Targeted Polymeric Nanotherapeutics

Jeff Hrkach

2008 U.S. Frontiers of Engineering Symposium

September 18, 2008

Dramatically improving lives with breakthrough targeted therapies

Outline

- Background on drug delivery systems and products
- Starting up a drug delivery start-up
- Transferring and translating academic innovation from technology platform to specific product candidates
- The pathway to drug approval

BIND BIOSCIENCES

Drug delivery systems

- Systems designed and engineered to administer drugs in a controlled fashion so that an optimum amount of drug reaches the target site in an optimum timeframe

- Accomplished by changing drug formulation or route of delivery to improve drug performance (efficacy and/or safety)

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Drug delivery systems - examples

- Oral controlled release
  - Sinemet CR ®
- Transdermal
  - Scopolamine
- Injectable particles
  - Risperdal consta ®
  - Doxil ®
- Insulin
  - fast onset (LisPro), medium-acting (NPH), long-acting (glargine)
  - Inhaled insulin

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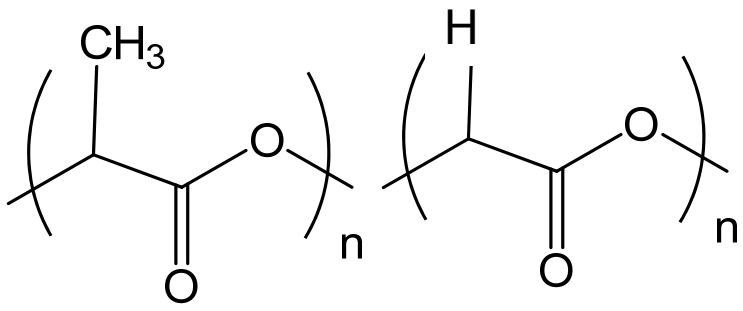
Degradable polyesters – PLA and PLGA

Lactide/lactic acid Glycolide/glycolic acid



- Commonly used biocompatible and biodegradable medical polymers
  - **Surgical/Implantable Use**

    Sutures, orthopedics, bone plates
  - **Extended Release Applications**

Zoladex®	(AstraZeneca)
Lupron Depot®	(TAP)
RISPERDAL® CONSTA®	(Janssen/Alkermes)
VIVITROL ®	(Alkermes / Cephalon)

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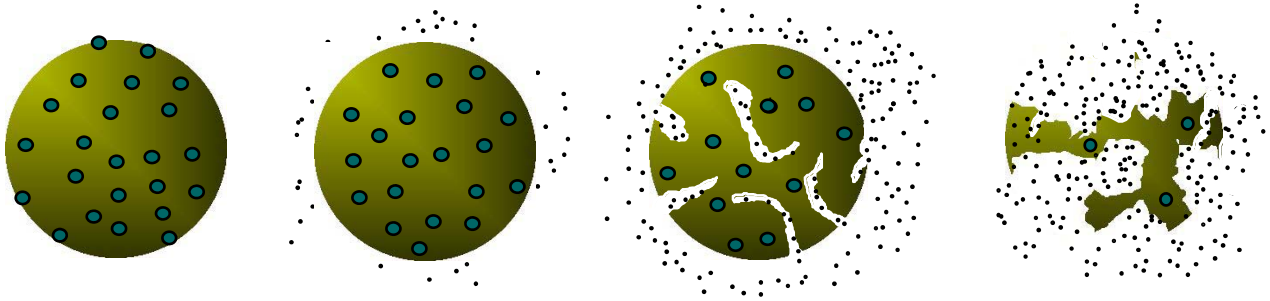
Mechanism of Drug Release



Drug

Polymer matrix

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RISPERDAL® CONSTA®

- First and only long-acting atypical antipsychotic
  - IM injection every two weeks versus daily treatment
  - Approved for schizophrenia
- Manufactured by Alkermes; marketed by Johnson & Johnson

