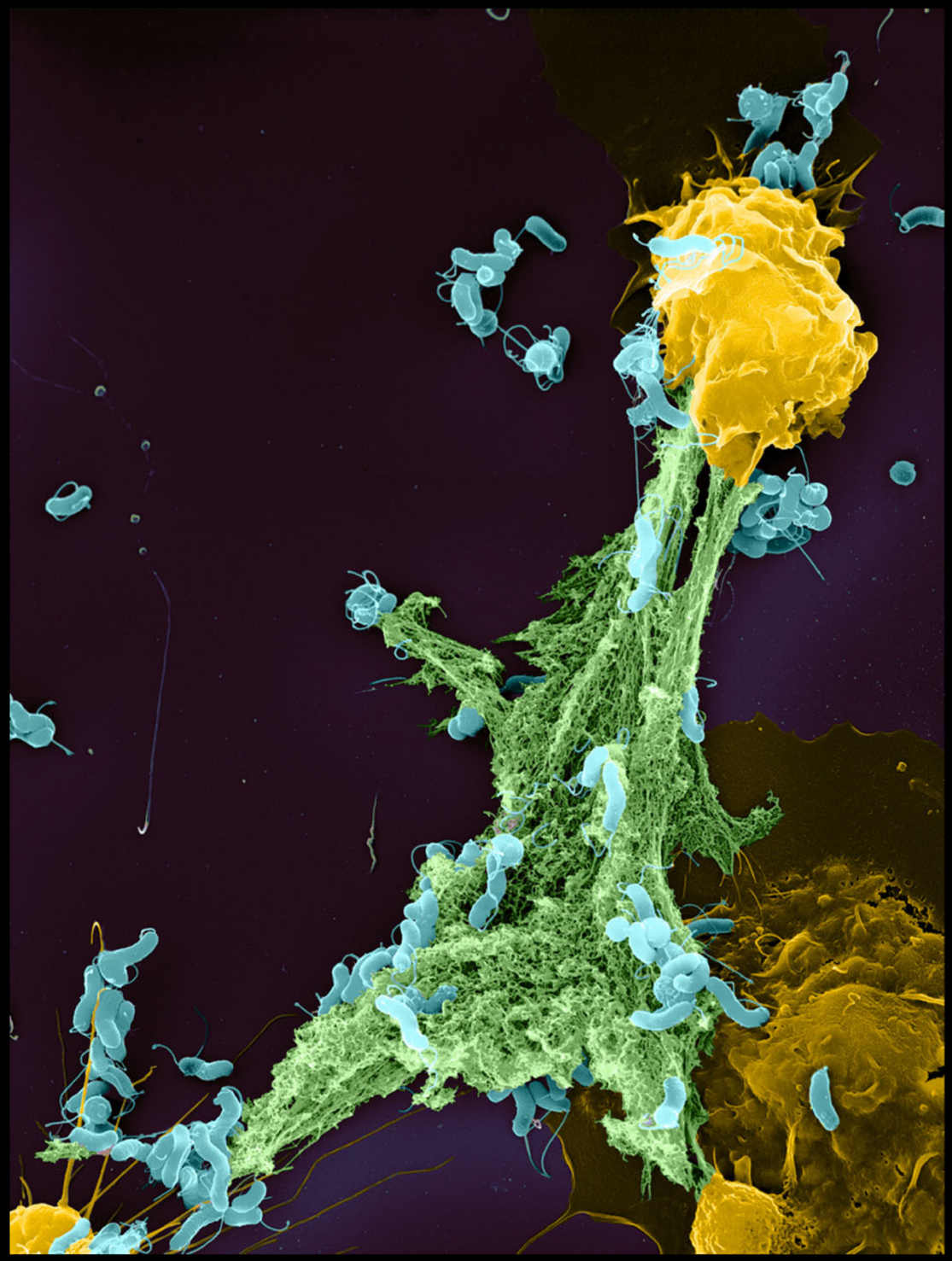
# Background and Rationale: Overview



Neutrophils casting a net entrapping Helicobacteria

Dr. Volker Brinkman, Max Planck Institute for Infection Biology, Berlin Germany (ref 28)

