About OMICS Group

OMICS Group is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

About OMICS International Conferences

OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

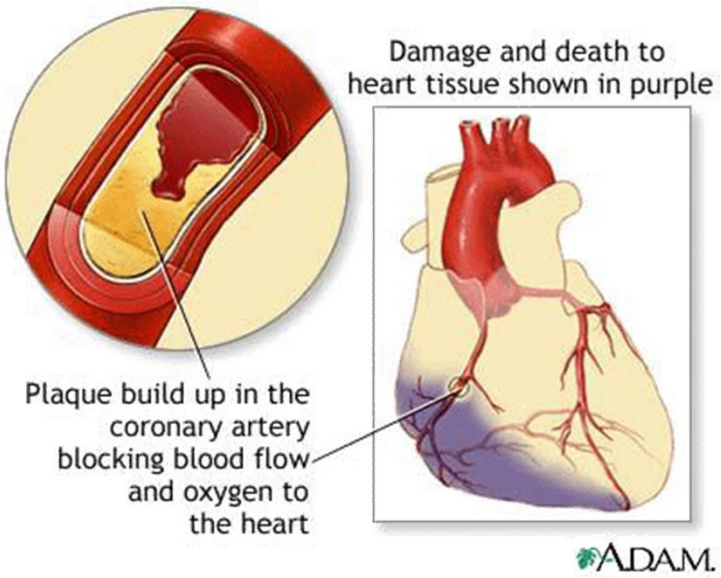
Nanoparticles for site-specific delivery of small-molecule drugs and biotherapeutics to injured vasculature

Michael Chorny, Ph.D.

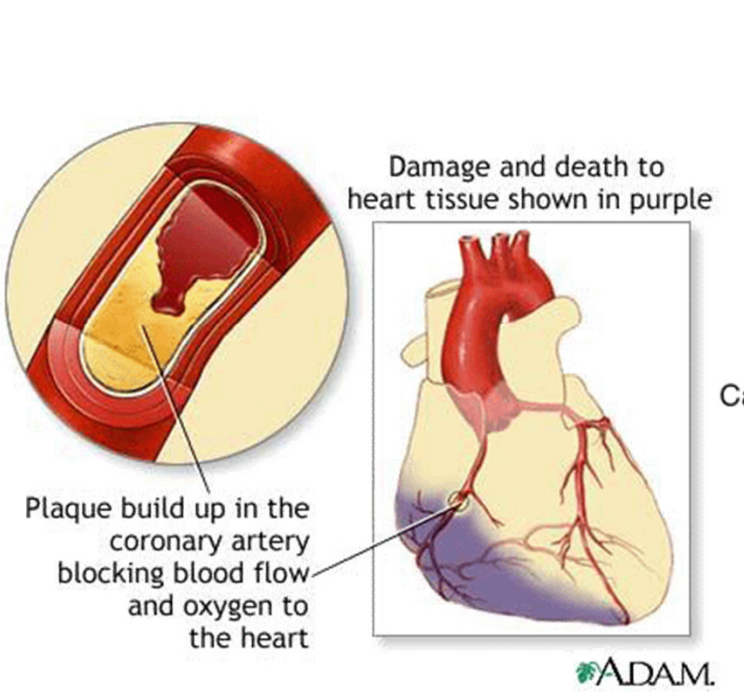
The Cardiology Research Laboratory

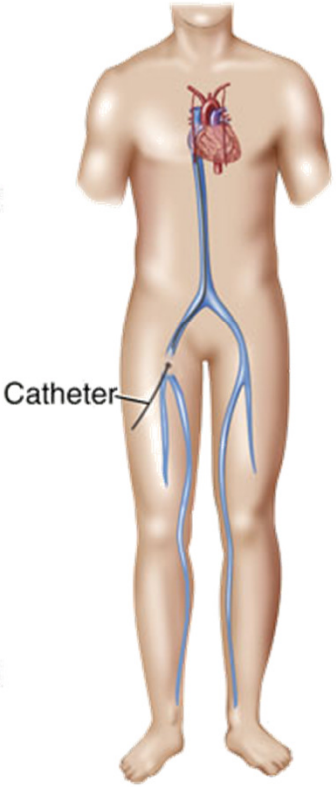
The Children's Hospital of Philadelphia

Angioplasty for obstructive vascular disease



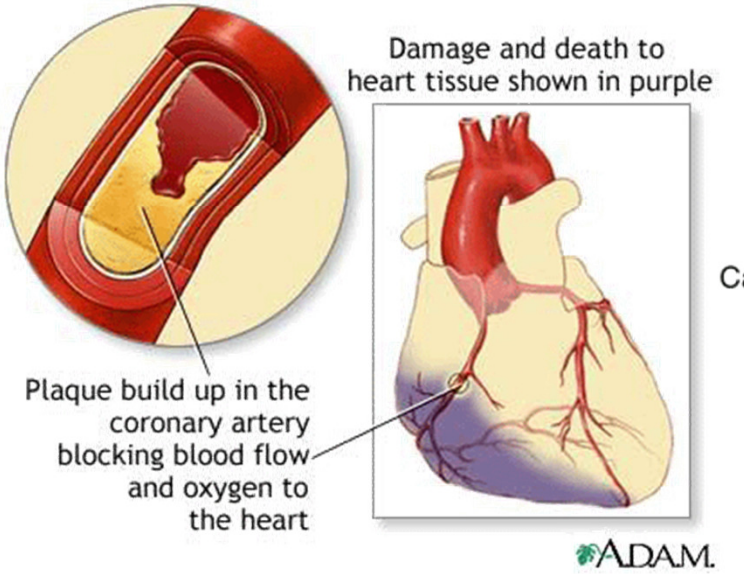
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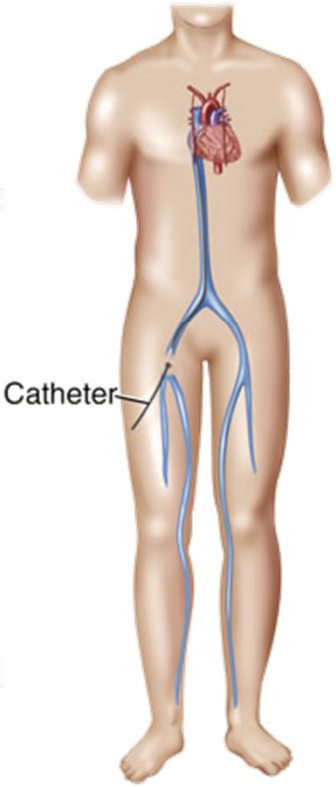