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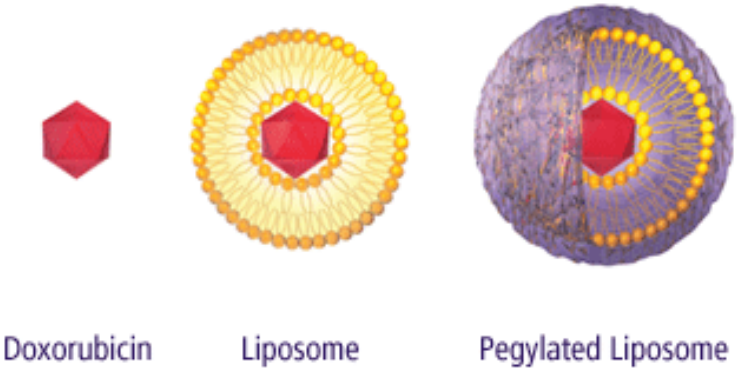
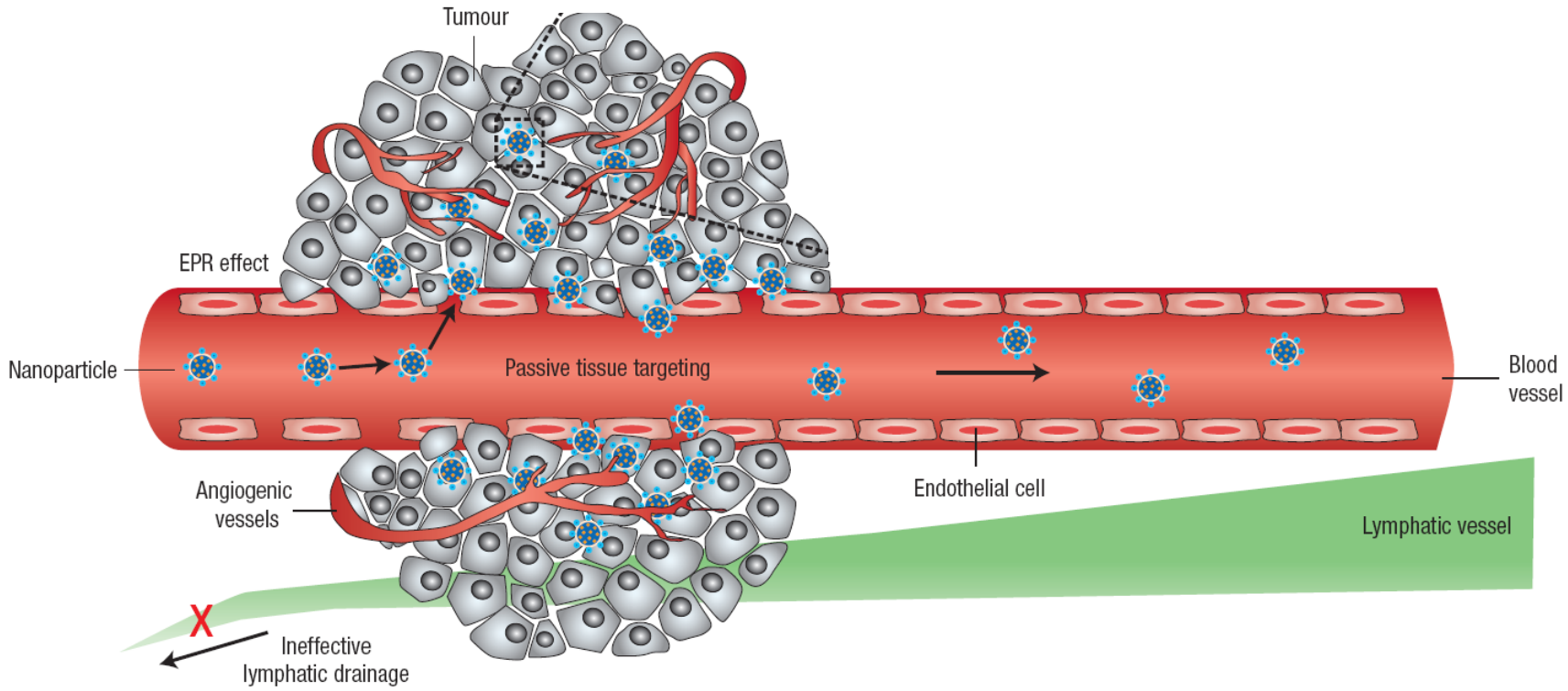
DOXIL®