**A. Increased NET formation and reduced degradation drives the morbidity/mortality in**

- Thrombotic conditions including
  - ANCA Vasculitis, Anti-phospholipid syndrome
  - Acute Kidney Injury, ST-elevation following MI
- Autoimmune disorders such as Lupus, Hypocomplementemic uticarial vasculitis syndrome (HUVS), others
- Severe COVID-19 infection
- Cancer Metastasis

**B. Neutrophils 'self destruct', shooting 'NETs' of DNA tin the presence of:**

- Foreign viral and micro-organisms
- Specific High Grade (highly metastatic) Tumor Cells including
  - Breast Cancer
  - Esophageal Cancer
  - Lung Cancer
  - Esophageal Cancer

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# Problem and Solution

A. Several human enzymes are reported to degrade NETs

- DNAse1
- Dnase1L3
- Others

B. Efficacy of enzymes limited by poor bioavailability and pharmacologic properties

- A 1999 study to determine efficacy of DNAse1 in Lupus (Genetech & NIH)
  - drug was well tolerated
  - no neutralizing antibodies
  - failed to achieve therapeutic bioactive concentrations and was therefore ineffective

C. Braddock Lab has expertise engineering stable and bioavailable enzyme therapeutics.

- ENPP1 enzyme for GACI:
  - Can be lyophilized to a powder and rehydrated, retaining full activity
  - Lyophilized enzyme can be heated to 100º F for 3 months, rehydrated, without aggregation or loss of activity
  - Half-life of 36 hours
  - Predicted human dose is 2 mg/Kg sub-Q, twice a week
  - First in human dosing to begin in first quarter, 2021
- Recently increased potency of ENPP1 ERT to enable bimonthly dosing at 0.3-0.6 mg/Kg

D. Braddock lab has applied their experience in enzyme biologics to design and optimize stable and long acting DNA degrading Biologics (DDB's)

- Stabach et al., 'Improving the Pharmacodynamics and In Vivo Activity of ENPP1-Fc Through Protein and Glycosylation Engineering' Clin Transl Sci. 2020 Oct 16. doi: 10.1111/cts.12887.