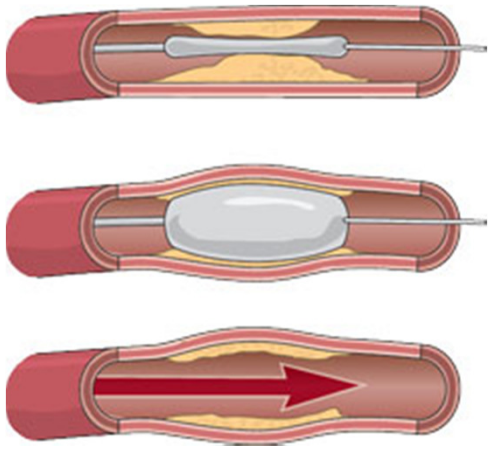
Site of catheter insertion

Angioplasty for obstructive vascular disease

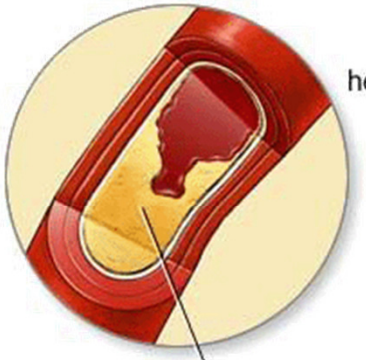




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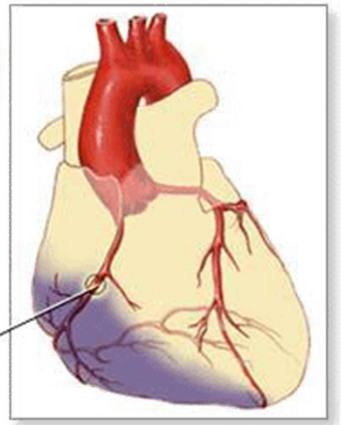


Angioplasty with stent placement for obstructive vascular disease

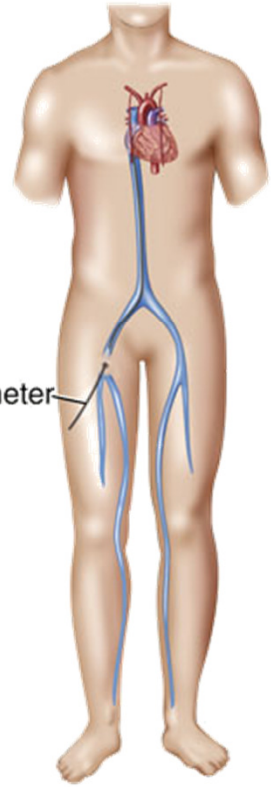


Plaque build up in the coronary artery blocking blood flow and oxygen to the heart

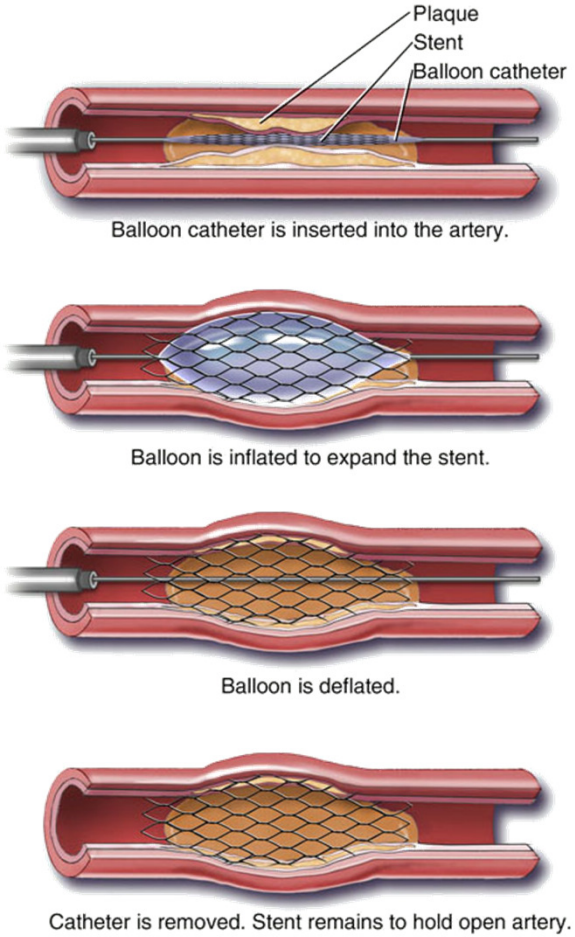
Damage and death to heart tissue shown in purple



ADAM.



Site of catheter insertion



Balloon catheter is inserted into the artery.

Balloon is inflated to expand the stent.

