

# NANOBIOTIX




**Accelerating the Future  
of Nanotherapeutics**

# Building New Therapies Atom by Atom

**COOUIITY NEUROLOGICAL DISEASE  
PLATFORM**

**CURADIGM NANOPRIMER  
PLATFORM**

**NANORADIOENHANCER  
NBTXR3**



# Addressing One of the Largest Untapped Markets in Oncology With Johnson & Johnson

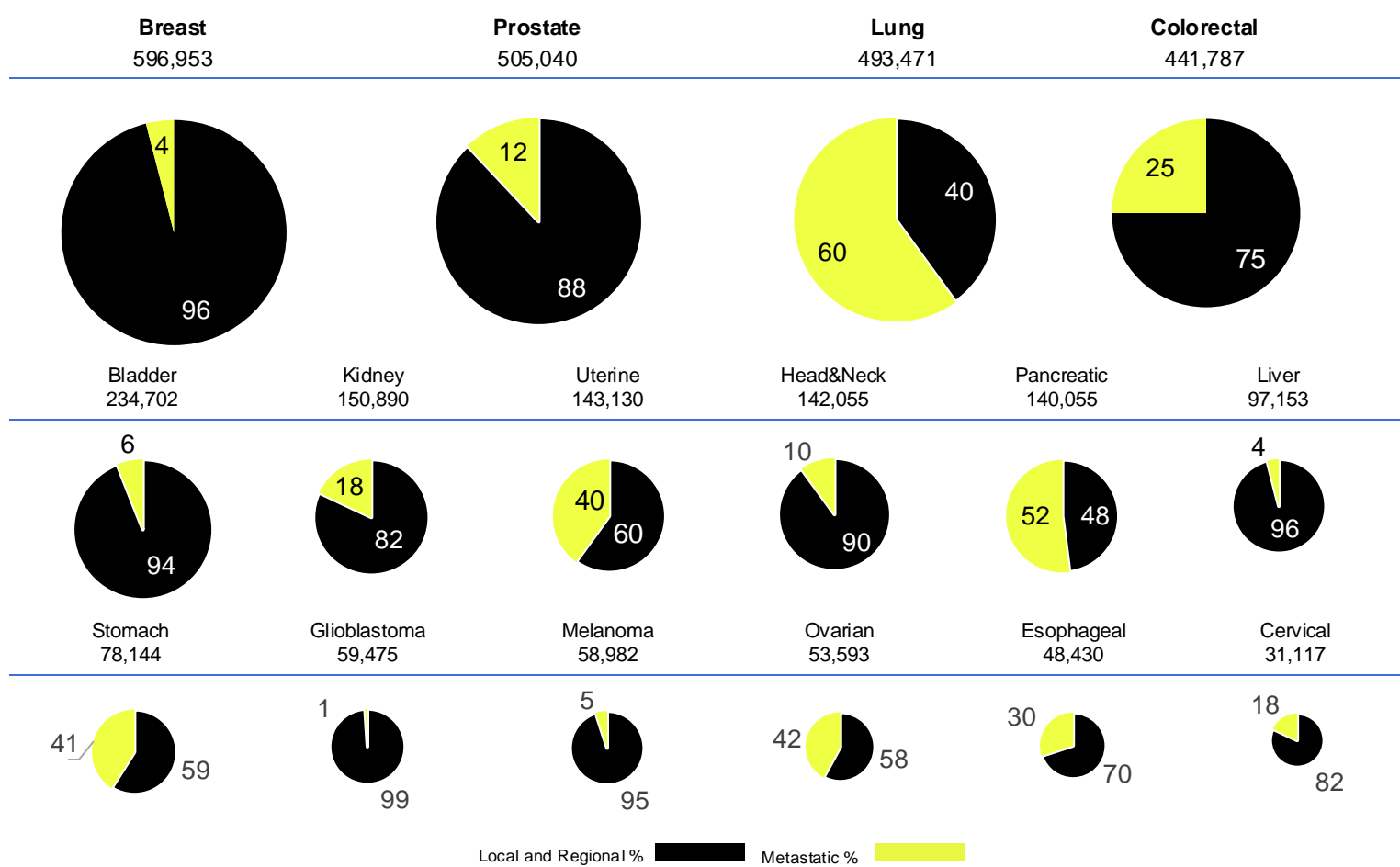
Potential First-in-Class Radioenhancer NBTXR3

**NANOBIOTIX**



# Interventional Oncology's Solution Could Be One of the Largest Untapped Oncology Markets

Millions of cancer patients share an unmet medical need for local treatment, whereas most drug development is focused on highly-segmented, later stages of disease – incidence data US, UK & EU4



Most patients are diagnosed with local or locoregional cancer

Mainstream treatment is radiotherapy and/or surgery

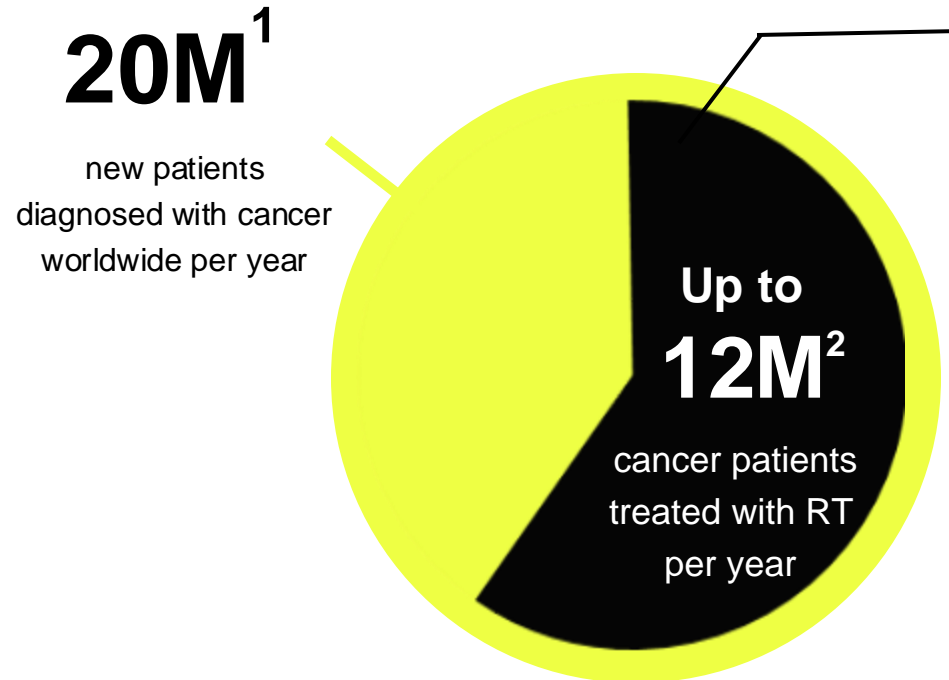
Most patients with metastatic disease come from the failure of local treatments

Pharma and Biotech have focused on metastatic and later-stage patients

Early line local control focused treatments can benefit millions of patients while facing limited competition

# Radiotherapy is One of the Largest Market Opportunities in Oncology

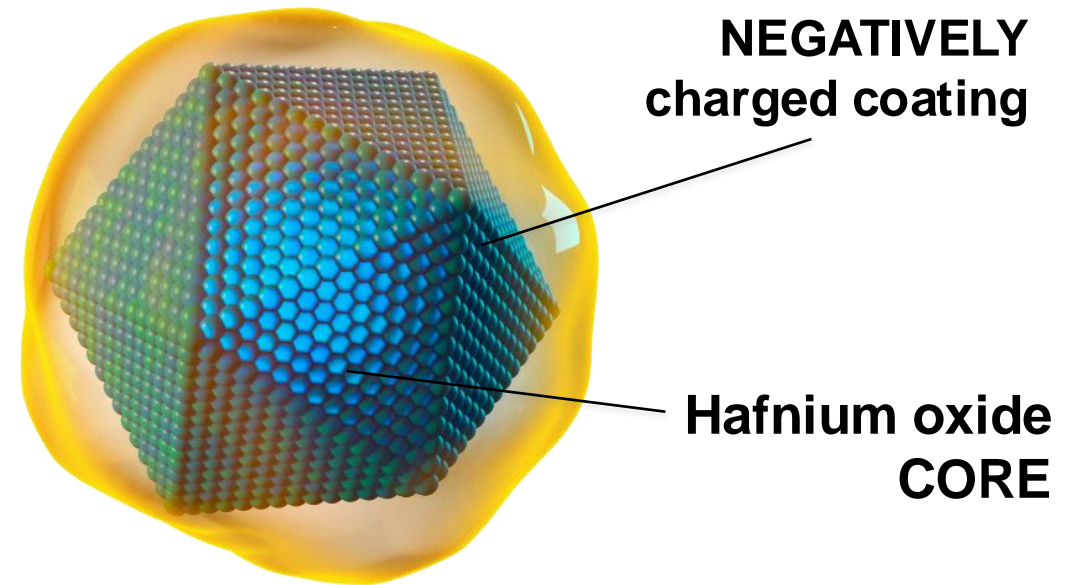
We seek to help many more patients by leveraging radiotherapy



% PATIENTS RECEIVING RT <sup>3</sup>	# PATIENTS RECEIVING RT <sup>1,3</sup>
87% Breast cancer	2.00M
77% Lung cancer	1.91M
74% H&N	0.70M
58% Prostate	0.85M
60% Rectum	0.44M
49% Pancreas	0.25M
80% CNS	0.26M