- Liposomal nanoparticle doxorubicin formulation prescribed for ovarian cancer, AIDS-related Kaposi's Sarcoma and multiple myeloma
- Administered as IV infusion once every four weeks
- Long-circulating liposomes allow more time for drug to reach tumor

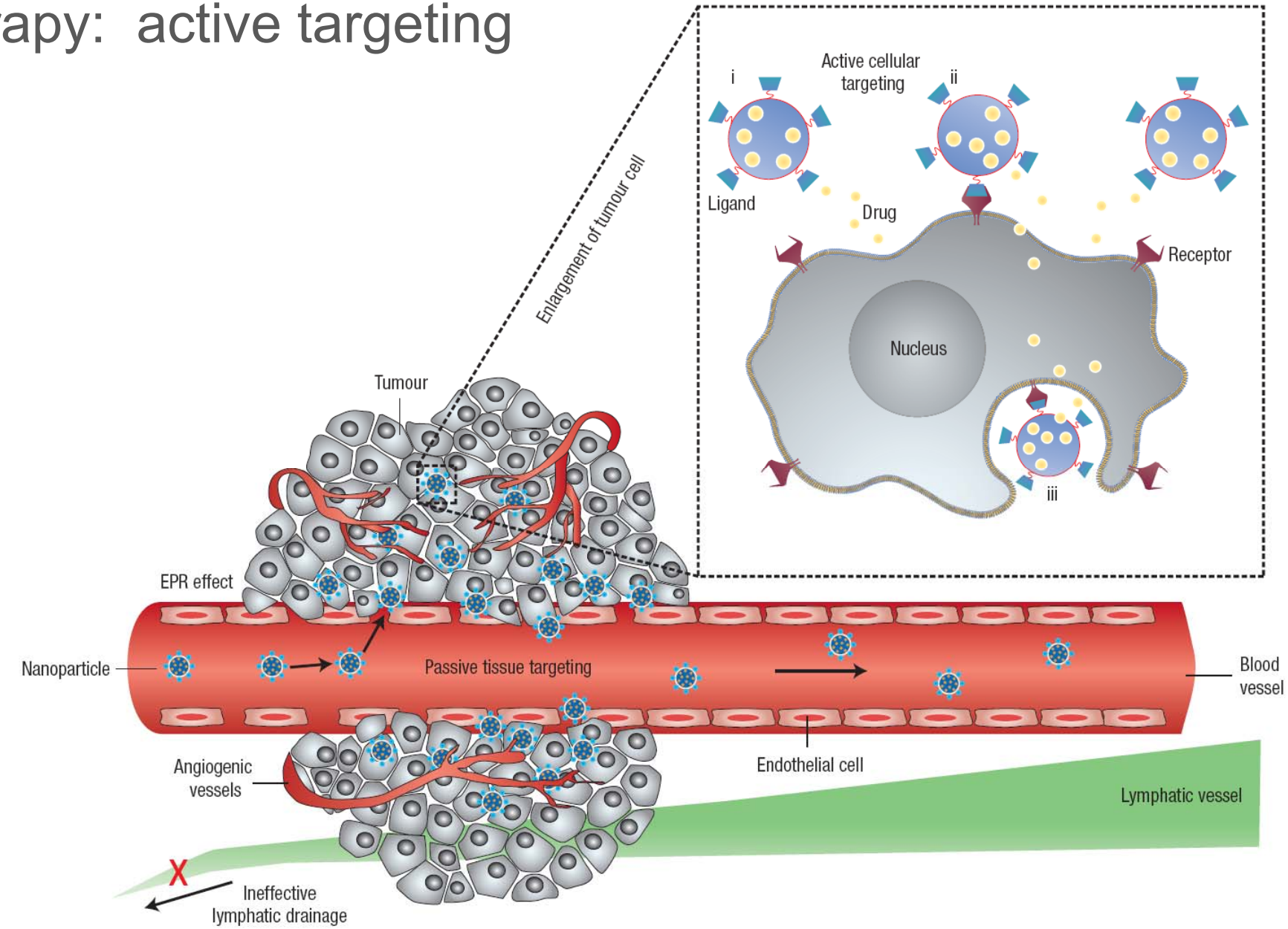
BIND BIOSCIENCES

Nanocarriers as emerging platform for cancer therapy: passive targeting



nature nanotechnology | VOL 2 | DECEMBER 2007 | PEER *et al*

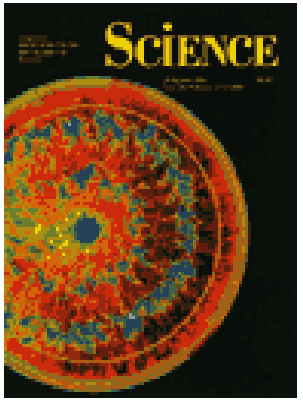
Nanocarriers as emerging platform for cancer therapy: active targeting



