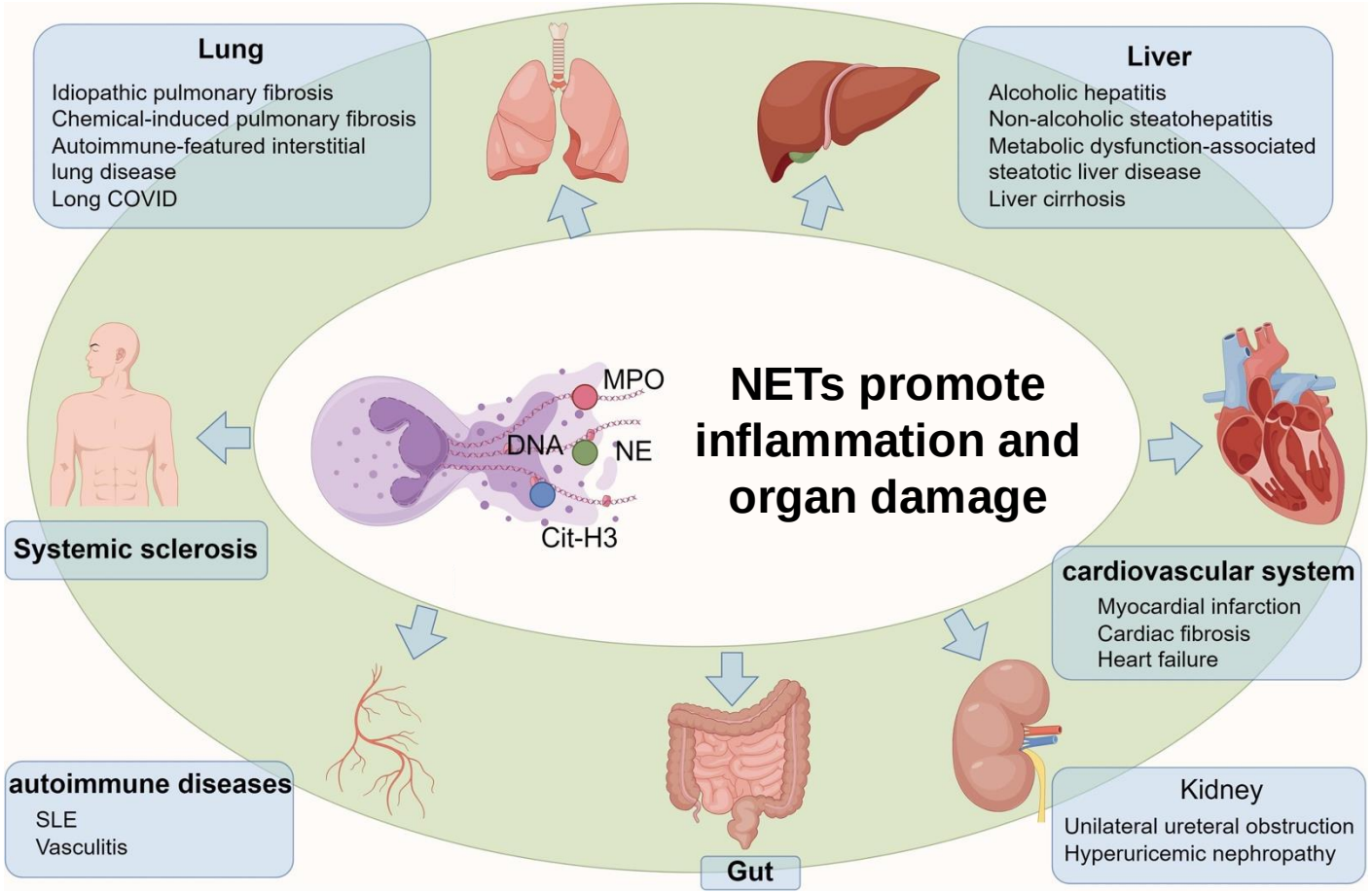
nucleicon

First-in-class antibody targeting NETosis

Inhibiting neutrophil extracellular traps (NETs): a major unmet need

- Neutrophils are the most abundant white blood cells (or innate immune effectors) of the human immune system
- Stimulated neutrophils release sticky aggregates of DNA/protein called “NETs” to trap invading organisms
- Release of NETs is pathologic when dysregulated and directly contributes to inflammation and many diseases