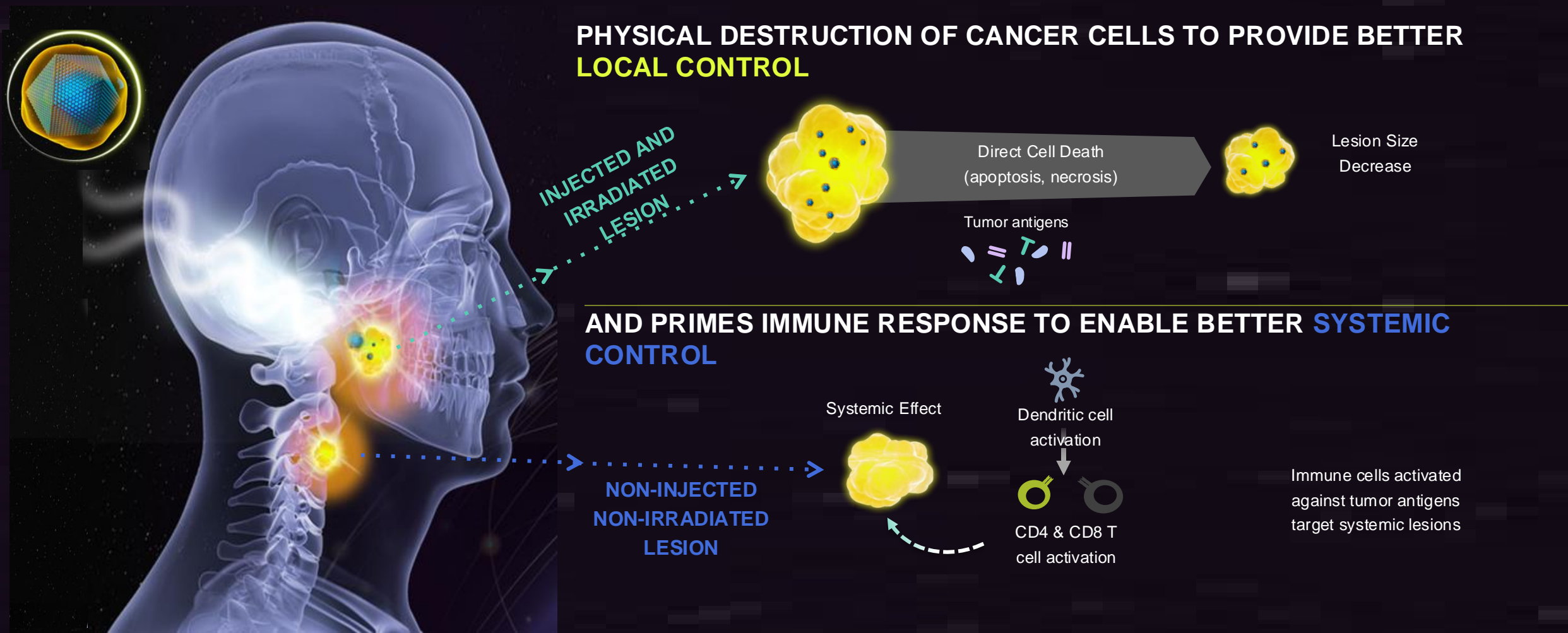
# NBTXR3 Causes Much Higher Energy Absorption Only in the Tumor

- 01** Aqueous suspension of inorganic crystalline hafnium oxide ( $\text{HfO}_2$ ) nanoparticles
- 02** High electron density (Atomic Number  $Z=72$ ) material providing highly efficient energy absorption
- 03** Inert in the absence of ionizing radiation: “Off” status  
Activated by ionizing radiation: “On” status
- 04** Physics-based MoA enables efficient destruction of any cancer cell



# NBTXR3 is Designed to Create Local and Systemic Effects

Local and systemic benefits through cell death and immune activation against tumor antigens



# Pan-Solid Tumor Potential, Beginning in Head and Neck and Lung Cancers

Patients (Current Study)	N	Phase 1	Phase 2	Phase 3	Operational Sponsor
<b>Head &amp; Neck</b>					
Elderly Cisplatin-ineligible (NANORAY-312, RT-NBTRX3 ± cetuximab vs RT ± cetuximab)	500				Nanobiotix / Janssen
R/M IO Naïve (Study 1100, RT-NBTRX3 fb anti-PD-1)	35+				Nanobiotix
R/M IO Resistant (Study 1100, RT-NBTRX3 fb anti-PD-1)	35+				Nanobiotix
R/M (MDA-0541, RT-NBTRX3 fb anti-PD-1)	60				MD Anderson Cancer Center
<b>Lung</b>					
Inoperable, Stage 3	NA				Janssen
Inoperable, Recurrent (MDA-0123, Reirradiation RT-NBTRX3)	24				MD Anderson Cancer Center
<b>Expansion Opportunities</b>					
Soft Tissue Sarcoma (Act.In.Sarc, RT-NBTRX3 fb resection)	180				Nanobiotix
Rectal (Study 1001, RT-NBTRX3 concurrent CT)	32				Nanobiotix
Advanced Solid (MDA-0618, RT-NBTRX3 with anti-PD-1)	40				MD Anderson Cancer Center
Cisplatin-eligible H&N (Study 1002, RT-NBTRX3 concurrent CT)	12				Nanobiotix
HCC & Liver Mets (Study 103, RT-NBTRX3)	23				Nanobiotix
Pancreas (MDA-1001, RT-NBTRX3)	24				MD Anderson Cancer Center
Esophageal (MDA-0122, RT-NBTRX3 concurrent CT)	24				MD Anderson Cancer Center
IO Resistant Multiple Primary Tumors (Study 1100, RT-NBTRX3 fb anti-PD-1)	35+				Nanobiotix

Completed Ongoing



# Nanobiotix Pathway to Sustainability and Growth

2-3 years pathway to reach financial sustainability and growth

Addressing One of the Largest Untapped Markets in Oncology with Johnson & Johnson  
First in class Nanoradioenhancer NBTXR3 (JNJ-1900)

\$2.5B+ Janssen\* 2023 license agreement for NBTXR3

Over 100,000 patients targeted with two first indications in lung and head and neck cancers in the US, UK & EU4 alone

\$10 B market for the first 2 indications\*\*

Potential for hundreds of millions of near-term milestones

- Phase 3 HNSCC interim data that could lead to registration
- Phase 2 in unresectable stage 3 NSCLC
- Multiple Phase 1/2 ongoing with read outs in the coming 12 months

# Nanobiotix Pathway to Sustainability and Growth

2-3 years pathway to reach financial sustainability and growth

Addressing One of the Largest Untapped Markets in Oncology with Johnson & Johnson  
First in class Nanoradioenhancer NBTXR3 (JNJ-1900)

\$2.5B+ Janssen\* 2023 license agreement for NBTXR3

Over 100,000 patients targeted with two first indications in lung and head and neck cancers in the US, UK & EU4 alone

\$10 B market for the first 2 indications\*\*

Potential for hundreds of millions of near-term milestones

- Phase 3 HNSCC interim data that could lead to registration
- Phase 2 in unresectable stage 3 NSCLC
- Multiple Phase 1/2 ongoing with read outs in the coming 12 months

Developing new first-in-class product with Curadigm platform

Transforming drug development

Multiple indications and product applications: nanomedicine, RNA & DNA based products, oncolytic viruses, cell therapies, etc.

Preclinical POC established with world-class partners: Sanofi, NCL, & MIT

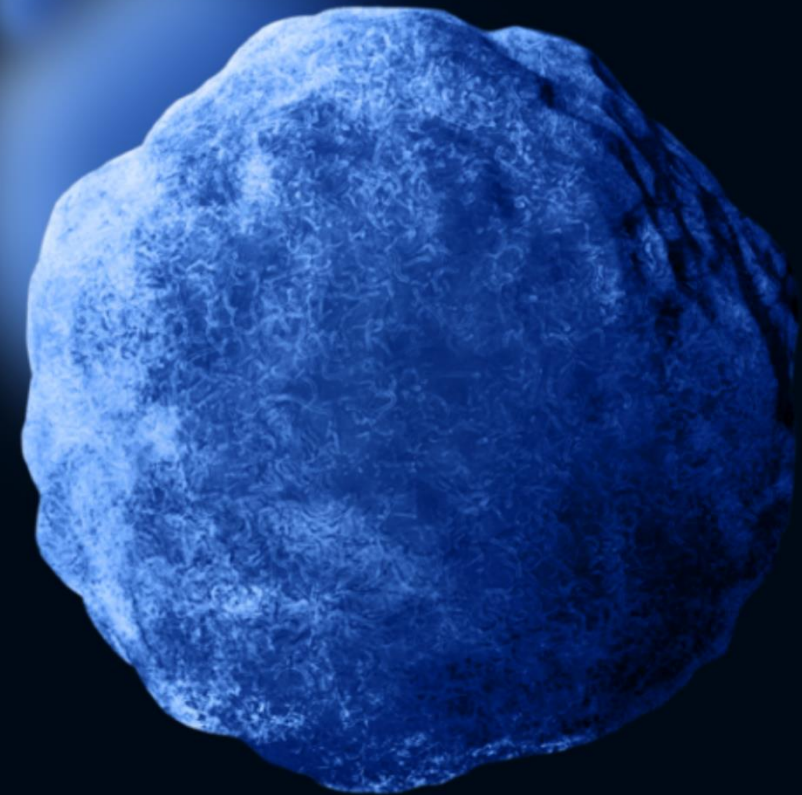
- Building internal drug pipeline and pathway to clinical trials
- Multiple opportunities for collaboration and licensing out in the short- to medium-term

# CURA⇒IGM

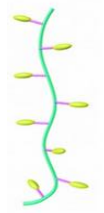
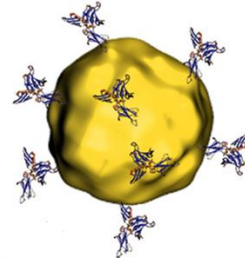
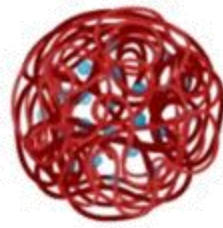
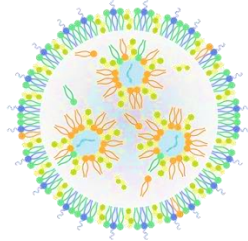
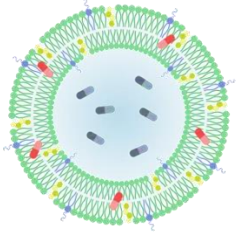
EXPANDING  
LIFE