Biodegradable Long-Circulating Polymeric Nanospheres

Ruxandra Gref,* Yoshiharu Minamitake,† Maria Teresa Peracchia,‡ Vladimir Trubetskoy,§ Vladimir Torchilin,§ Robert Langer‖¶

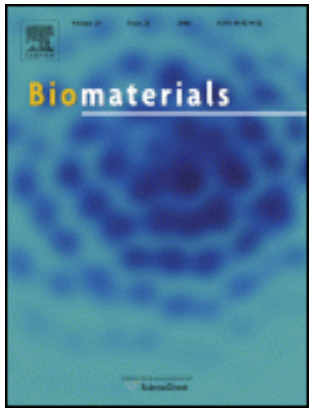
SCIENCE • VOL. 263 • 18 MARCH 1994



Nanotechnology for biomaterials engineering: structural characterization of amphiphilic polymeric nanoparticles by ^{1}H NMR spectroscopy

Jeffrey S. Hrkach, Maria Teresa Peracchia*, Avi Domb†, Noah Lotan‡ and Robert Langer

Biomaterials **18** (1997) 27–30



Drug delivery and targeting

Robert Langer

NATURE | VOL 392 | SUPP | 30 APRIL 1998

Nanoparticle-Aptamer Bioconjugates: A New Approach for Targeting Prostate Cancer Cells

Omid C. Farokhzad,[1,2] Sangyong Jon,[3] Ali Khademhosseini,[4] Thanh-Nga T. Tran,[2] David A. LaVan,[2] and Robert Langer[2,4,5,6]

CANCER RESEARCH 64, 7668–7672, November 1, 2004

Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy *in vivo*

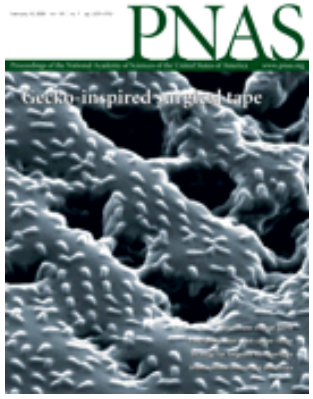
Omid C. Farokhzad*†‡§, Jianjun Cheng‡¶‖, Benjamin A. Teply*‡¶, Ines Sherifi*¶, Sangyong Jon**, Philip W. Kantoff††, Jerome P. Richie‡‡, and Robert Langer†§¶

PNAS | April 18, 2006 | vol. 103 | no. 16 | 6315–6320

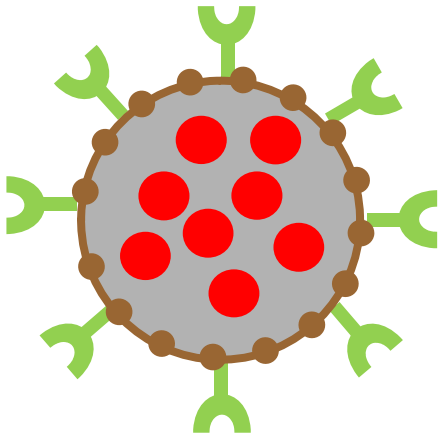
Precise engineering of targeted nanoparticles by using self-assembled biointegrated block copolymers

Frank Gu*†, Liangfang Zhang*, Benjamin A. Teply*‡, Nina Mann*, Andrew Wang†‡, Aleksandar F. Radovic-Moreno*†, Robert Langer*†§, and Omid C. Farokhzad†‡§