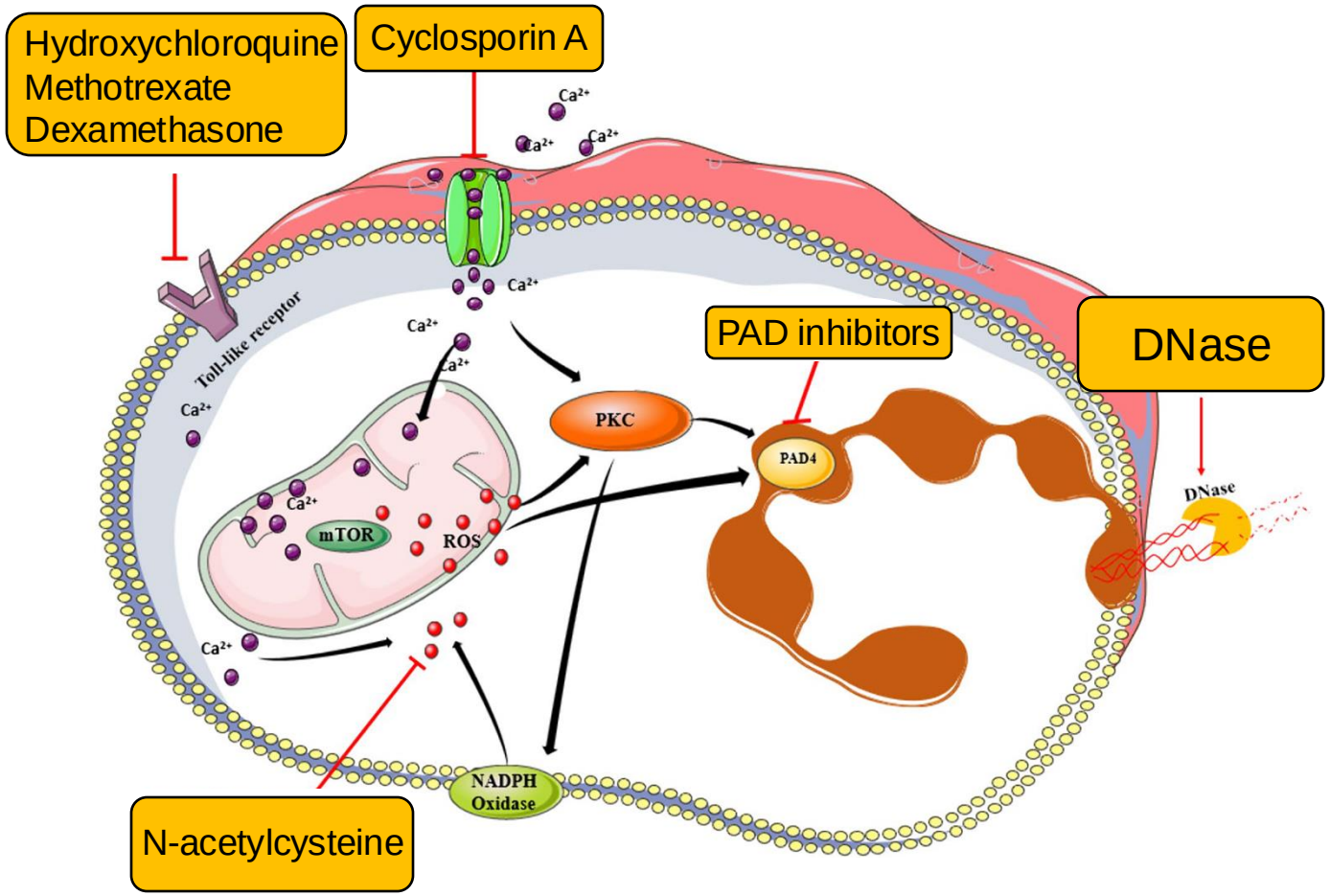


Adapted from: Int Immunopharmacol 2024;137:112516.

nucleicon

Competitive Landscape and Commercialization Opportunity

Off-target toxicity and immunosuppression are **major limitations** of current drugs



	targets DNA	binds NETs	inhibits NETosis
Global immune suppressants	✗	✗	✓
MPO, PAD, NE inhibitors	✗	✗	✓
DNases	✓	✓	✗
tACPA	✗	✓	✗
Deoxymab	✓	✓	✓

Adapted from: Mol Biotechnol 2024; doi: 10.1007/s12033-024-01171-0.