**Transforming the Way Innovative Drugs are  
Designed and Developed**

**Next Lever for Growth**



# Innovative Therapeutics



**Small molecule-loaded liposomes**

**RNA / DNA-loaded lipid nanoparticles**

**Viruses**

**Small molecule-loaded polymeric nanoparticles**

**Inorganic nanoparticles**

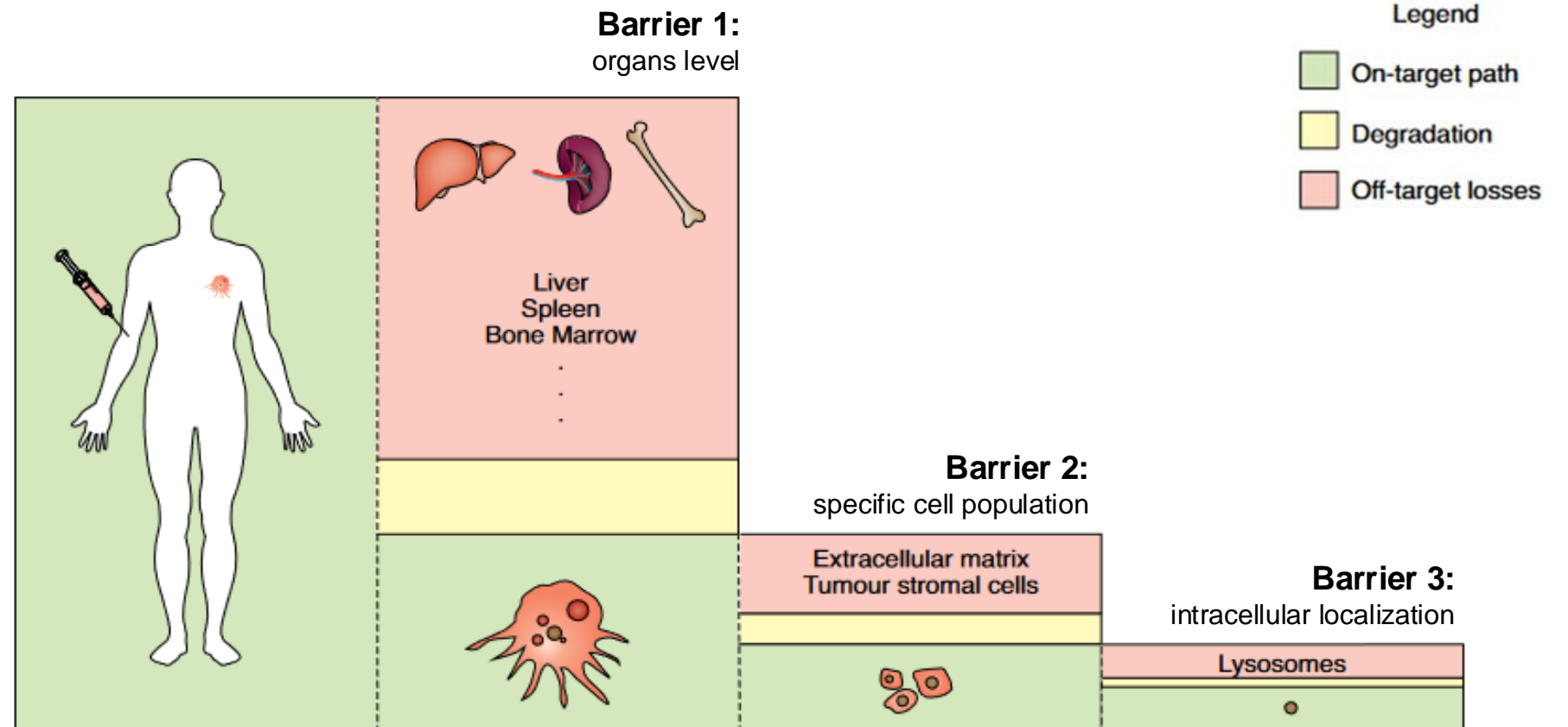
**Recombinant proteins**

**Small molecule- or RNA-polymer conjugates**



# Intravenous Administration Must Overcome Barriers to be Safe and Effective

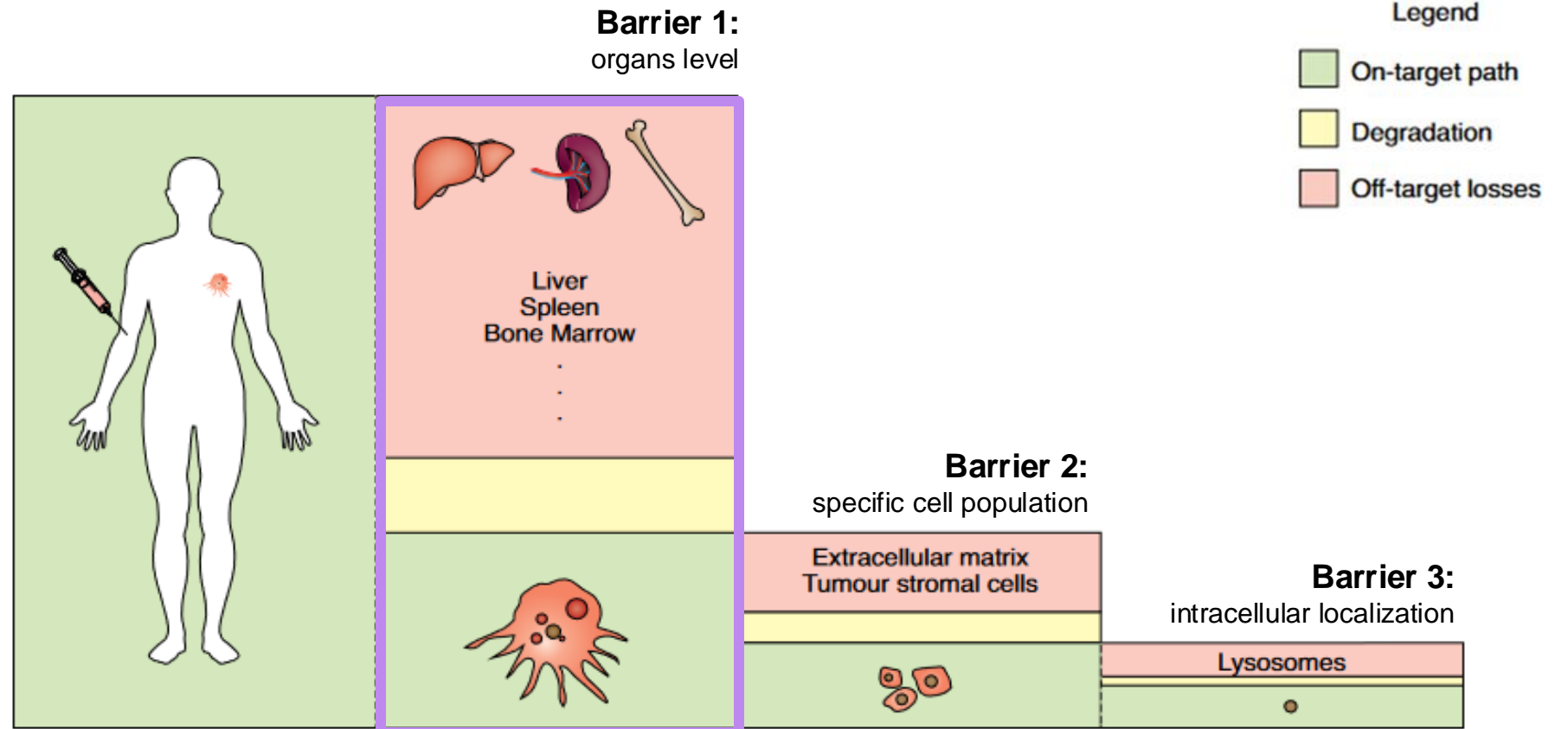
Treatment delivery in oncology by IV administration\*



# Intravenous Administration\* Must Overcome Barriers to be Safe and Effective

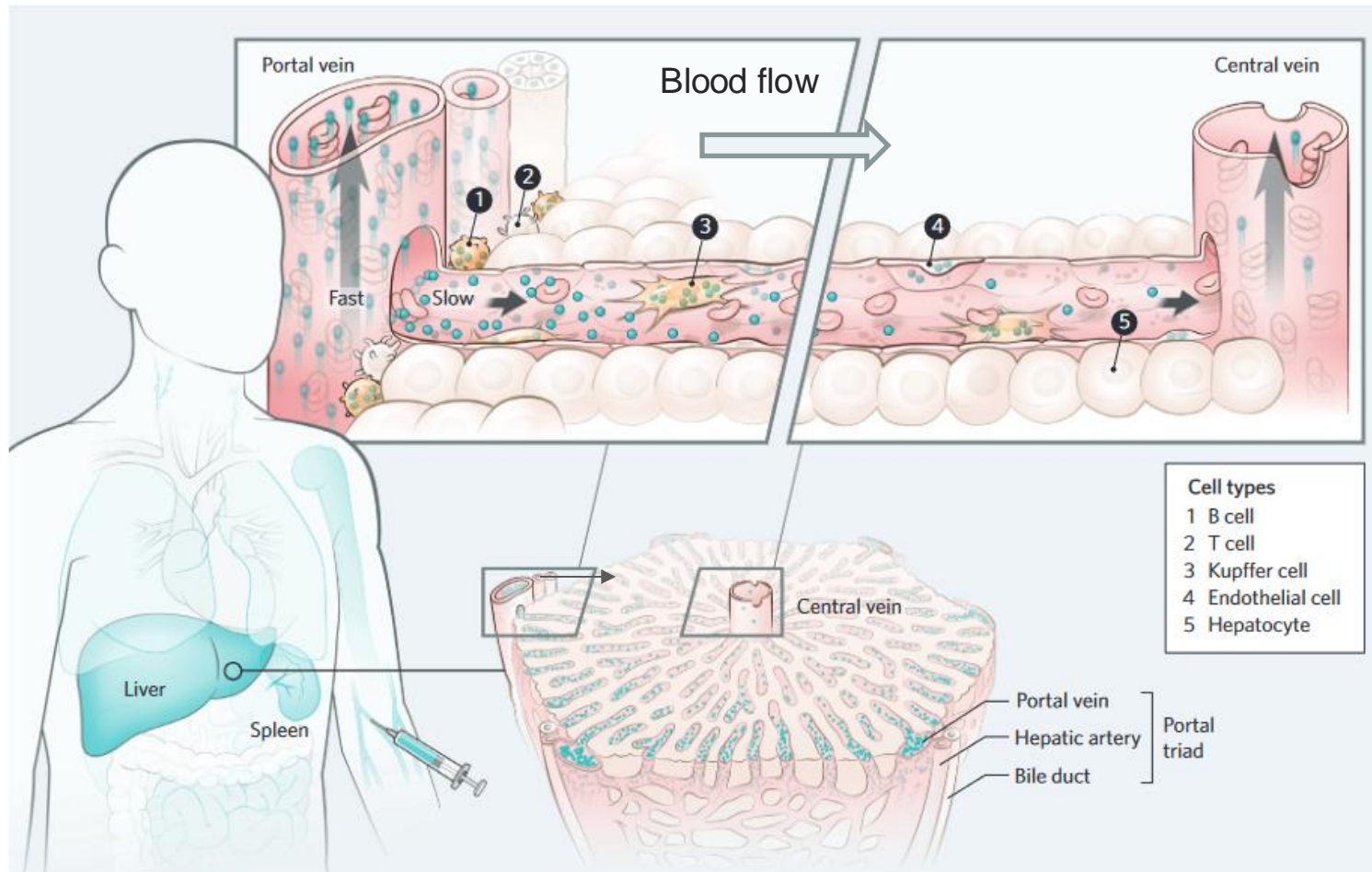
Treatment delivery in oncology by IV administration\*