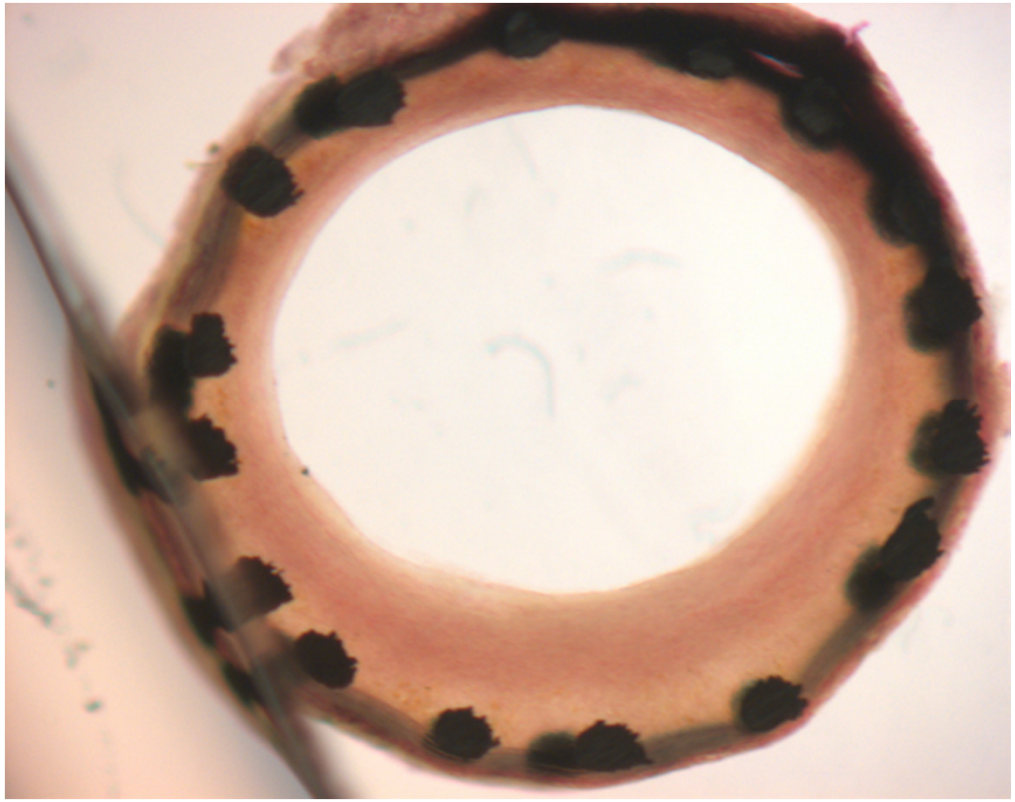
Balloon is deflated.

Catheter is removed. Stent remains to hold open artery.

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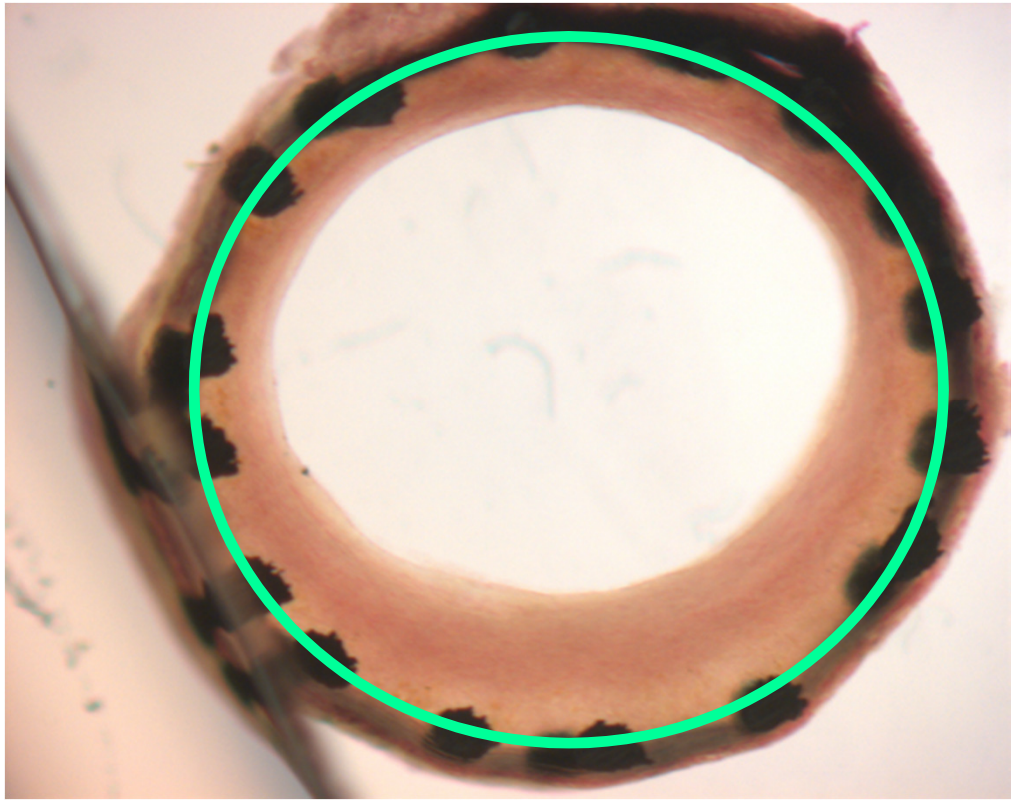
Angioplasty with stent placement for obstructive vascular disease