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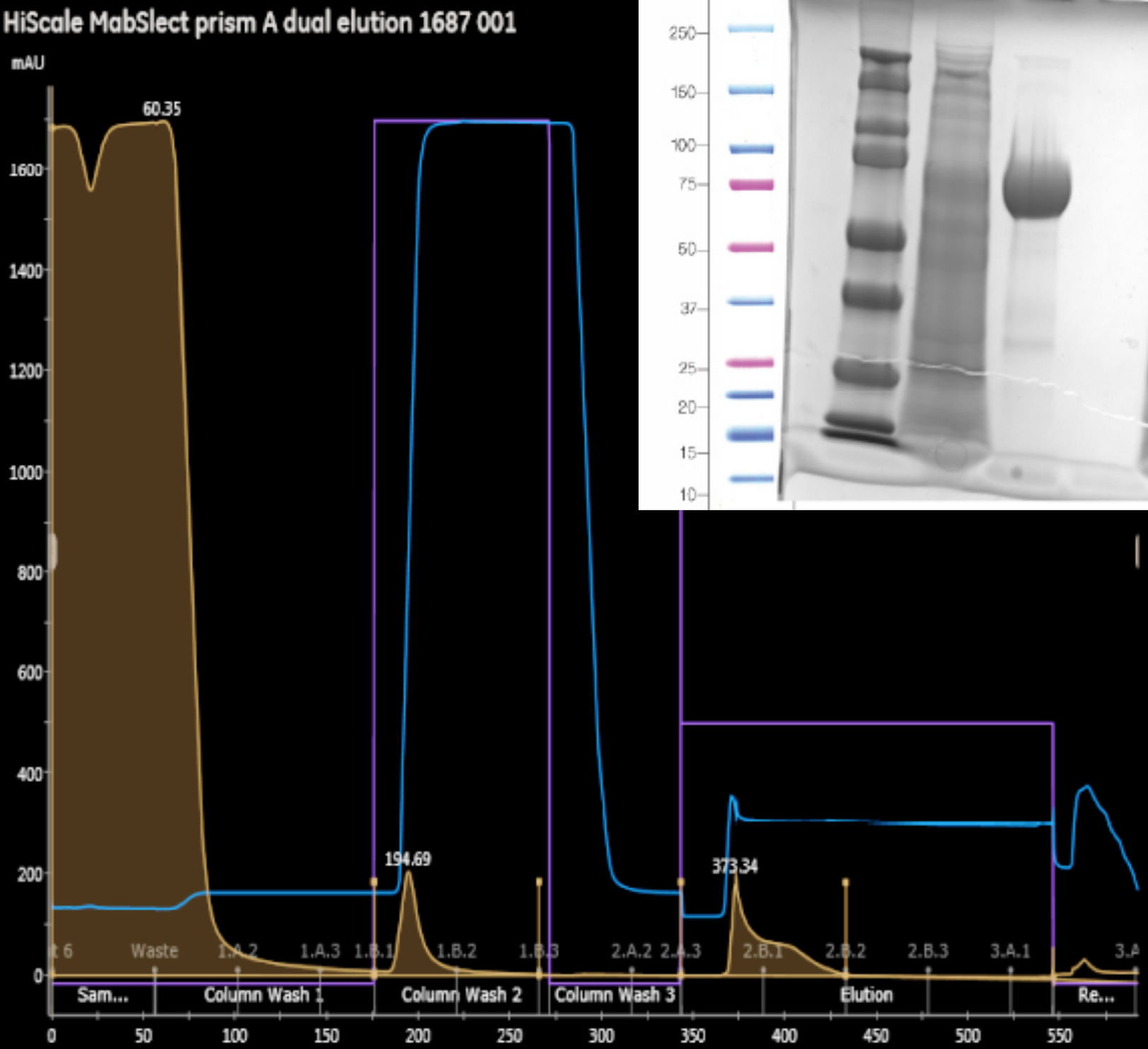
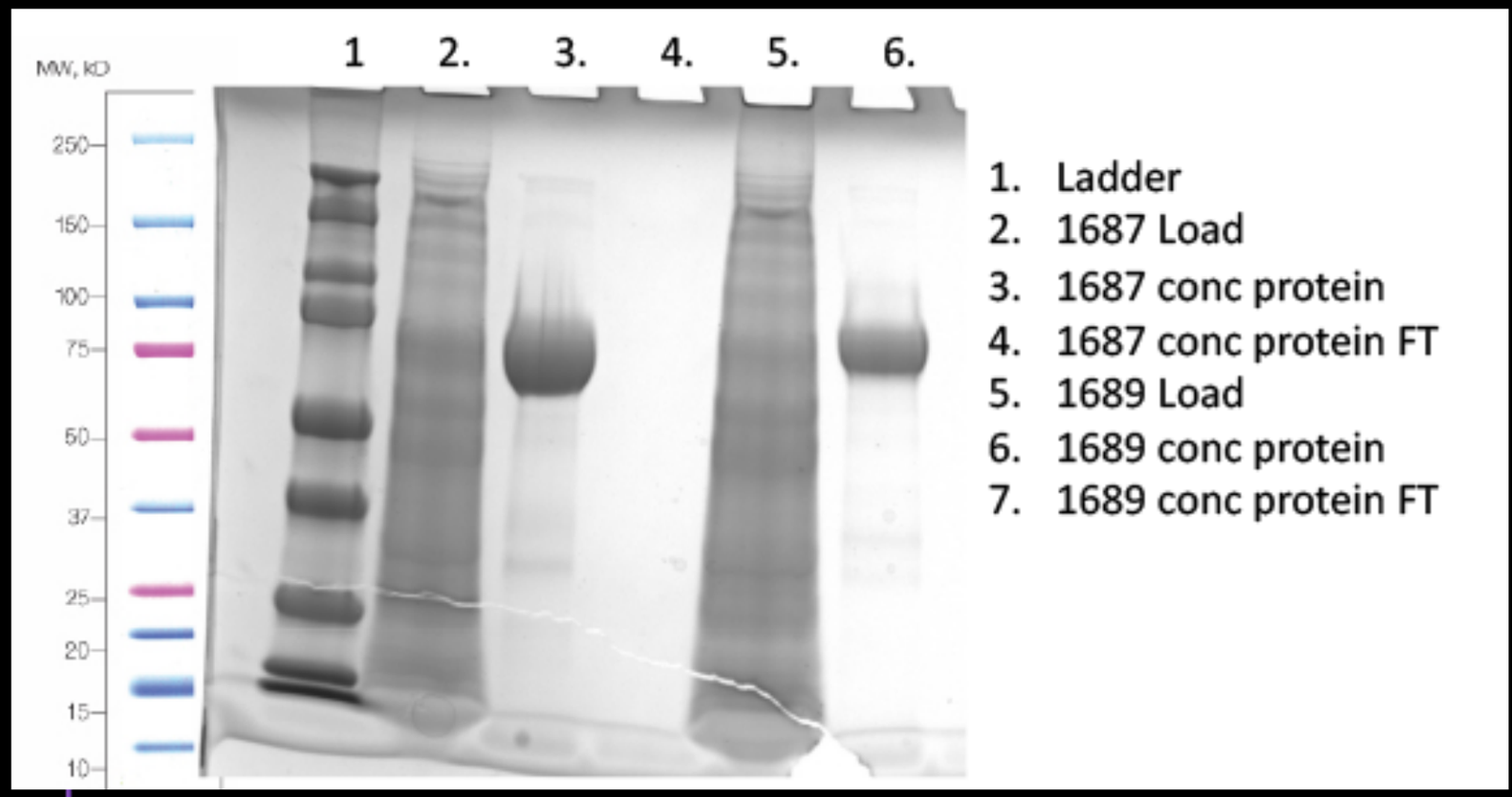
# CMC