nucleicon

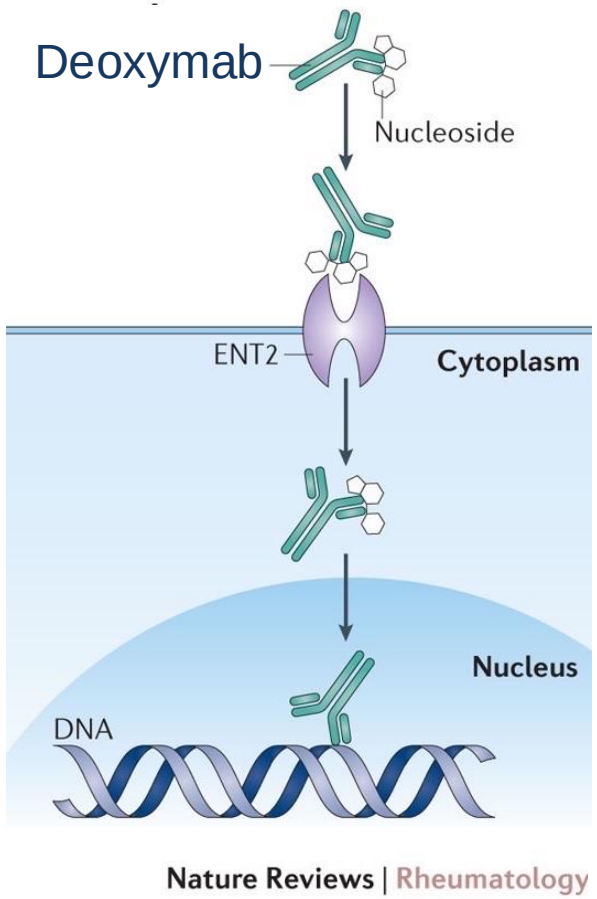
Deoxymab – a nuclear-penetrating anti-DNA antibody

Deoxymab is a DNA-binding antibody that:

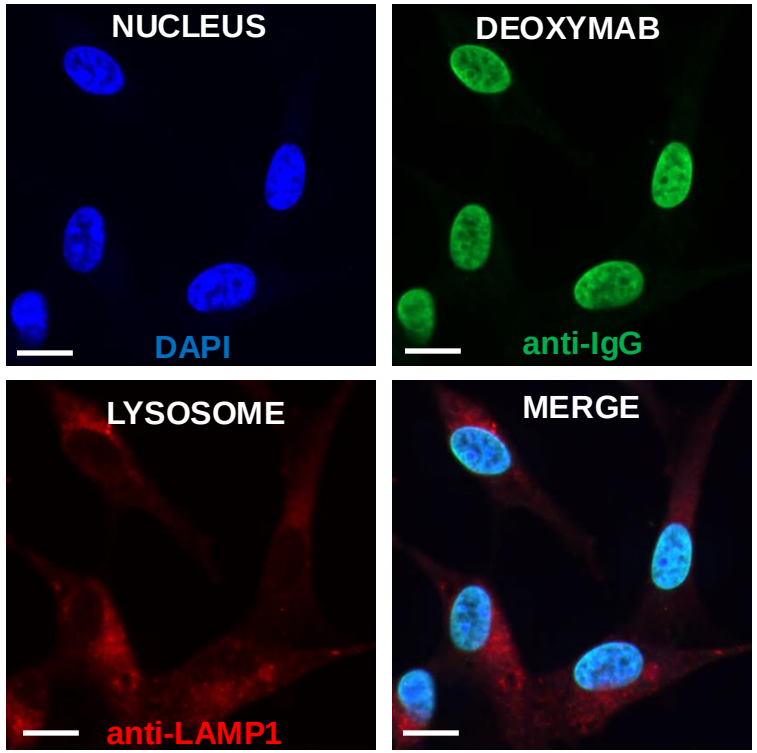
- targets areas enriched in DNA
- is taken into live cells in the area salvaging DNA by ENT2
- avoids endosomes/lysosomes but **binds DNA in the nucleus**

Master cell bank and procedures for Deoxymab GMP manufacturing have been established, and first Deoxymab fragment di-scFv passed toxicology studies in rodents and primates