In-stent restenosis



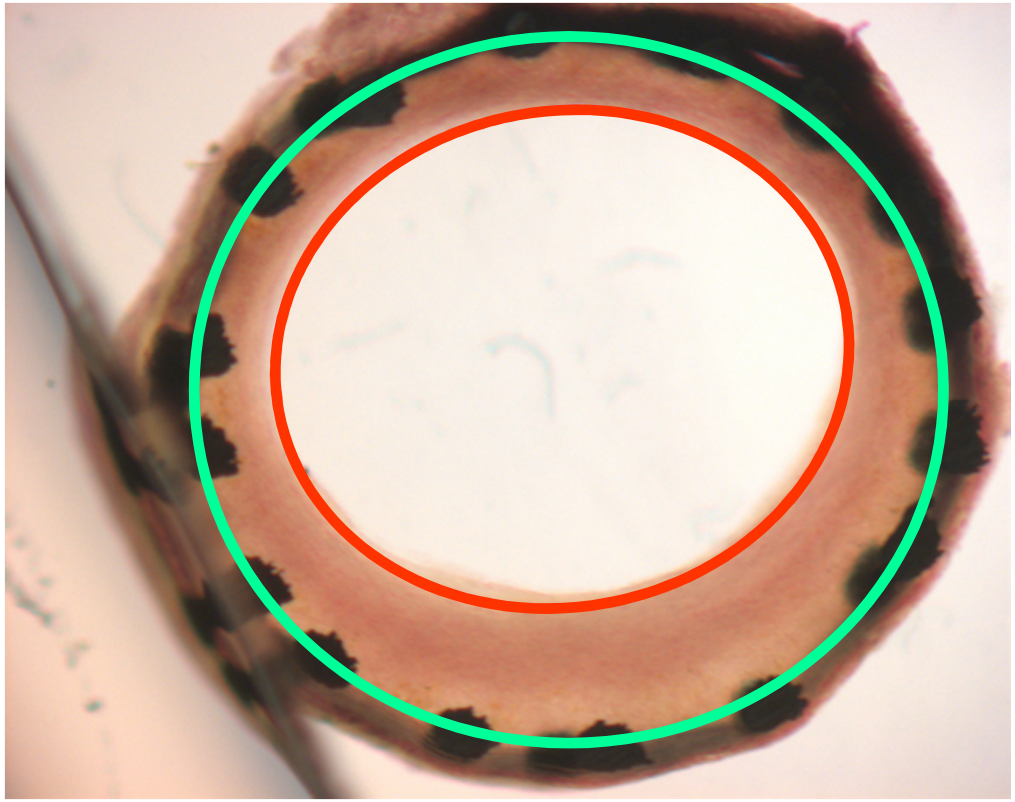
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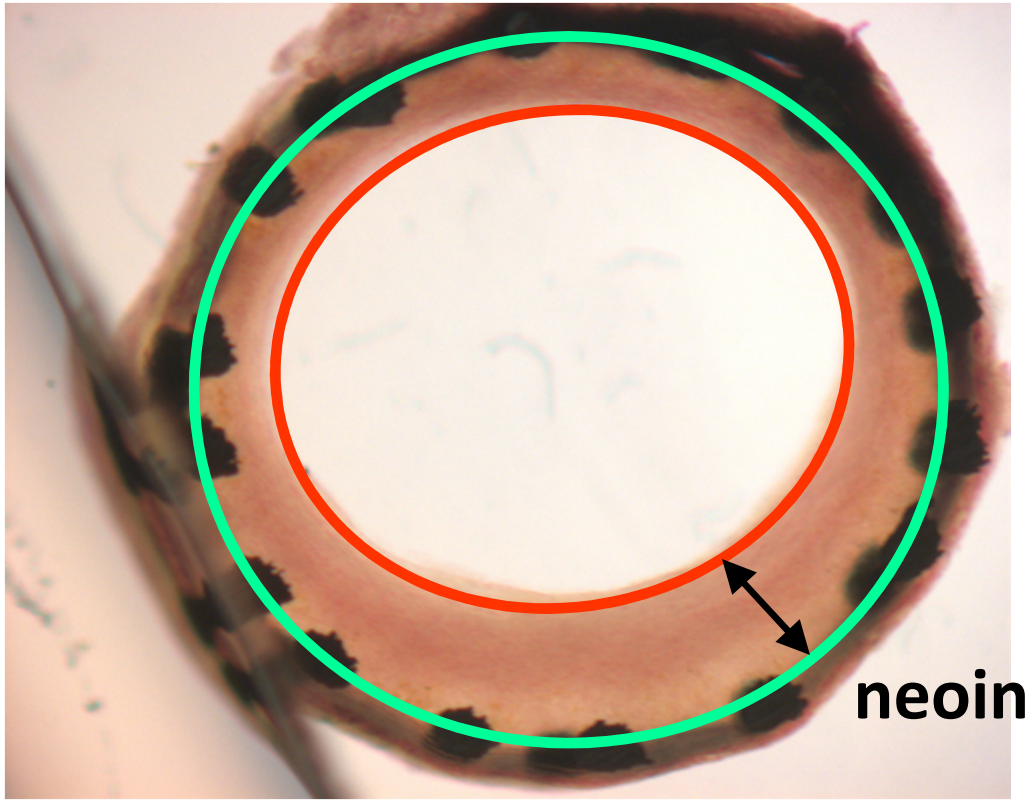
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Angioplasty with stent placement for obstructive vascular disease

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Drug Eluting Stents (DES): a clinically used treatment modality for ISR

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- *Prevent proper endothelial healing*
  - *Promote stent thrombosis and neointimal hyperplasia*

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- ***Safety issues***
- ***Suboptimal efficacy in real-world patients***
- ***Lack of flexibility***

Magnetically Targeted Therapy

Potential advantages as a therapeutic strategy

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- ***site-specificity ↔ improved therapeutic index***
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  1. *individually optimized drug dose regimens*
  2. *drug combinations*
  3. *multiple drug dosing*
  4. *controlled release kinetics (drugs, gene vectors)*

Magnetically Targeted Therapy

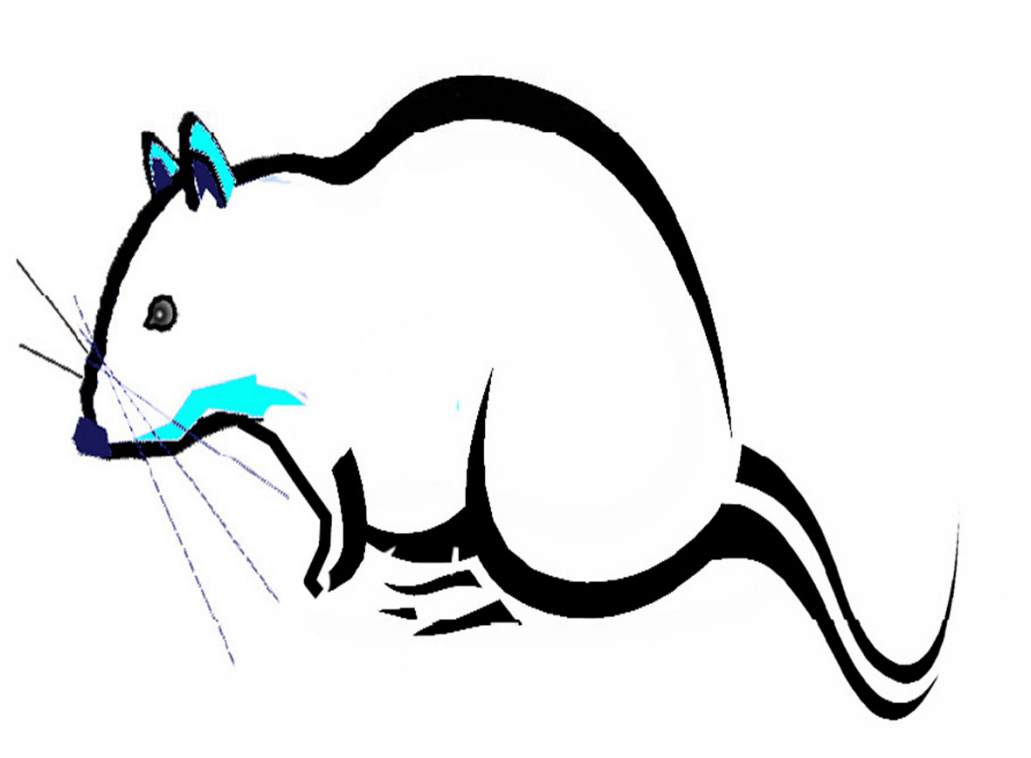
- *Magnetic nanoparticles*
  - *Fully biodegradable, nontoxic to cells and tissues*
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  - *No magnetic memory (remanent magnetization = 0)*