According to a meta-analysis from Chan *et. al.*, the **median accumulation in tumor of nanoparticle-based therapeutics is less than 1% of the administered dose #**



# Liver Clearance: a Key Challenge to Overcome for Therapeutics

The liver is the main organ of the reticuloendothelial system (RES) dedicated to the clearance of endogenous waste and exogenous material from the systemic circulation



**Organ structuration decreases blood flow to maximize interaction with hepatic cells**

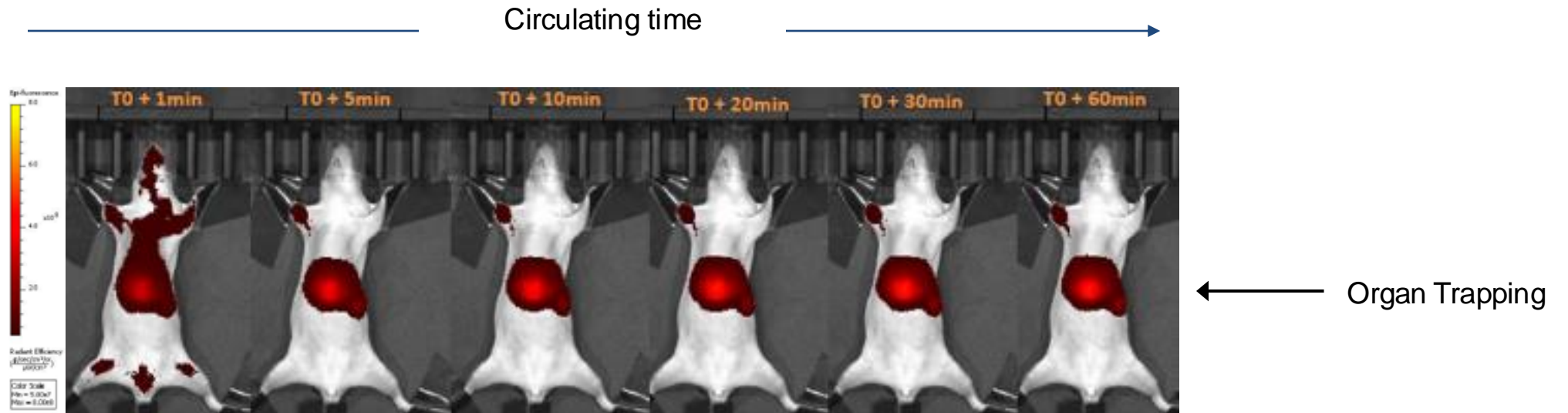
**RES cell populations (e. g. Kupffer cells and liver sinusoidal endothelial cells) dedicated to recognize and clear:**

- Dead or damaged cells
- External pathogens
- **Foreign substances including therapeutics (e.g., lipid- or polymer-based NPs, Viruses, etc.)**

# Therapeutic Bioavailability is a High Unmet Need

Often only low amounts of therapeutic dose reach target tissues leading to decrease efficacy or safety issues

Traditional  
therapeutic  
intravenous  
administration



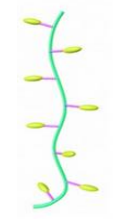
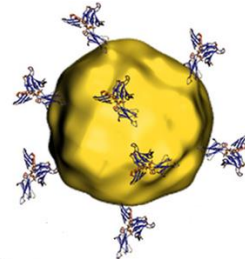
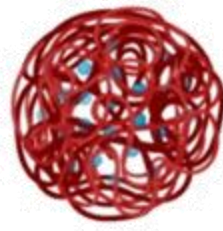
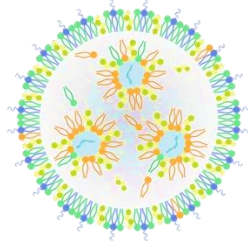
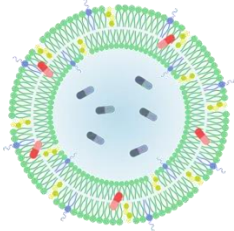
The therapeutic is rapidly trapped by the liver, only few percents of the dose will reach the target tissue



# Clearance of Therapeutics is Driven by Common Physico-Chemical Attributes

Size	Surface Charge	Shape	Hydrophobicity	Hardness
Nanometric scale (>10nm)	Charged nanoparticles are more prone to interact with cells	Impact velocity in blood flow and potential interaction	Higher hydrophobicity increases interaction with proteins	Flexibility impact interaction with cell surface

# Universal Features Lead to the Clearance of Therapeutics



Small molecule-loaded liposomes

RNA / DNA-loaded lipid nanoparticles

Oncolytic viruses

Small molecule-loaded polymeric nanoparticles

Inorganic nanoparticles

Recombinant proteins

Small molecule- or RNA-polymer conjugates

# Curadigm Nanoprimer Technology: Priming the Body to Receive Treatment

Nanoprimer is administered prior to a therapeutic to transiently occupy liver pathways and limit therapeutic clearance

## PRIME with Nanoprimer



Nanoprimer  
Administration


Nanoprimer  
Accumulation





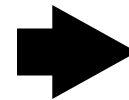
# Curadigm Nanoprimer Technology: Priming the Body to Receive Treatment

Nanoprimer is administered prior to a therapeutic to transiently occupy liver pathways and limit therapeutic clearance


## PRIME with Nanoprimer

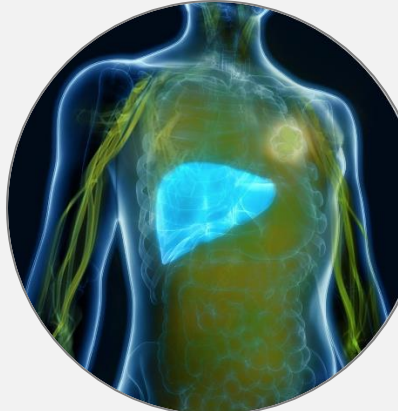
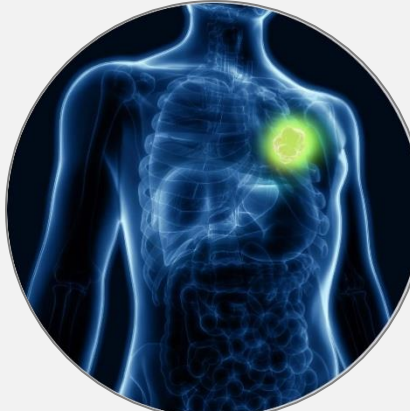


Nanoprimer Administration	Nanoprimer Accumulation
	



## TREAT with the Therapeutic



Therapeutic Administration	Therapeutic Accumulation in Target Tissue
	

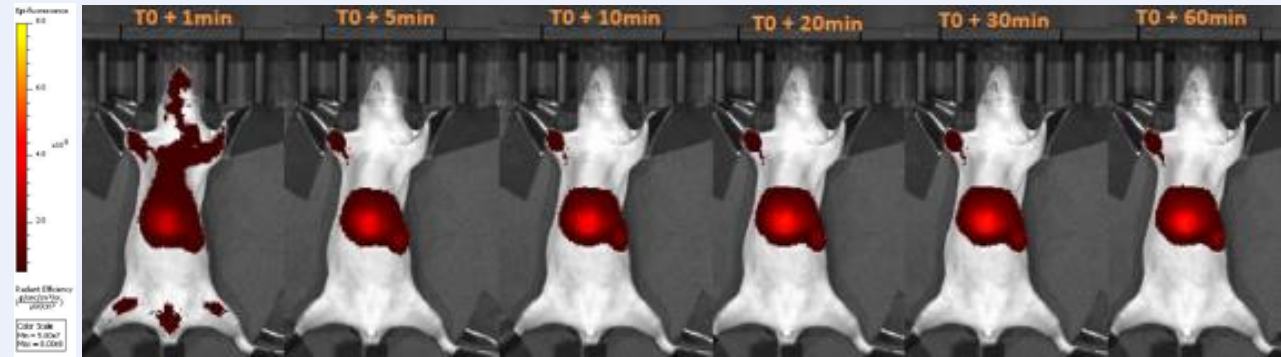




# Curadigm's Technology Improves Systemic Bioavailability of Therapeutics

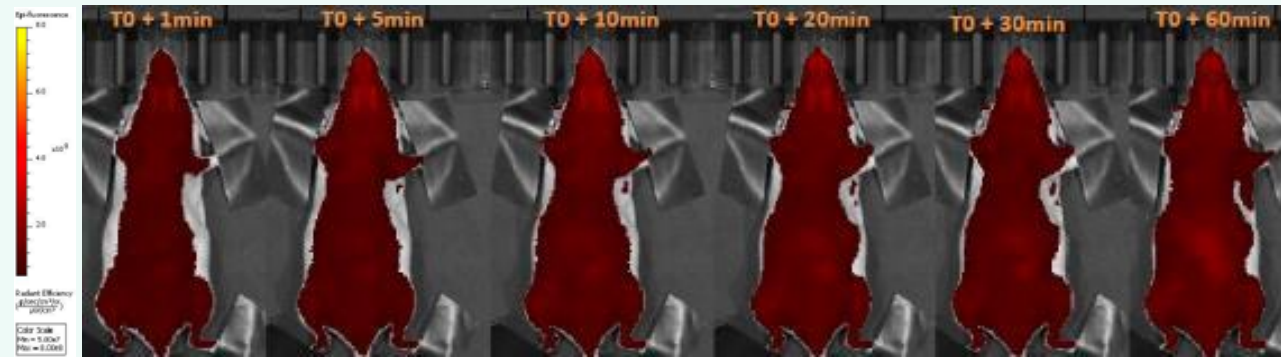
By reducing liver clearance, Nanoprimer increases blood bioavailability by enabling increased accumulation in target tissues

Traditional therapeutic administration



Organ (liver) Trapping

Curadigm Nanoprimer + Therapeutic



Increased blood bioavailability

# Preventing Rapid Drug Clearance by the Liver is a Longstanding Challenge

Several approaches to preventing liver clearance have been tested with limited success

## Conventional Liposomes

Concept

- The first attempt to use the concept of a “liver priming” strategy<sup>1</sup>
- The **same liposome for pre-treatment primer and for therapeutic encapsulation**