Mechanism

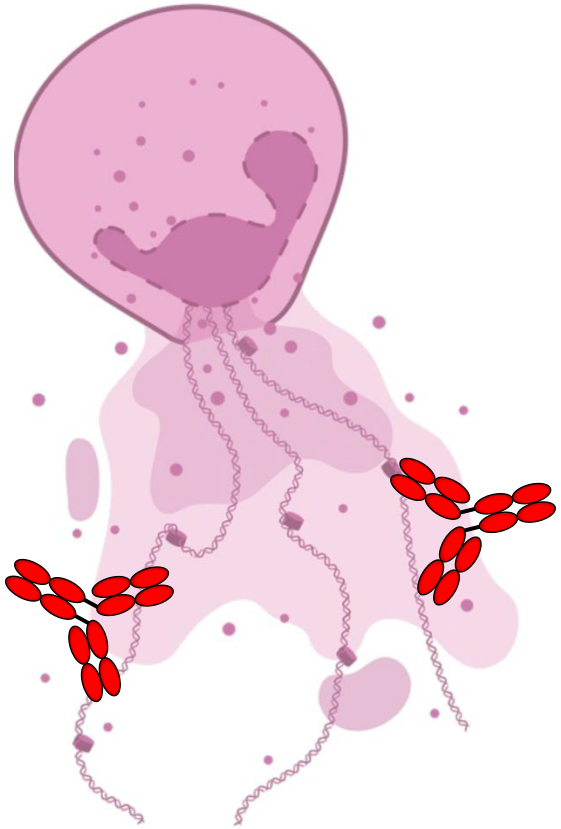


Images of cell nuclei penetrated by Deoxymab

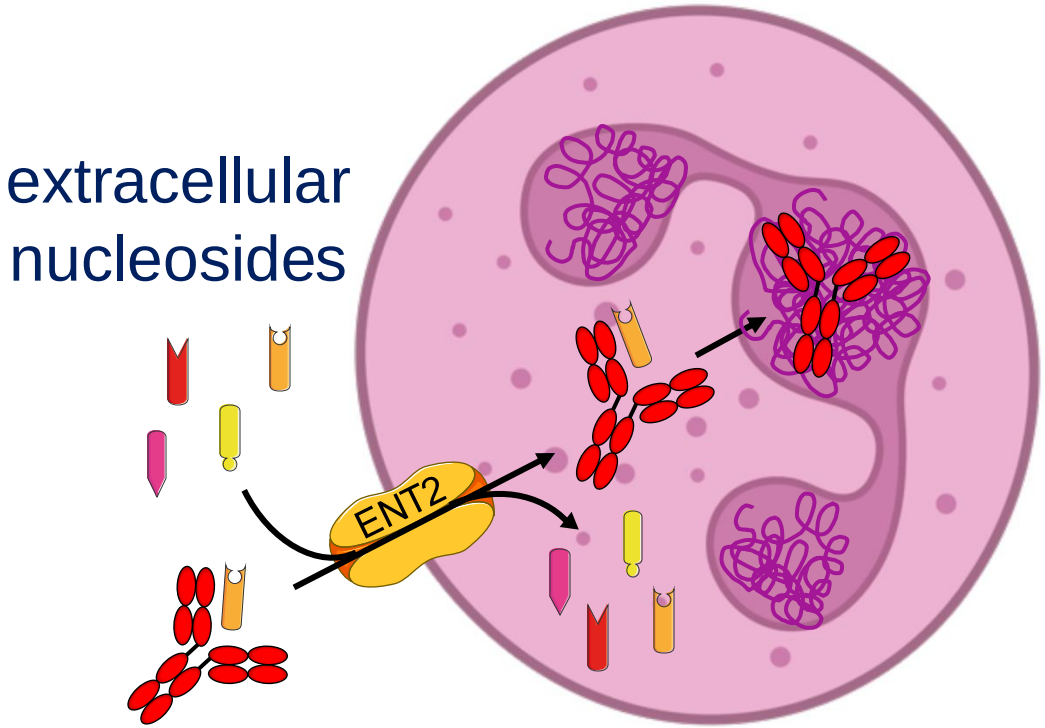


nucleicon

Deoxymab – An innovative solution for NET-driven diseases



- [x] targets DNA
- [x] binds NETs



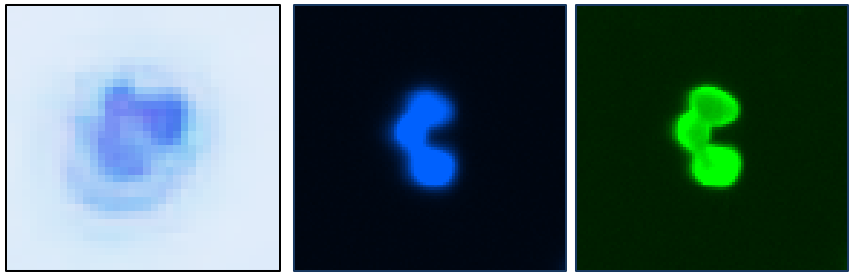
- [x] inhibits NETosis

nucleicon

Discovered at Yale and confirmed around the world

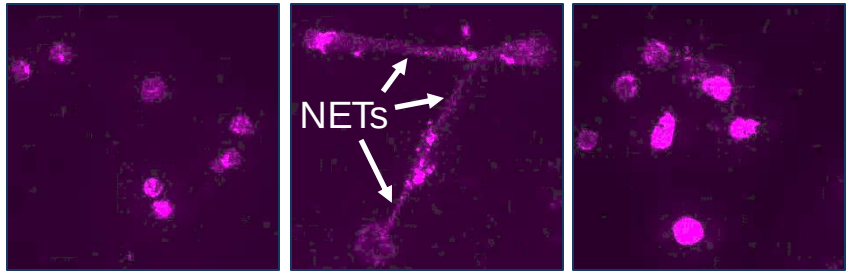
1. Hansen lab at Yale develops Deoxymab and discovers:

- Deoxymab penetrates neutrophil nuclei and binds DNA