## Rigorous, scalable, amenable to GMP production

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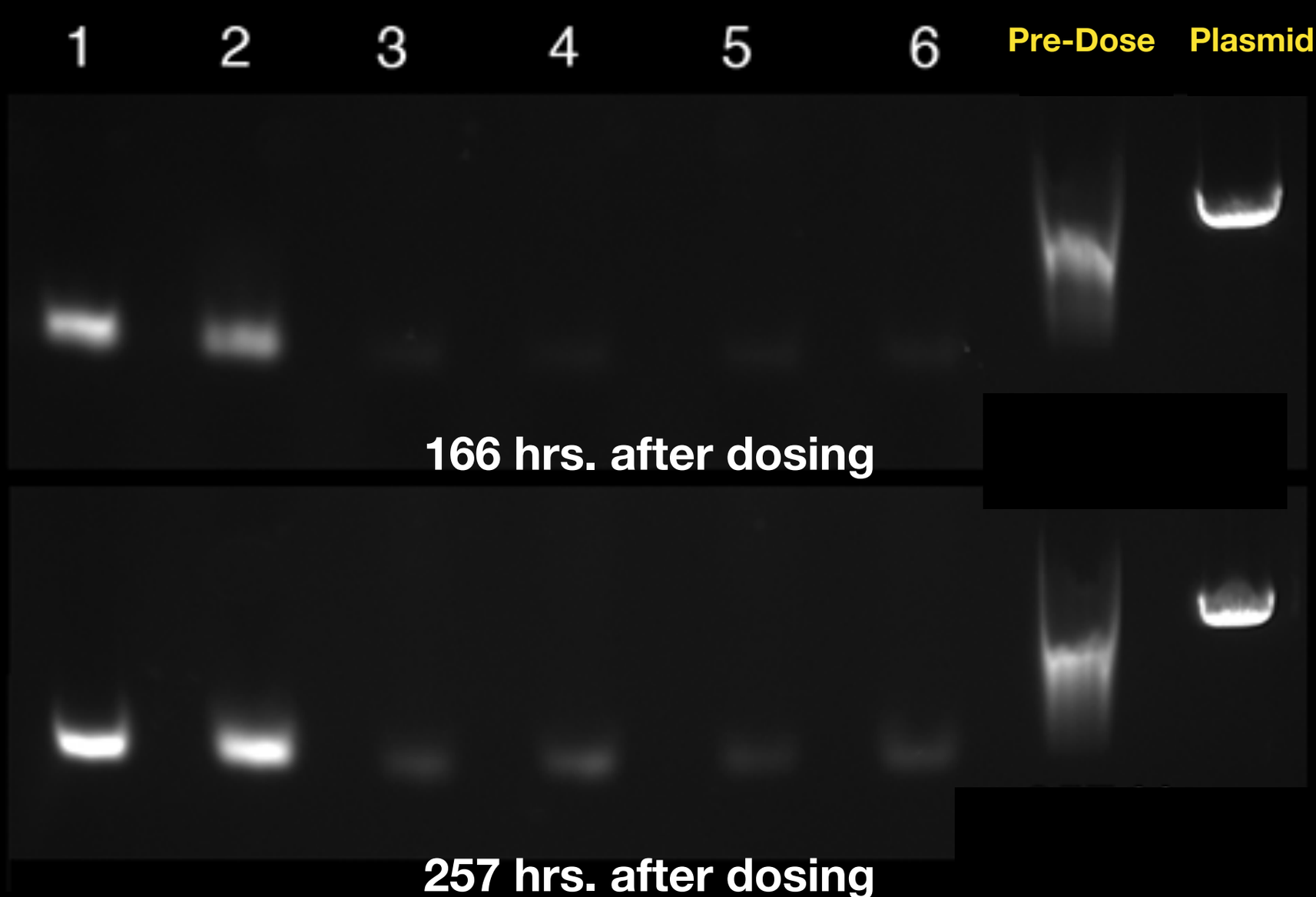
# Pharmacodynamics

## Bioactivity for over 10 days following single sub-Q dose

1 mg/Kg 1671

1 mg/Kg 1687

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# Murine models of NET driven Thrombosis and Tumor Metastasis