Problems

- **Required a high dose** of the priming liposome for a modest effect
- Did not allow for separate optimization of the primer and the carrier
- **Toxicity** related to the high lipid dose

## Lipid Emulsion

- **High dose of lipid** given to prevent rapid liver clearance of the therapeutic

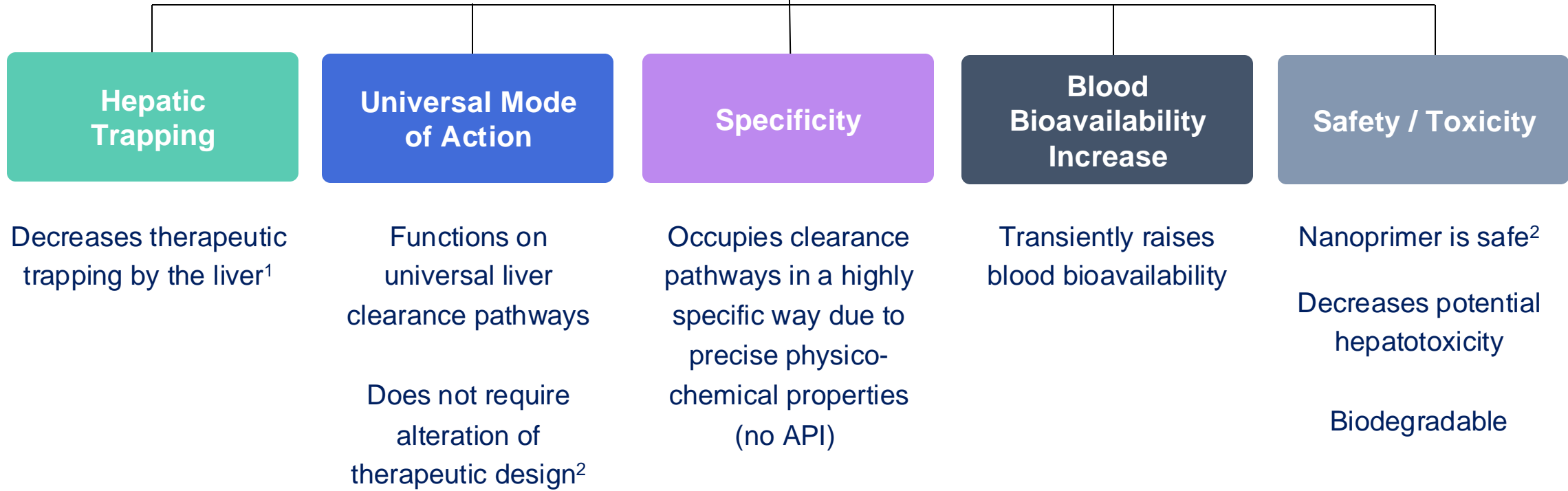
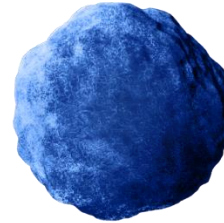
- **High size polydispersity** of the emulsion
- **Very high dose** generated only a moderate effect on therapeutic bioavailability<sup>2</sup>
- **Toxicity** related to the high lipid dose

## Drug Hepatic Priming

- **Specific compounds/drugs** administered to prevent liver cell function and reduce therapeutic clearance

- **Impacted multiple cell-types, which affected necessary liver functions** (e.g., chloroquine approaches)<sup>3</sup>
- Priming effect based on **toxicity to Kupffer cells** (e.g., chlodronate approaches)<sup>4</sup>
- Norepinephrine to **increase blood flow is associated with blood pressure & heart risk**<sup>5</sup>

# Nanoprimer Has Key Differentiating Factors



# Curadigm's Technology Address Unmet Needs for Therapeutic Delivery

Therapeutic agent alone



- Potential Toxicity

- Efficacy

Only a small part of the dose  
is responsible for efficacy



# Curadigm's Technology Address Unmet Needs for Therapeutic Delivery

## Therapeutic agent alone

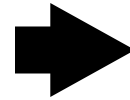


- Potential Toxicity

- Efficacy

Only a small part of the dose  
is responsible for efficacy

+ Nanoprimer



For a product limited by its efficacy:



+



Higher efficacy for the  
same dose

# Curadigm's Technology Address Unmet Needs for Therapeutic Delivery

## Therapeutic agent alone

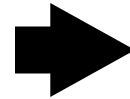


- Potential Toxicity

- Efficacy

Only a small part of the dose is responsible for efficacy

+ Nanoprimer



For a product limited by its efficacy:



+



Higher efficacy for the same dose

For a product limited by its liver toxicity:



+



Lower toxicity for the same efficacy.

# IV-administered RNA-based Therapeutics

Tremendous potential but still limited by specific challenges



**RNA-based therapeutics face significant delivery challenges to targeted tissues**

**Encapsulation of RNA makes them highly susceptible to rapid liver clearance  
=> Low availability / poor accumulation in target tissues**

**Despite billions in funding, RNA therapeutics have had limited success targeting tissues outside the liver, limiting clinical applications**

# IV-administered RNA-based Therapeutics

Tremendous potential but still limited by specific challenges

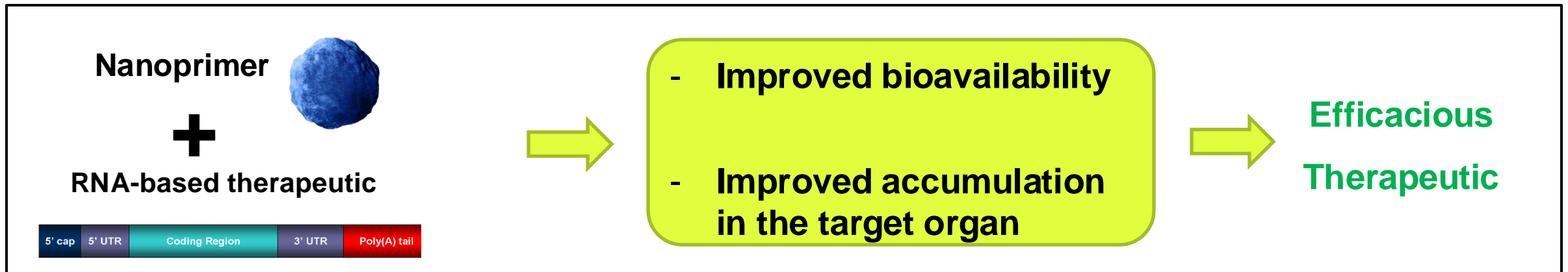


**RNA-based therapeutics face significant delivery challenges to targeted tissues**

**Encapsulation of RNA makes them highly susceptible to rapid liver clearance  
=> Low availability / poor accumulation in target tissues**

**Despite billions in funding, RNA therapeutics have had limited success targeting tissues outside the liver, limiting clinical applications**

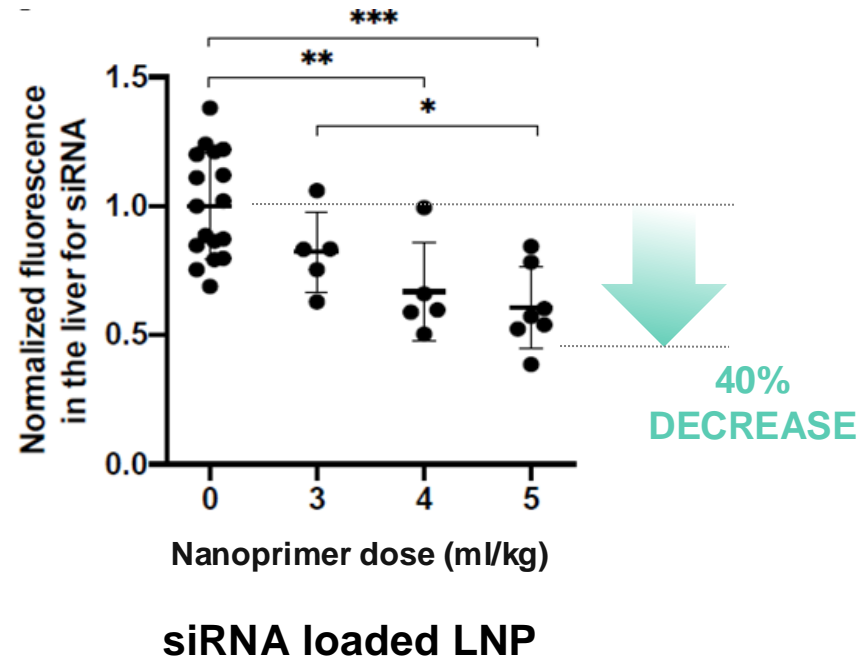
## UNLEASHING THE POWER OF RNA-BASED THERAPEUTICS