Magnetically Targeted Therapy

- *Magnetic field source*

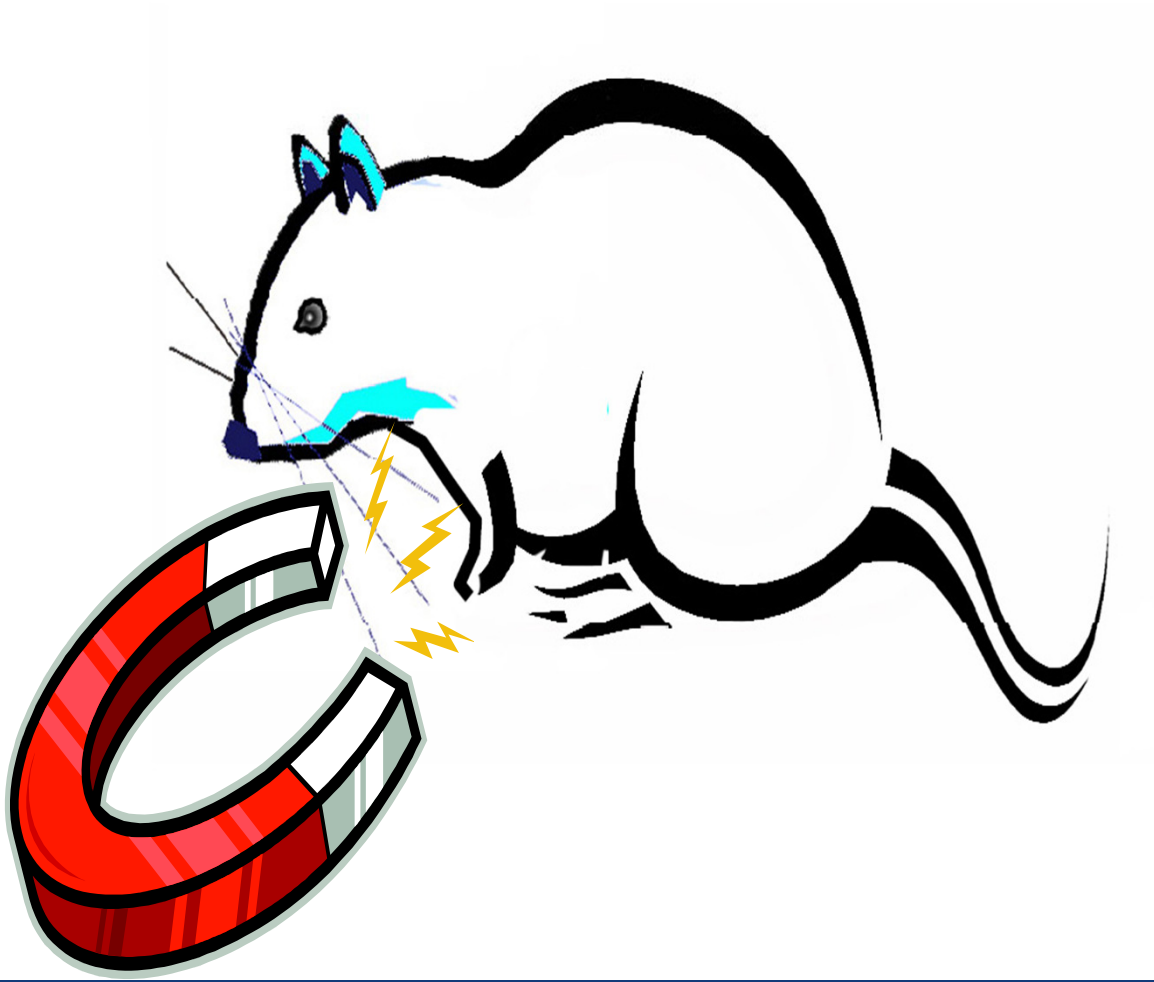
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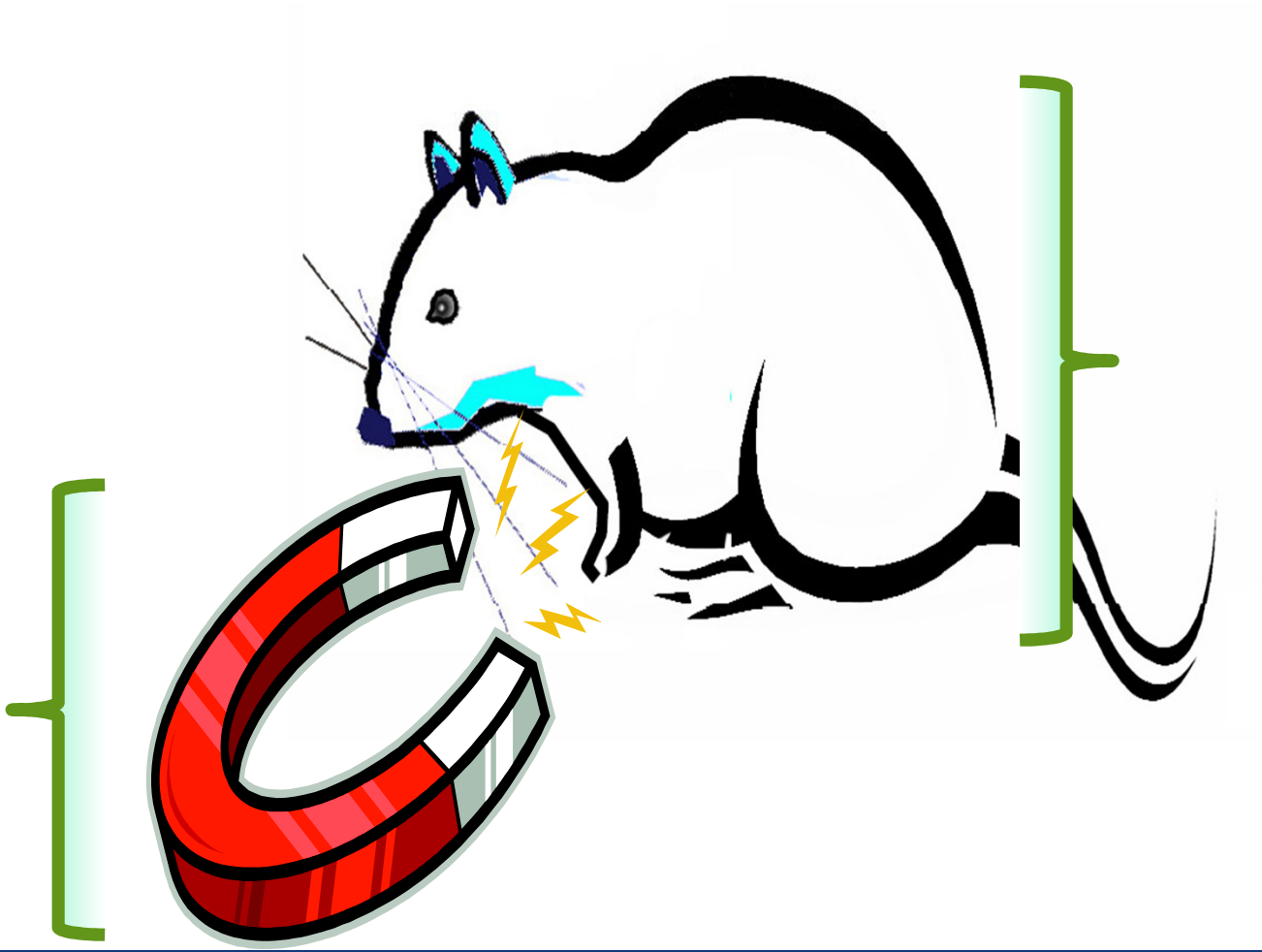