neutrophil Giemsa stain | DAPI DNA stain | Deoxymab stain

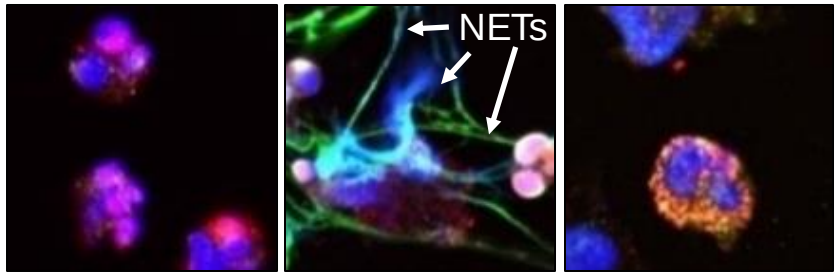
- Deoxymab inhibits NETosis



unstimulated neutrophils | PMA (induces NETs) | PMA + Deoxymab

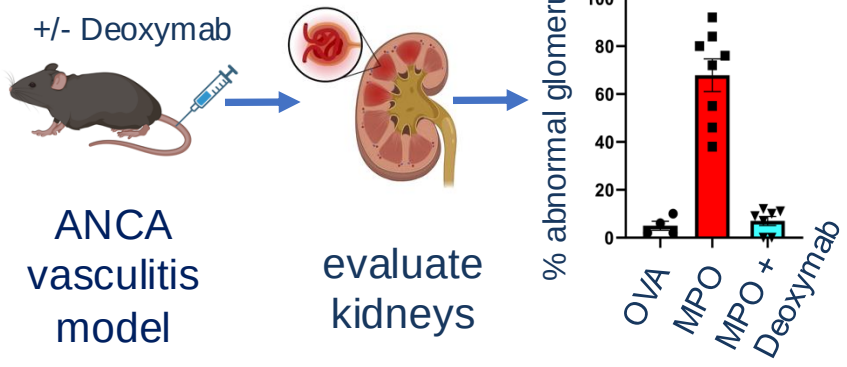
2. O'Sullivan lab at Monash University confirms Deoxymab:

- inhibits NET release but leaves other neutrophil functions intact



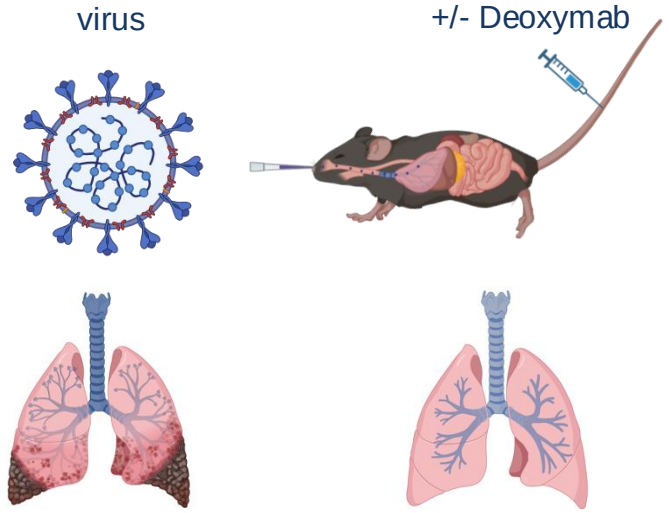
unstimulated neutrophils | Ionomycin (induces NETs) | Ionomycin + Deoxymab