# Nanoprimer Increases Blood Bioavailability of Nucleic Acid-based Therapeutics

Results from the collaboration with the Langer Lab, MIT

## Reduced hepatic trapping of RNA therapy with the Curadigm platform

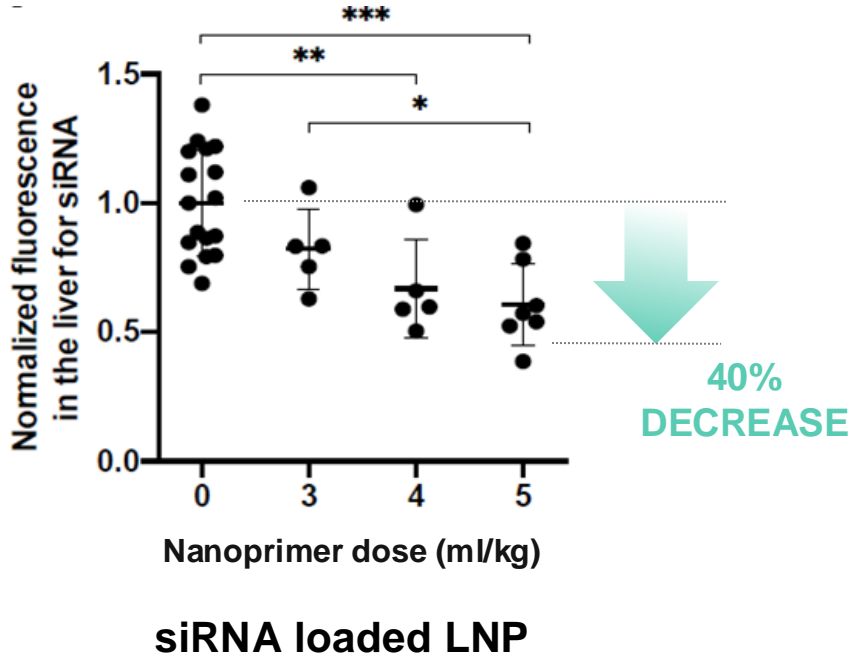




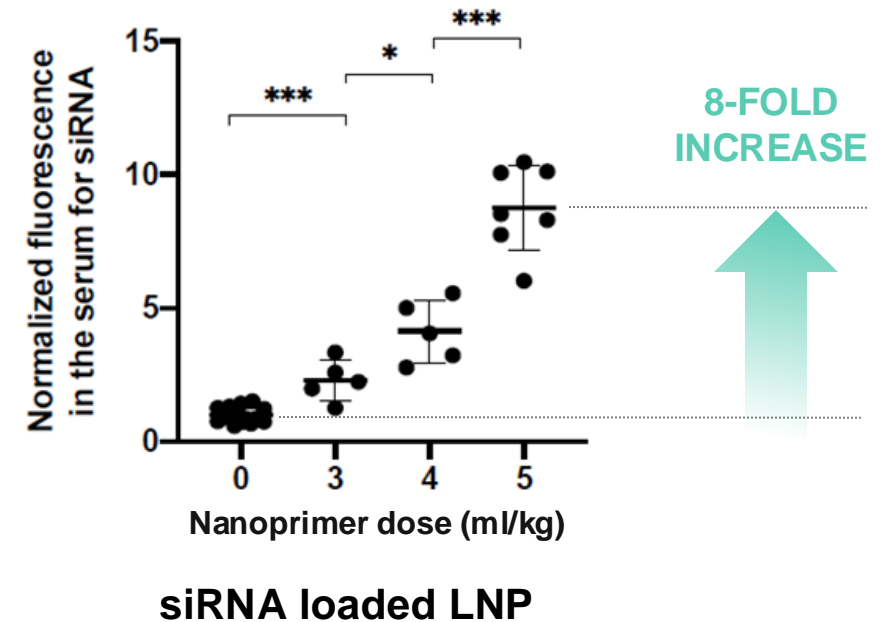
# Nanoprimer Increases Blood Bioavailability of Nucleic Acid-based Therapeutics

Results from the collaboration with the Langer Lab, MIT

## Reduced hepatic trapping of RNA therapy with the Curadigm platform

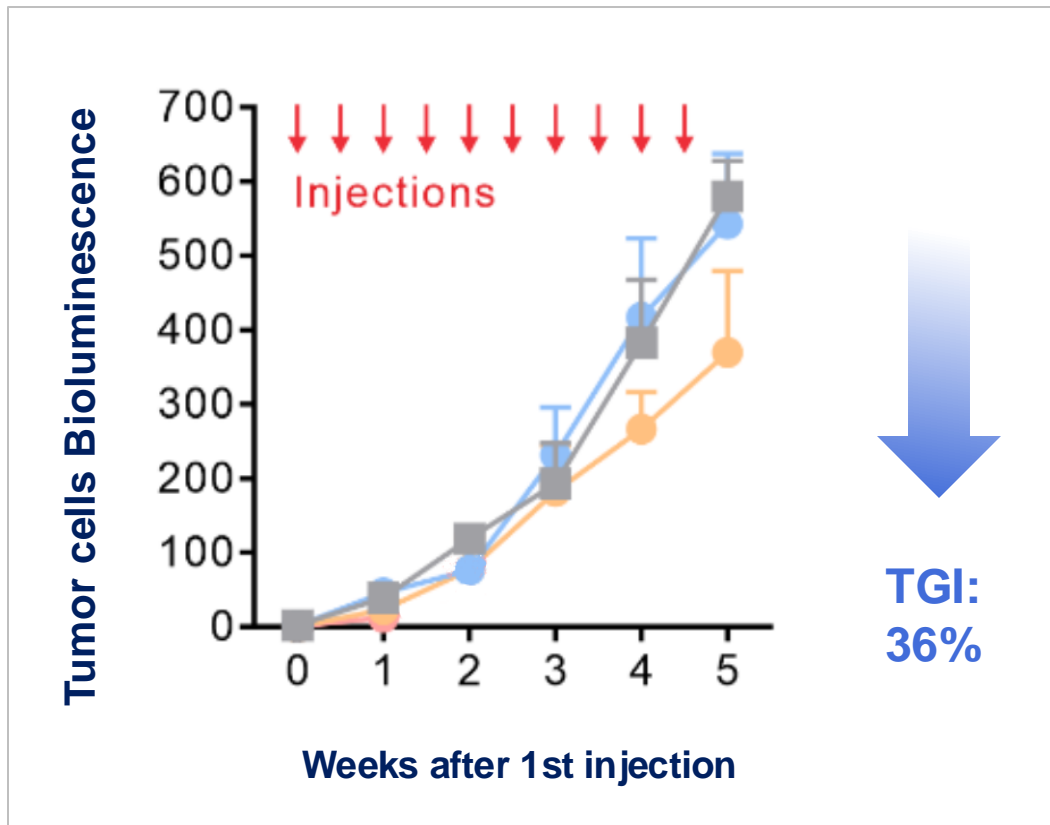


## Increased blood bioavailability of RNA therapy with the Curadigm platform



# Nanoprimer Increases Anti-tumor Efficacy of Nucleic Acid-based Therapeutics

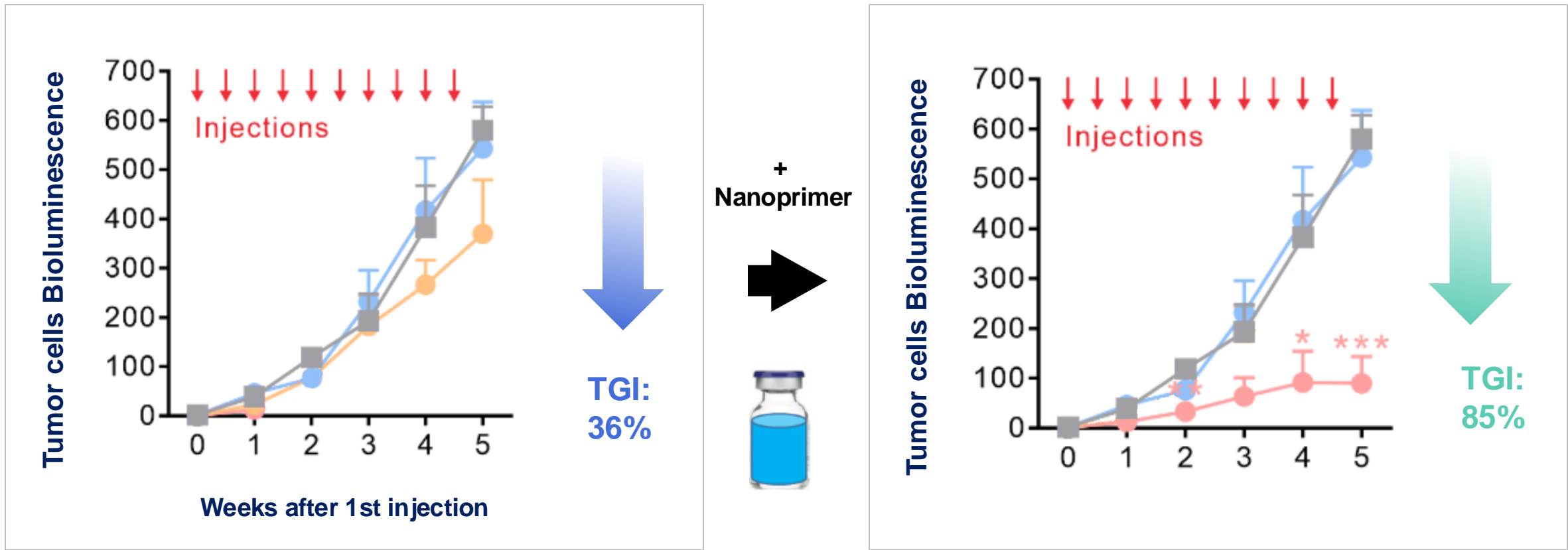
Si-RNA LNP leads to higher tumor growth inhibition (TGI) when combined with the Nanoprimer



- LNP-control SiRNA
- Nanoprimer alone
- AP-01 (siRNA LNPs)
- Nanoprimer + AP-01

# Nanoprimer Increases Anti-tumor Efficacy of Nucleic Acid-based Therapeutics

Si-RNA LNP leads to higher tumor growth inhibition (TGI) when combined with the Nanoprimer

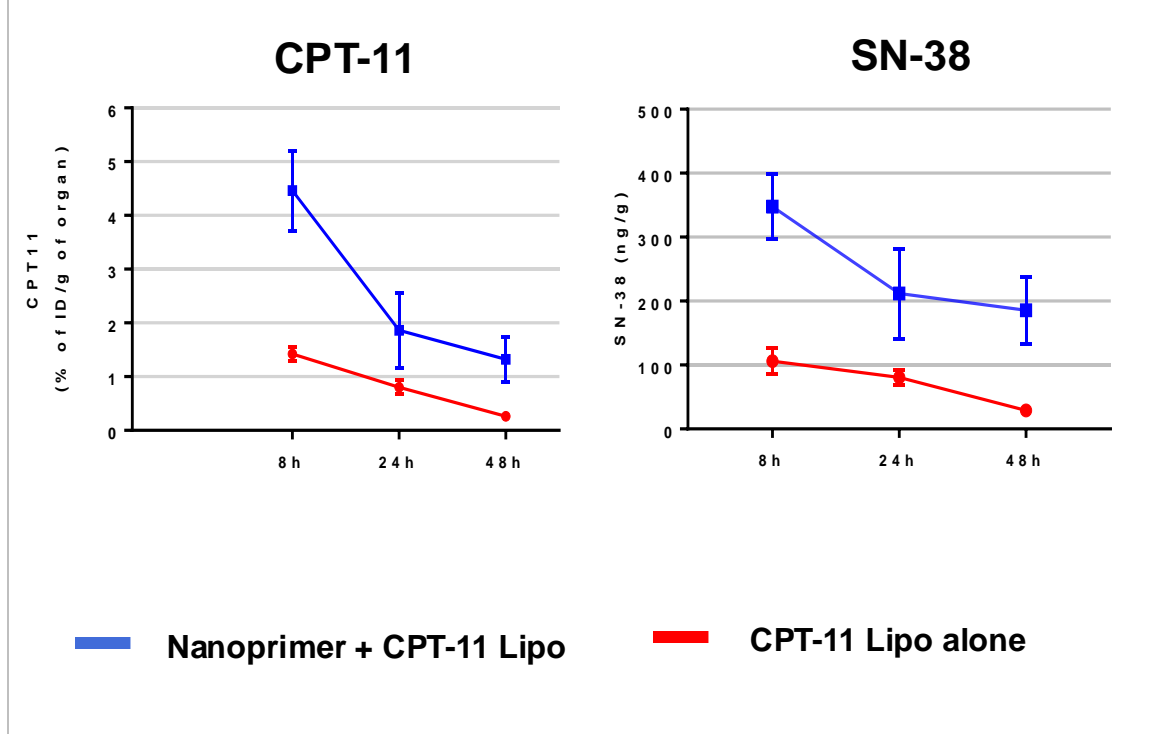


- LNP-control SiRNA
- AP-01 (siRNA LNPs)
- Nanoprimer alone
- Nanoprimer + AP-01

# The Nanoprimer Improves the Efficacy of Small Molecule-loaded Nanomedicines

Clear correlation between the impact of the Nanoprimer on the accumulation of small molecule-loaded liposomes in the tumor and efficacy of treatment