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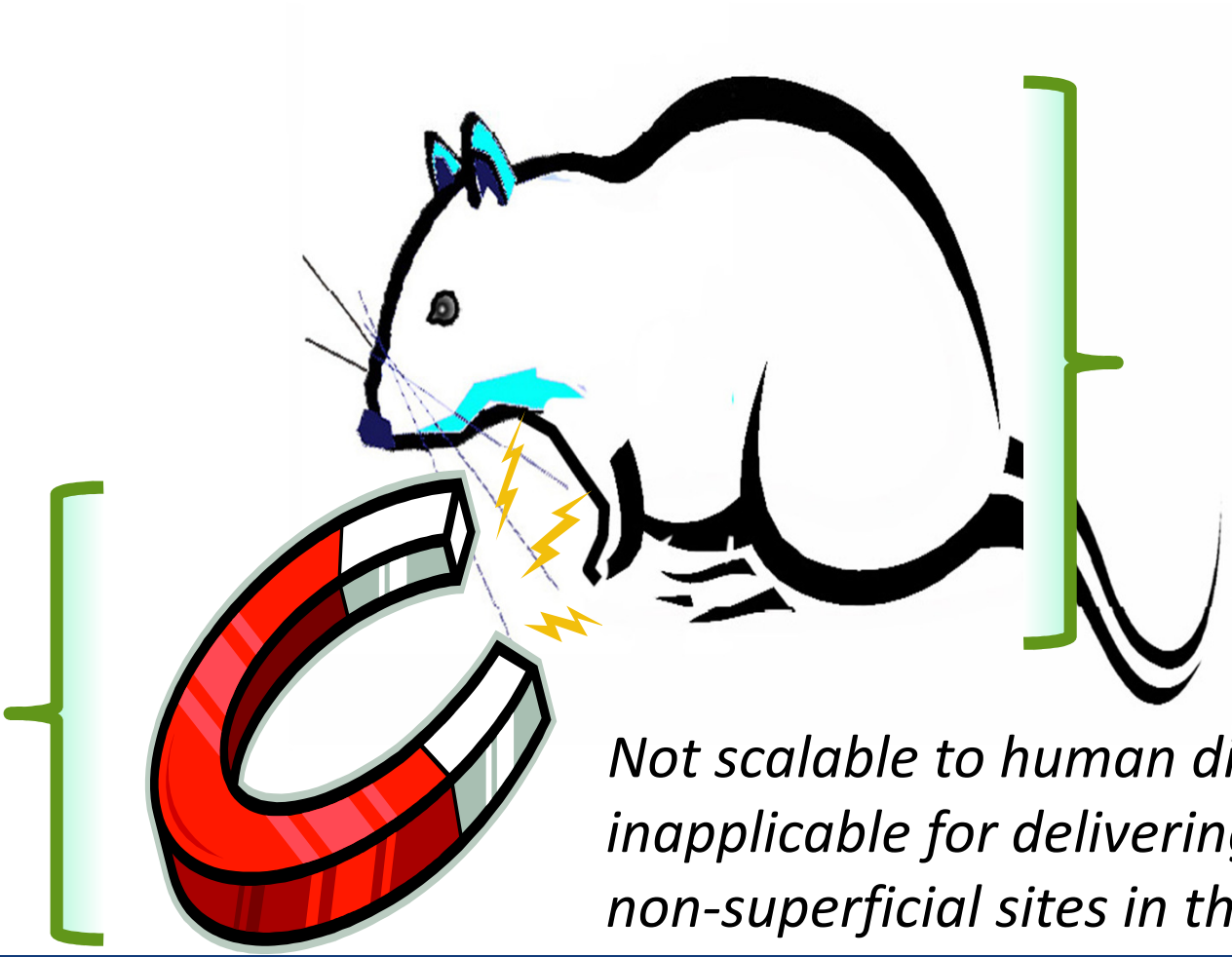
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Not scalable to human dimensions, inapplicable for delivering therapy to non-superficial sites in the human body