- ameliorates NET-driven nephritis



3. Sefik and Flavell labs at Yale confirm Deoxymab:

- inhibits viral-induced NETosis to reduce NETs in blood and lungs of virally-infected mice and and ameliorate lung pathology



Virus promotes lung inflammation and damage

Deoxymab significantly reduces lung pathology

nucleicon

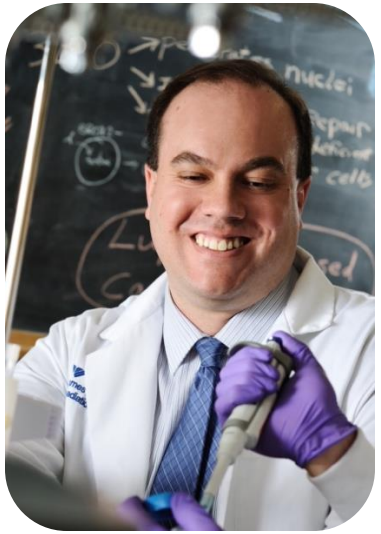
Proprietary Intellectual Property

- Deoxymab was developed by Yale faculty (Drs. Hansen and Zhou) and advanced by Yale licensee (Patrys Ltd, Australia)
- IP portfolio includes:
  - 12 active patent families
  - 18 patents granted
  - 32 patents pending
- completion of Deoxymab development and advancement to clinical trials as NETosis inhibitor to be finished by new Yale startup: **nucleicon**

IP protection extends to at least 2044 in all major markets

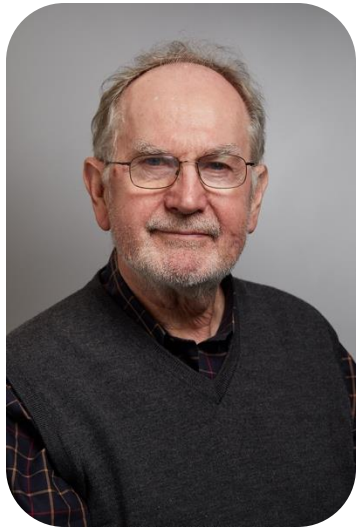
IP protection granted

Nucleicon Founders



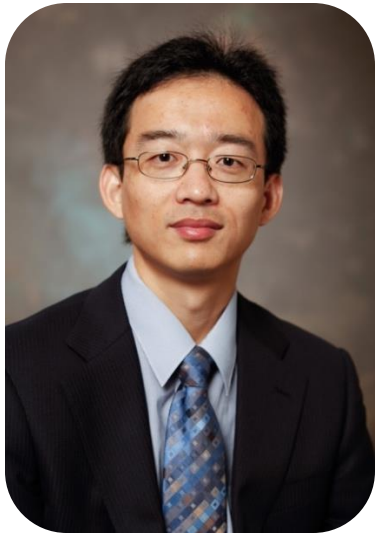
James Hansen, MD

- Associate Professor of Therapeutic Radiology, Yale University
- Chief of Yale Gamma Knife Center
- 15 patents on cell-penetrating antibodies
- Inventor of Deoxymab



Richard Flavell, PhD, FRS

- Sterling Professor of Immunobiology, Yale University
- Investigator, Howard Hughes Medical Institute
- Member, National Academy of Sciences
- Found Deoxymab effect on viral-induced NETosis



Jiangbing Zhou, PhD

- Professor of Neurosurgery and Biomedical Engineering, Yale University
- Co-Founder, Couragene Inc and CourageAS Bio
- Co-inventor of Deoxymab

Esen Sefik, PhD

- Assistant Professor of Immunobiology, Yale University
- Expert in the study of human-microbe interactions through humanized models of disease
- Found Deoxymab effect on viral-induced NETosis

nucleicon

Advisor Board (in progress)

James Campbell, PhD
Chair of AusBiotech

>20 years biotechnology research management & leadership, with approved FDA therapeutic and multiple partnering and M&A transactions

Alexandra J. Miele, CFP
Founder and Managing Director, Hierax Wealth Partners

>15 years in business development and wealth management, Chief Business Development Officer for billion-dollar team in the Hightower enterprise, Financial Advisor for Merill Lynch