**Thrombosis:** DNAse1 and DNase1L3 knockout mice stimulated with GCSF: Mortality in 7 days

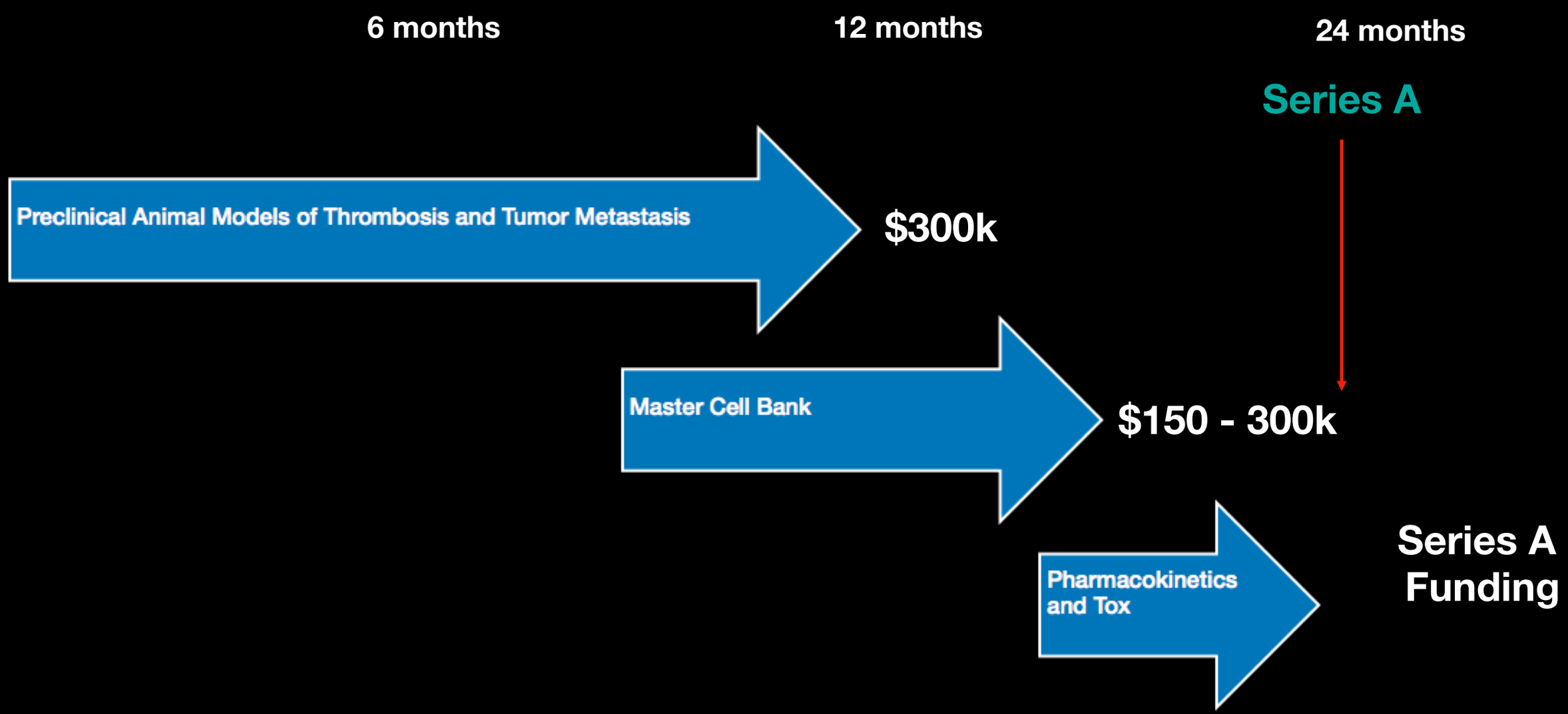
**Acute Kidney Injury:** Rodent model of renal injury on ventilator

**Tumor Metastasis:**

1. Tail vein injection of high grade metastatic tumors
   - Breast
   - Lung
   - Esophageal
   - Pancreas
2. Spontaneous Metastasis
   - Breast: implantation into mammary fat pad w/ and w/o resection
   - Lung/esophageal/pancrease: Implantation into flank

# Timelines and Budget

- Preclinical animal models of Thrombosis and Oncology: Begin upon funding, Thrombosis models of Acute Kidney Injury, Oncology models to include Triple neg breast, Pancreatic, and Esophageal cancer
- Clinical cell bank and Master cell lines: To begin within 3 months of successful preclinical animal models
- Series A raise: To begin after Master Cell Bank established

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# Summary

**We have developed optimized DDB ready for *in vivo* efficacy studies in established animal models of NET driven thrombotic and oncologic diseases**

- DBB's are highly stable
  - Retain activity for 3 months at room temperature
  - Can frozen and stored in an aqueous buffer at -80C without loss of activity
  - Amenable to multiple freeze-thaw cycles without loss of activity
- Rigorous purification amenable to high-throughput bio-production has been established.
- PK and PD have been determined
  - *in vivo* bioactivity of lead constructs is confirmed out to at least 257 hours.
- IP on composition of matter and indications filed by Yale OCR (OCR7857)
- In vivo efficacy studies are now underway

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