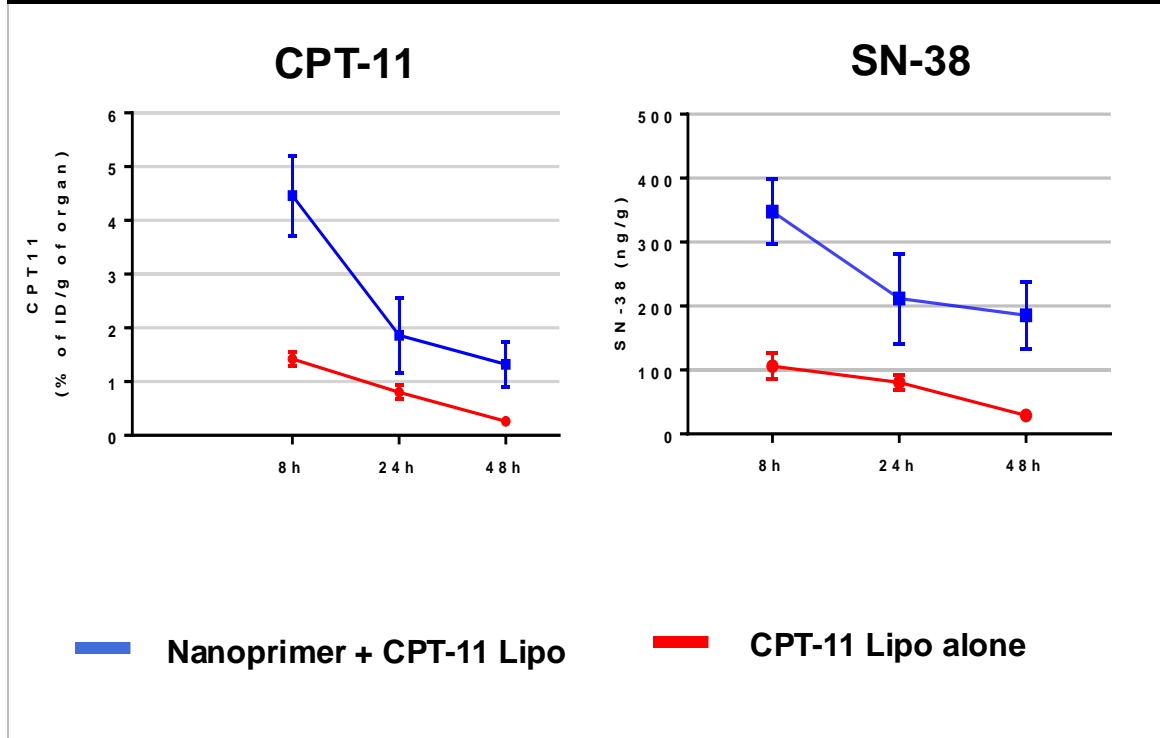
## Drug (CPT-11 and SN-38) accumulation in the tumor



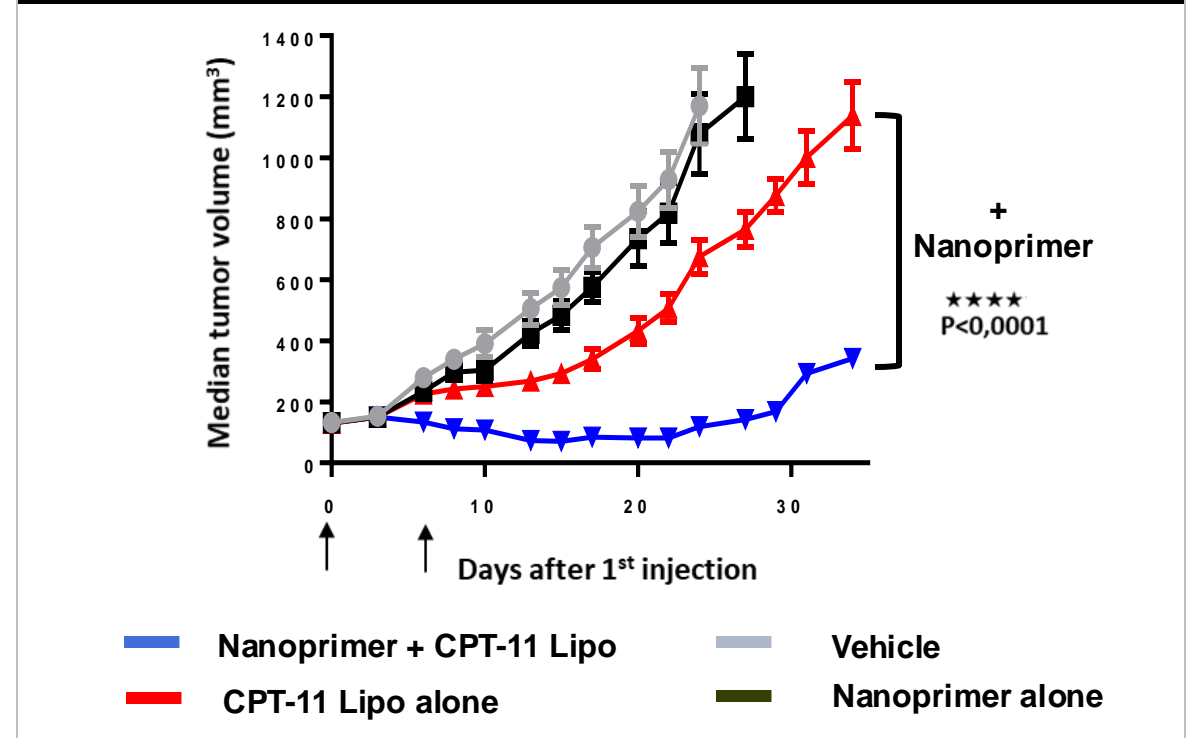
# The Nanoprimer Improves the Efficacy of Small Molecule-loaded Nanomedicines

Clear correlation between the impact of the Nanoprimer on the accumulation of small molecule-loaded liposomes in the tumor and efficacy of treatment

## Drug (CPT-11 and SN-38) accumulation in the tumor



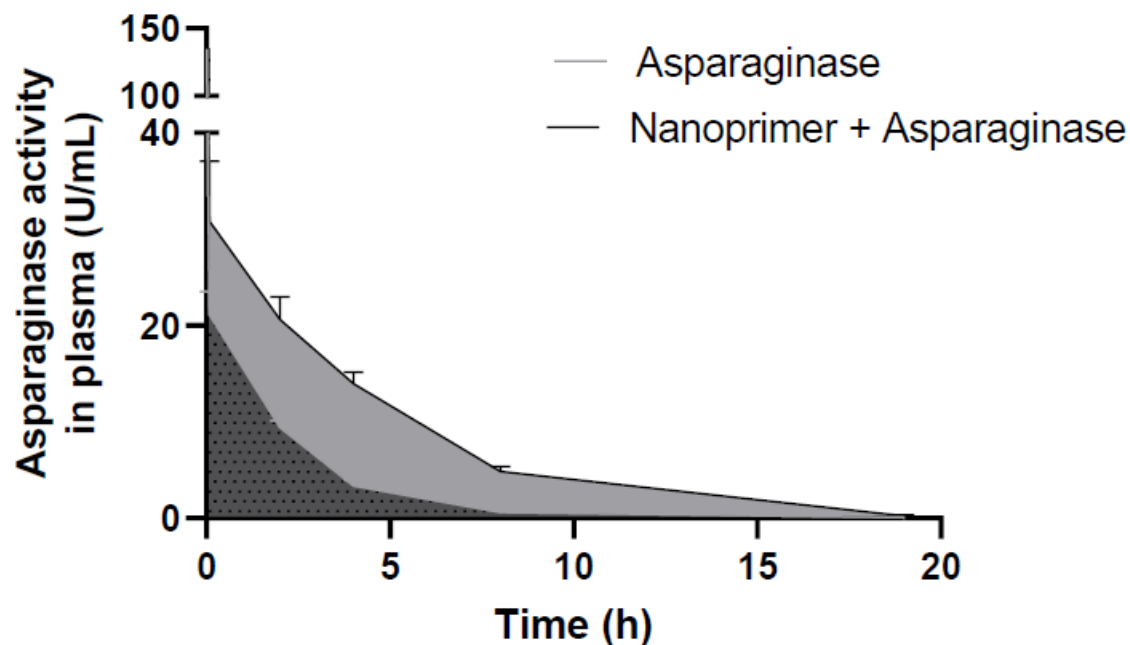
## Enhanced Tumor Growth Inhibition by Irinotecan loaded liposome (CPT-11 Lipo)



Similar efficacy results were generated with Onivyde



# The Nanoprimer Redefines the Bioavailability of Recombinant Protein Asparaginase



	Asparaginase	Nanoprimer + Asparaginase
Total Area	60.00	156.2
Std. Error	3.252	7.972

Nanoprimer drastically increases the systemic bioavailability of E. Coli Asparaginase

By preventing liver accumulation of Asparaginase and increasing its systemic bioavailability, the Nanoprimer could allow a decrease in the number of injections required for the treatment and a reduction in hepatic toxicity