2586–2591 | PNAS | February 19, 2008 | vol. 105 | no. 7



Targeted nanoparticles

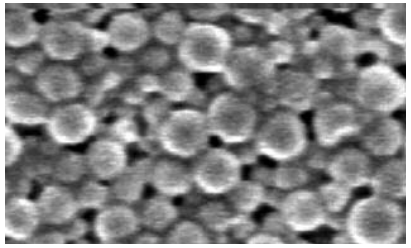


Targeting ligand

Stealth layer

Controlled release polymers

Therapeutic payload



BIND BIOSCIENCES

BIND overview

Founded in 2006

Robert Langer, ScD
Institute Professor, MIT

Omid Farokhzad, MD
Assistant Professor , Harvard

Raised $18.5M venture funding 2007

FLAGSHIP VENTURES

POLARIS VENTURE PARTNERS

ARCH Venture Partners

- ► Large IP portfolio from MIT/Harvard
- ► 22 employees
- ► 11,000 SQF lab/office facility
- ► $2.1M in NIST ATP & SBIR grants

Oncology program
►File IND mid-2009

CV Program
►Pharma collaboration

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Product candidate opportunities

- Several cancers have highly expressed molecules on their cell surfaces that can be selectively targeted
- Targeting will significantly increase drug exposure at the tumor site
- Targeted nanotherapeutics will be better tolerated and may allow more frequent dosing
- Sustained high levels of drug within tumor cells will inhibit the development of resistance and may overcome resistance

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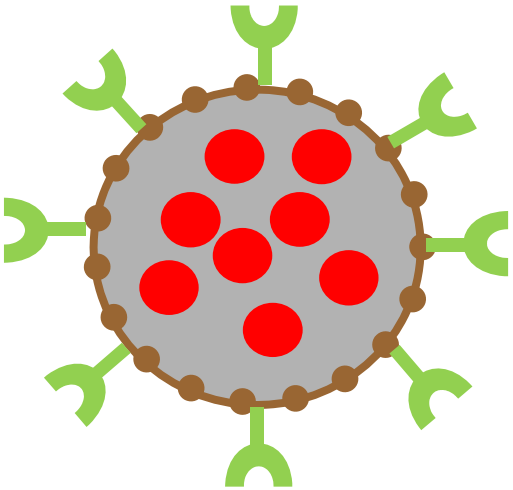
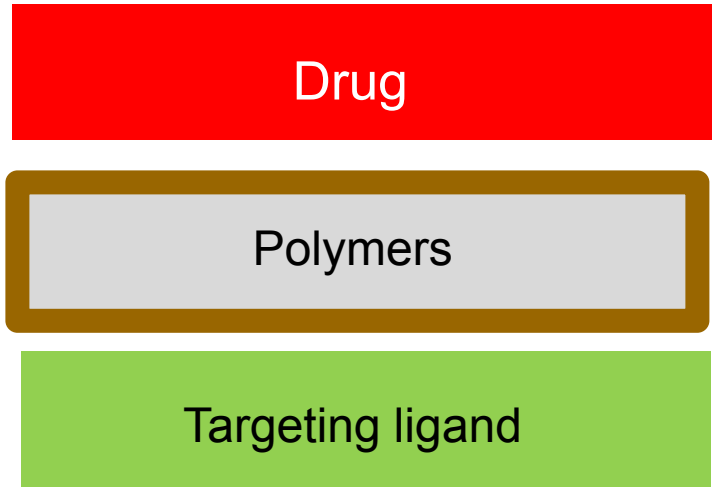
Targeted cancer nanotherapeutics

- Goals
  - Optimally engineer nanoparticles to maximize drug targeting to tumors
  - Significantly improve quality of life and increase survival for cancer patients





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Key steps to translating academic innovation into clinical drug development