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  ***Primary source**: uniform, deep-penetrating magnetizing field*
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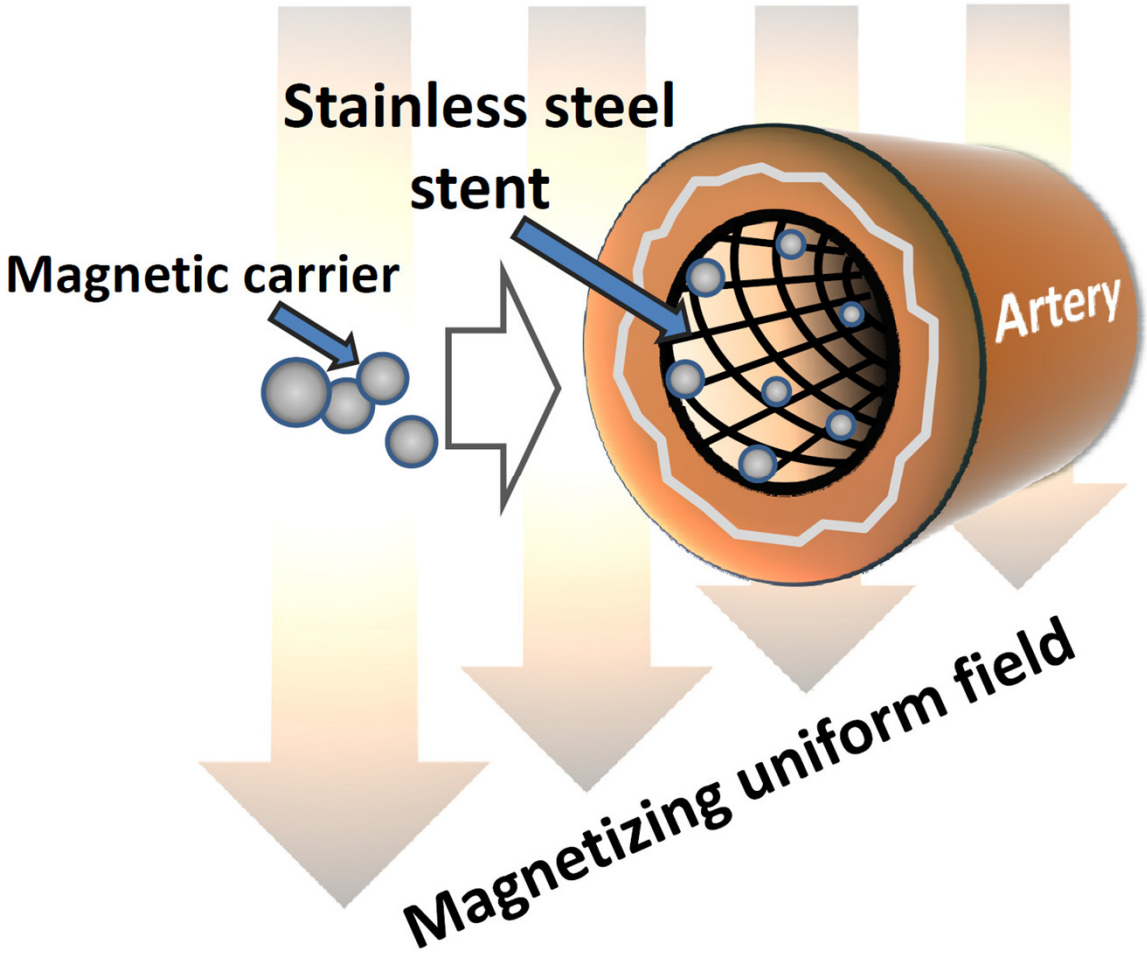
  ***Primary source**: uniform, deep-penetrating magnetizing field*
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  1. MAGNETIZING MNP, MAKING THEM RESPONSIVE TO MAGNETIC FORCE

  ***Secondary source**: magnetizable implant (stainless steel stent)*

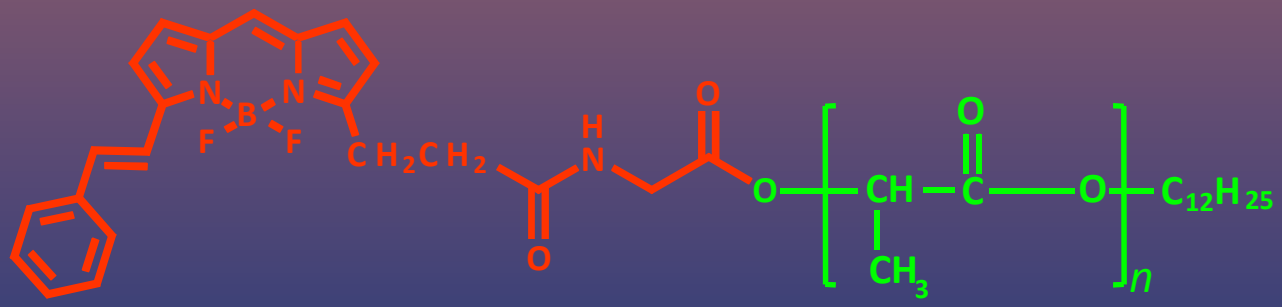
  2. CREATING LOCALIZED FIELD NON-UNIFORMITY AND FOCUSING MAGNETIC FORCE IN THE STENTED SEGMENT

Magnetically Targeted Therapy



Polylactide

Polylactide (PLA) is a synthetic, nontoxic, biodegradable aliphatic polyester. The biodegradation products of aliphatic polyesters are nontoxic, noncarcinogenic, and nonteratogenic. Due to their safety and biodegradability, these polymers are used to formulate implantable and injectable drug delivery systems for human and veterinary use.