Robert Nishimura, MD
Professor of Neurology
UCLA

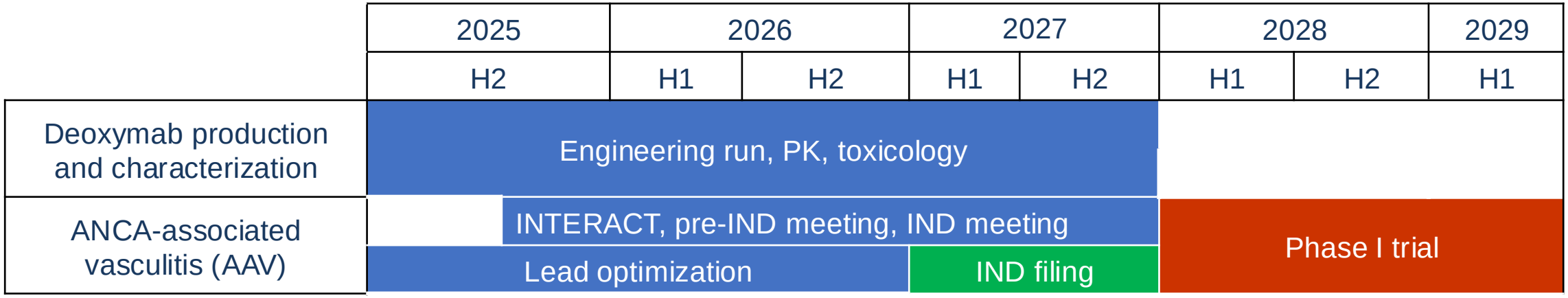
Expert in cell-penetrating antibodies with multiple patents and companies based on his discoveries

nucleicon

First indication - ANCA-associated Vasculitis (AAV)

AAV is an orphan NETosis-driven disease w/o effective therapy

- NETs drive vasculitis and kidney damage in AAV, and current therapies are limited by toxicities and do not address the central NETosis problem
- Deoxymab provides a promising solution confirmed in pre-clinical models
- Clear path to clinical trials with master cell bank and GMP manufacturing protocols in place and Deoxymab prototype passed toxicology in rodents and primates



nucleicon

Proposal for Blavatnik Fund Development Award

Goal: Advance Deoxymab technology to next value inflection points.
Plan: Establish new Deoxymab indications in NET-driven:
1) acute tubular necrosis (ATN) and **2) viral disease (COVID19)**

Aim 1. Establish Deoxymab indication in ATN.
Deoxymab efficacy/safety will be tested in humanized mouse models of 1) drug-induced ATN and 2) ischemic ATN.

Aim 2. Establish Deoxymab indication in viral disease.
Deoxymab efficacy and safety will be tested in a humanized mouse model of SARS-CoV-2 (COVID19).

Where work will be done:
Hansen, Zhou, Sefik, and Flavell labs at Yale

Timeline/Milestones (months):

1-3	4-10	11-12
Establish models	Deoxymab testing	data analysis, IP filings

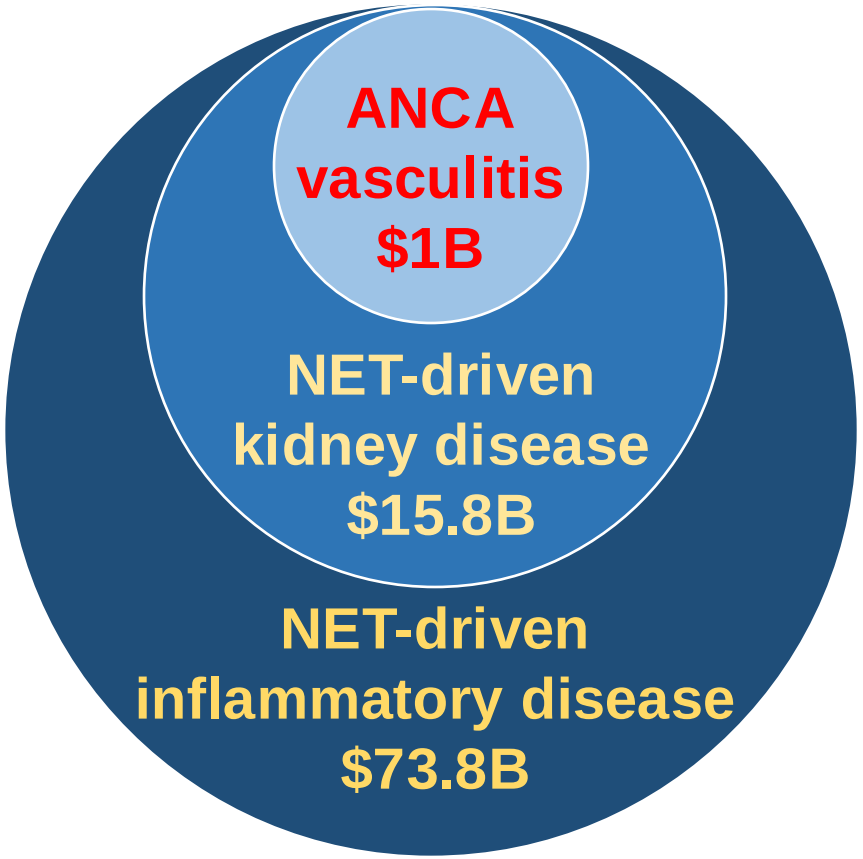
Estimated Budget:

- antibody prep for 3 models: $60,000
- 3 model humanized mice testing: $120,000
- Tissue/data analysis: $30,000
- Technician support: $90,000

Total: $300,000

Deliverables:
Enhanced Yale IP value through new market opportunities in NET-driven diseases.

Market Estimates

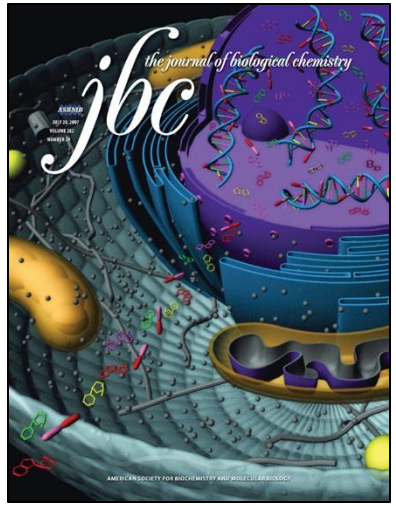


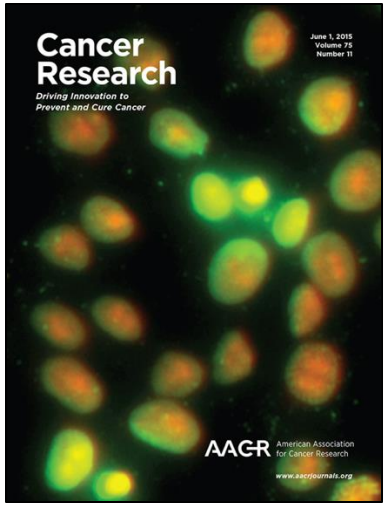
nucleicon

Key References (founders Hansen and Zhou underlined)

- **Hansen et al.,** Intranuclear protein transduction through a nucleoside salvage pathway. J Biol Chem 2007; 282(29): 20790-3.
- **Hansen et al.,** Targeting cancer with a lupus autoantibody. Sci Transl Med. 2012; 4(157): 157ra142.
- Noble…**Hansen JE**. Optimizing a lupus autoantibody for targeted cancer therapy. Cancer Res 2015; 75(11): 2285-91.
- Weisbart…**Hansen JE**. DNA-dependent targeting of cell nuclei by a lupus autoantibody. Sci Rep 2015; 5:12022.
- Noble…**Hansen JE**. DNA-damaging autoantibodies and cancer: the lupus butterfly theory. Nat Rev Rheumatol. 2016 12(7): 429-34.
- Chen… **Hansen JE, Zhou J**. A lupus anti-DNA autoantibody mediates autocatalytic, targeted delivery of nanoparticles to tumors. Oncotarget 2016; 7(37): 59965-59975.
- Rattray…**Zhou J, Hansen JE**. ENT2 facilitates brain endothelial cell penetration and blood-brain barrier transport by a tumor-targeting anti-DNA autoantibody. JCI Insight. 2021; 6(14): e145875.
- Chen…**Zhou J**…**Hansen JE**. Inhibition of NETosis by a nuclear-penetrating anti-DNA autoantibody. ImmunoHorizons. 2022; 6(6): 356-365.
- Cao…**Zhou J, Hansen JE**. Cathepsin B nuclear flux in a DNA-guided “antinuclear missile” cancer therapy. ACS Cent Sci 2024; 10(8): 1562-1572.

Deoxymab on journal covers





Data in these slides is from the references above and unpublished data from Hansen, O’Sullivan, Sefik, and Flavell labs shown with permission. Some illustrations created in https://BioRender.com.

nucleicon