- **CMC**

Formulation development and optimization

Process development and optimization

Analytical method development and qualification

Scale-up

Toxicology study materials manufacturing

cGMP clinical study materials manufacturing

- **Pre-clinical**

In vitro assay screening

Non-GLP in vivo studies

    Efficacy, PK, biodistribution

GLP toxicology studies

- **Clinical**

Study design

    Patient population

    Dose

    Dosing schedule

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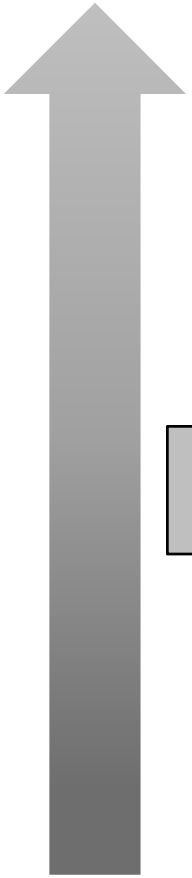
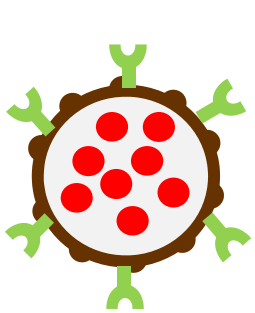
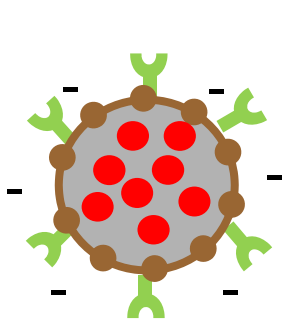
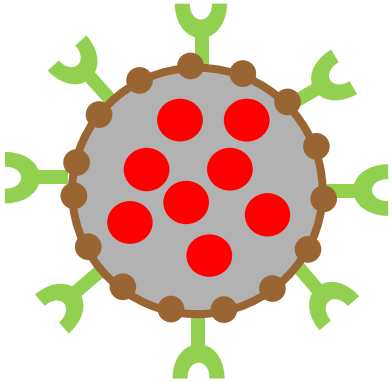
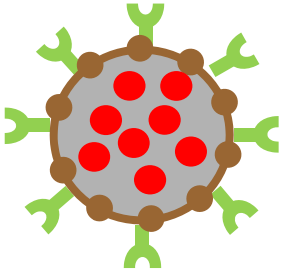
Combinatorial optimization



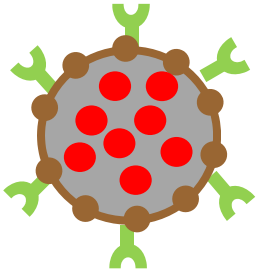


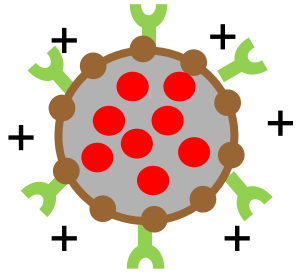


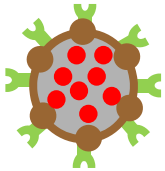


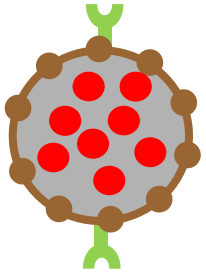


POLYMER PROPERTIES	PARTICLE CHARGE	PARTICLE SIZE	LIGAND DENSITY









BIND's combinatorial technology allows for <u>precise</u> and <u>reproducible</u> engineering of optimized nanoparticles