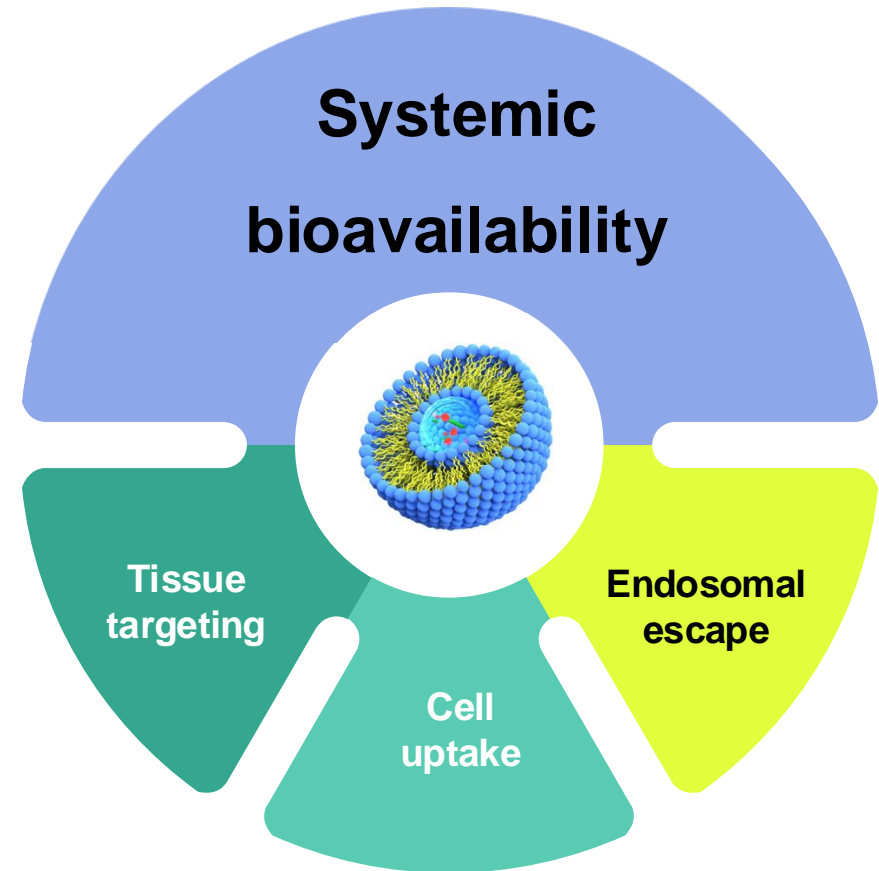
# The Nanoprimer has Potential to Transform Therapeutic Design

Paving the way to the next generation of therapeutics

Multiple functions ensured in a single nano-object

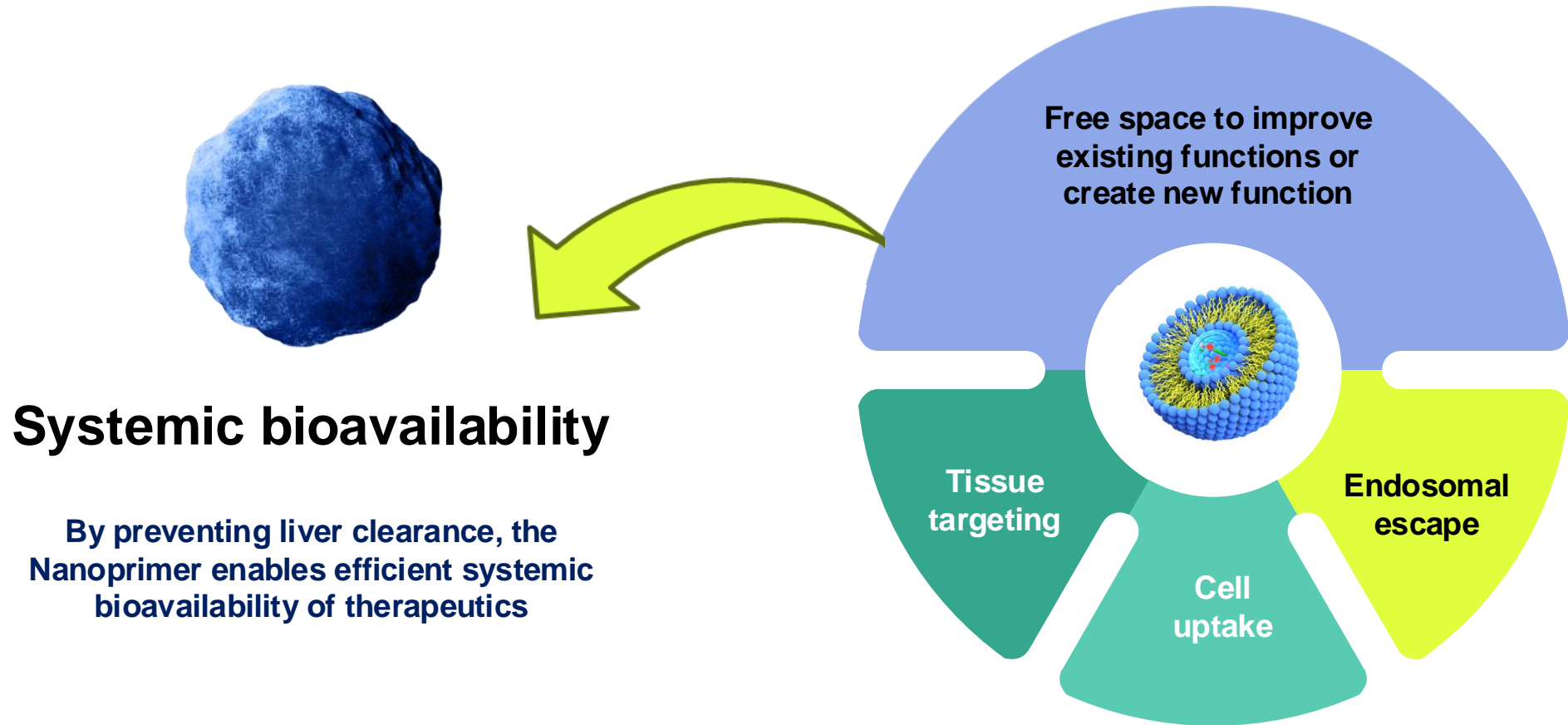


Notion of compromise in the design of the therapeutic



# The Nanoprimer has Potential to Transform Therapeutic Design

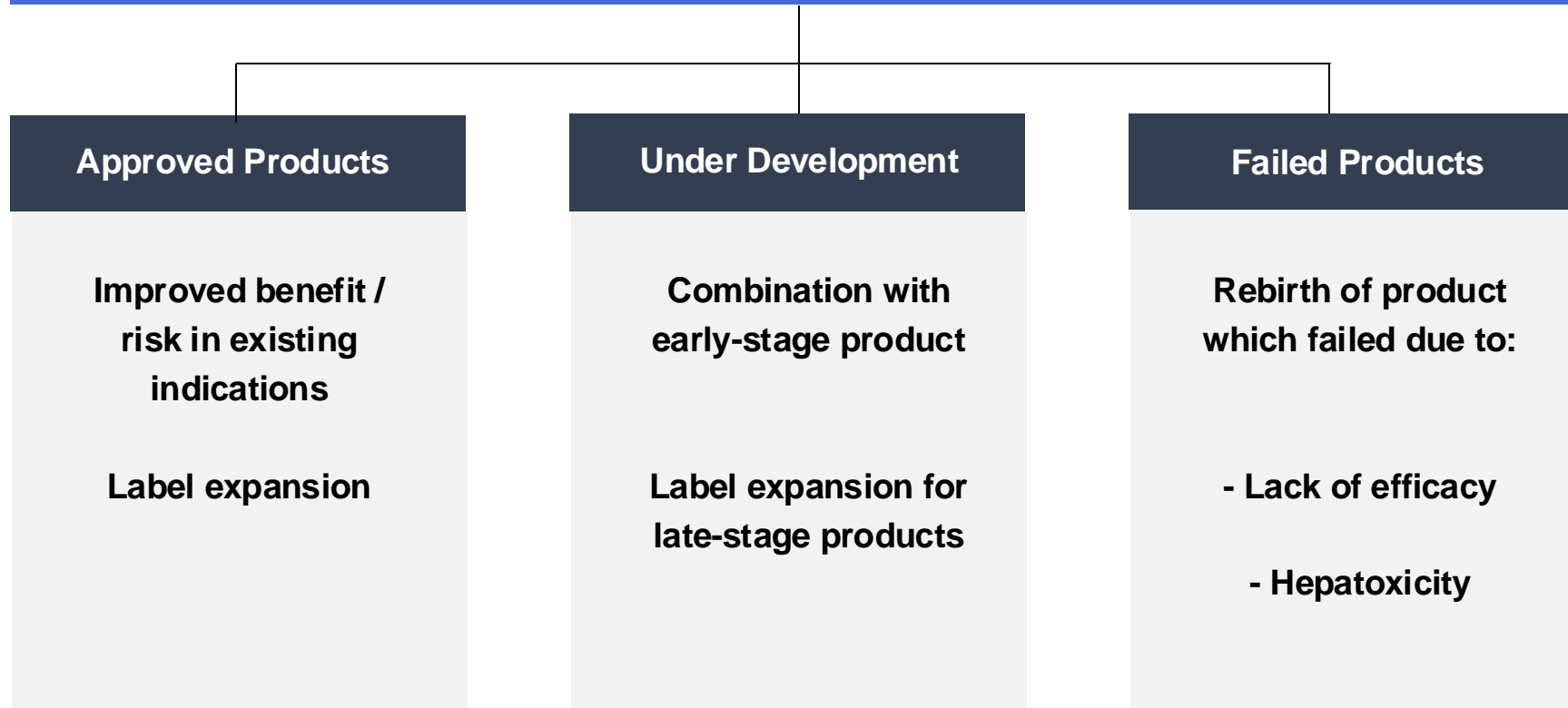
Paving the way to the next generation of therapeutics



Dissociating functions in two objects creates space to boost other functions of the therapeutic

# Curadigm Platform has Broad Market Opportunities

The Nanoprimer's universal mode of action may improve efficiency of different therapeutics across stages of development



# Curadigm Platform has Broad Market Opportunities

The Nanoprimer's universal mode of action may improve efficiency of different therapeutics across stages of development

## Approved Products

Improved benefit / risk in existing indications

Label expansion

## Under Development

Combination with early-stage product

Label expansion for late-stage products

## Failed Products

Rebirth of product which failed due to:

- Lack of efficacy
- Hepatotoxicity

Create new platforms/products

Creation of:

- New products and platforms for extrahepatic delivery through intravenous administration





**NANOBIOTI** 

**NANO**  
LISTED  
EURONEXT

**NBTX**  
Nasdaq Listed