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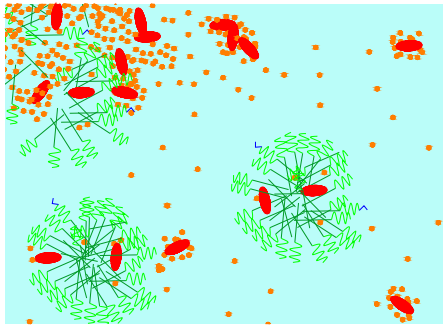
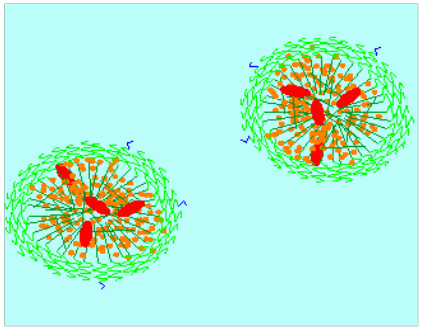
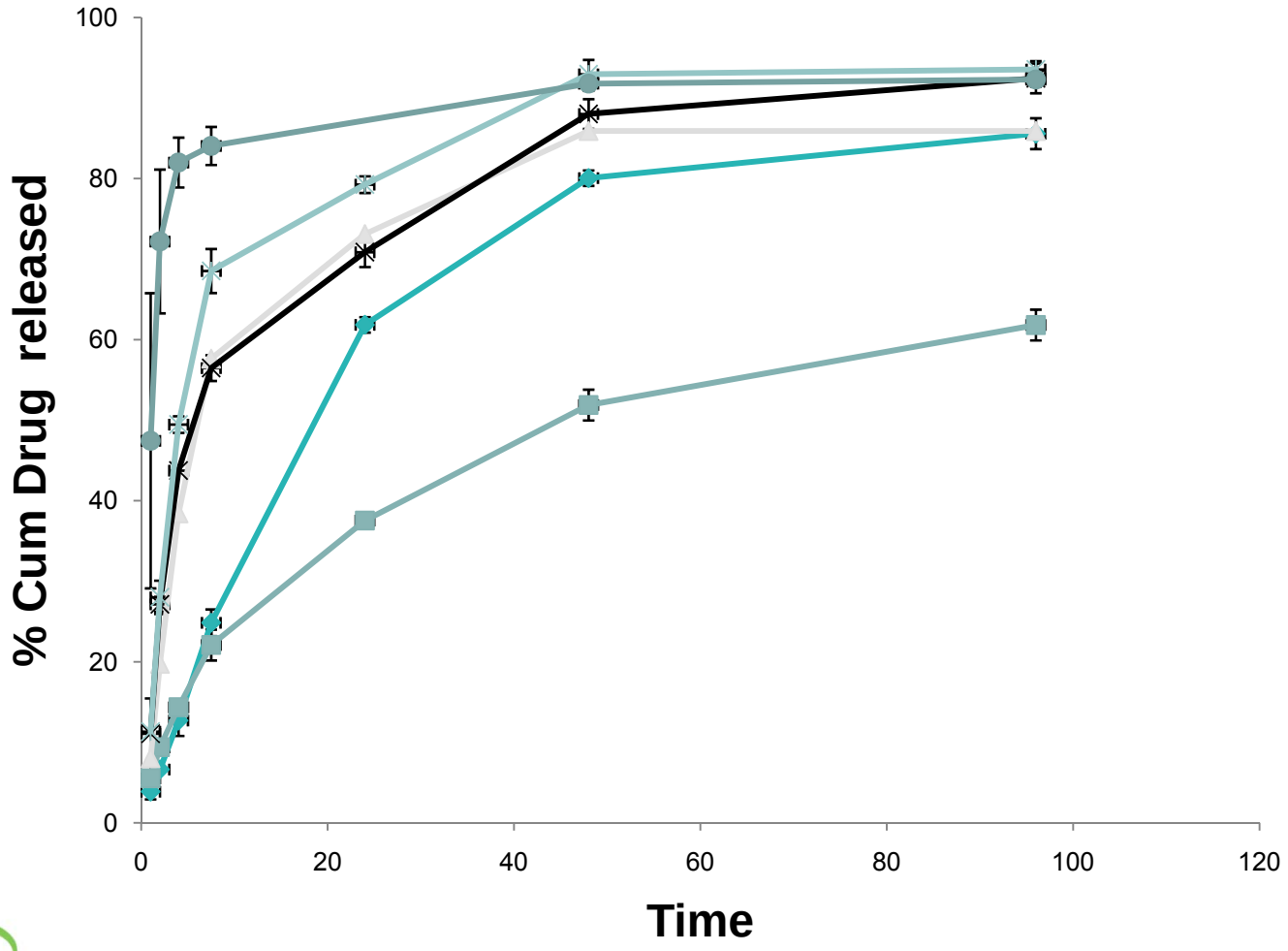
Nanoparticle production process

	Academic	BIND
		
Scalability	?	✓
Particle Size	✓	✓
Particle Surface	?	✓
Drug Load	✗	✓

In vitro drug release optimization



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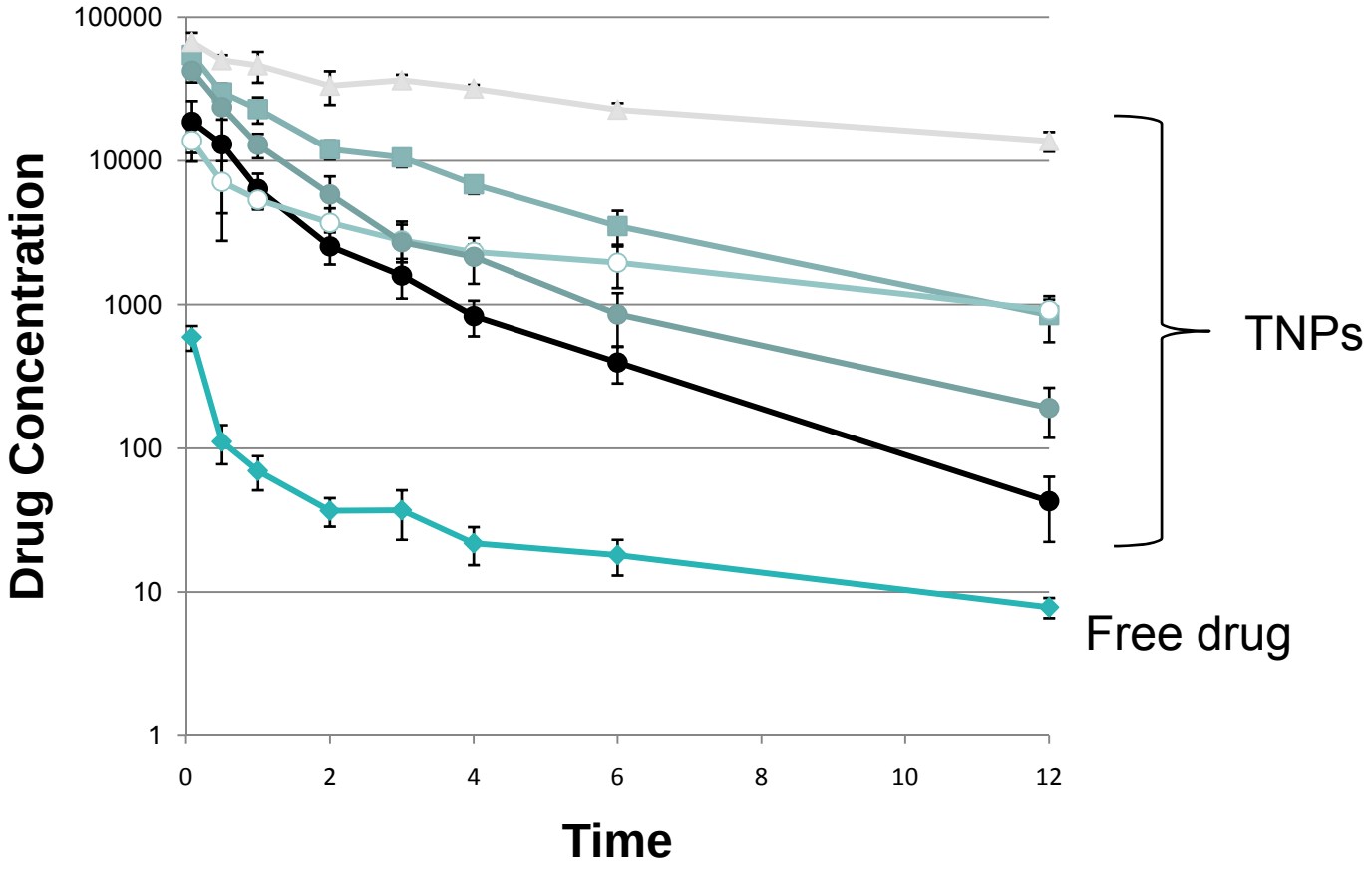
TNP formulations demonstrate improved pharmacokinetic profiles over free drug



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Nanoparticle production scale-up

Research	100 mg
Pre-clinical	10 g
Tox	1 kg
Clinical	10 – 100 kg
Commercial	100-1000 kg

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Drug development and approval pathway

Development Stage	Clinical Study Design	FDA interactions
Research		
Pre-clinical		Pre-IND meeting
Tox		IND submission
Phase I clinical studies	Healthy volunteers: safety and tolerability	
Phase II clinical studies	Patients in controlled settings: safety, tolerability, activity	Post-Phase II FDA meeting
Phase III clinical studies	Patients in everyday use: safety and efficacy	NDA submission
FDA approval		
Product launch		

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