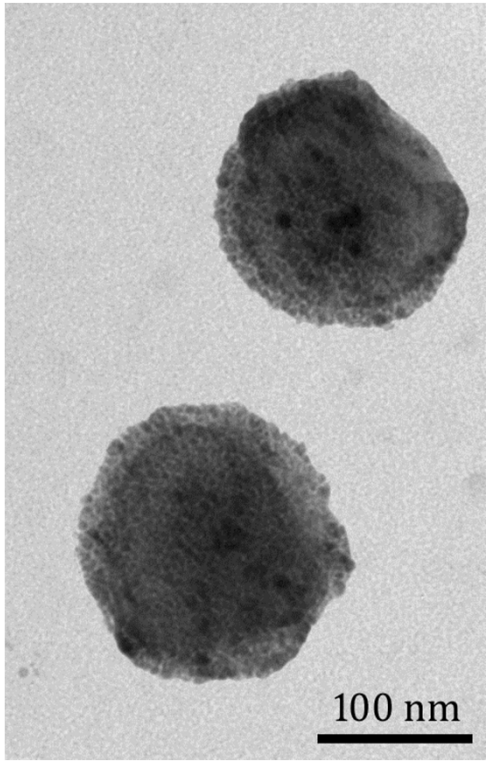
Polylactide

Fluorescent conjugates of PLA with BODIPY fluorophores were synthesized for MNP uptake and distribution studies

Magnetic nanoparticles

design and characterization

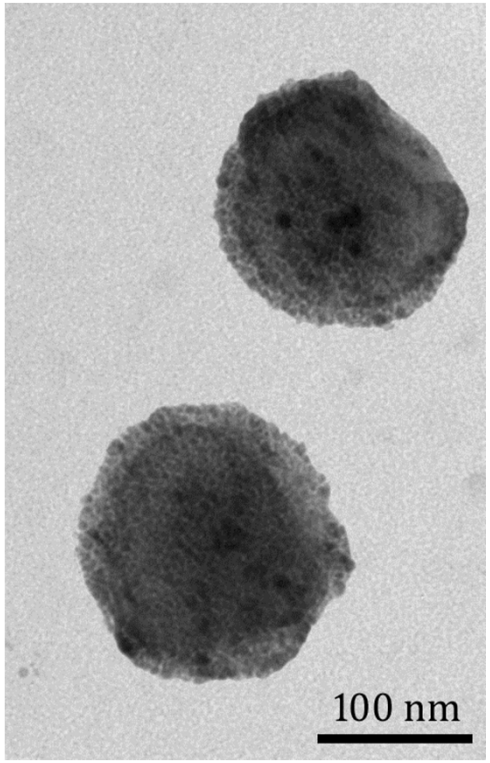
TEM



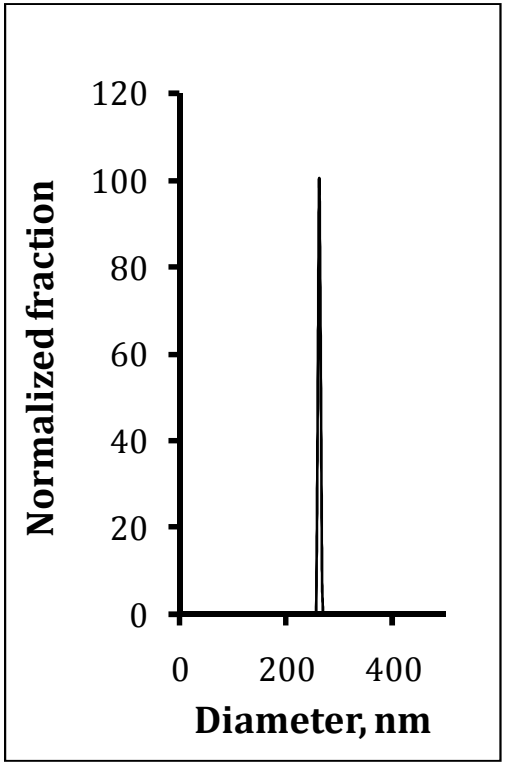
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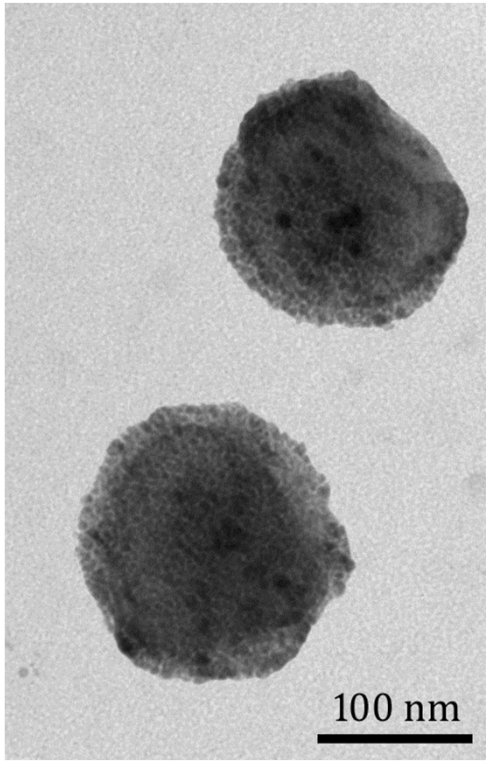
DLS



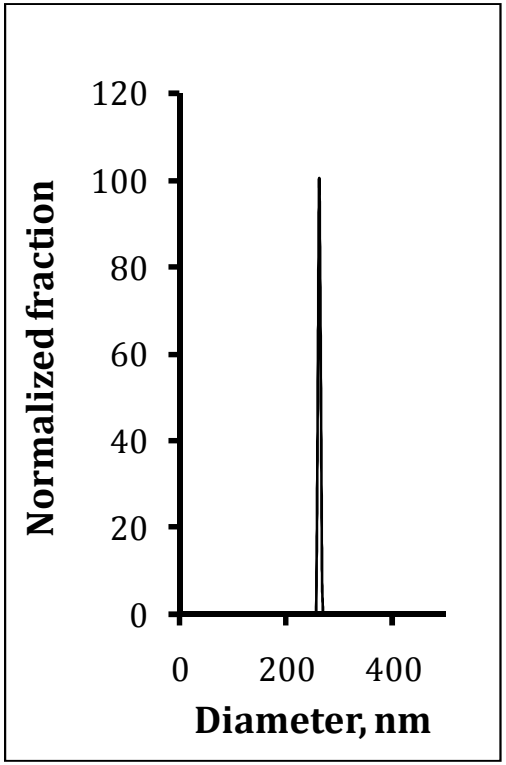
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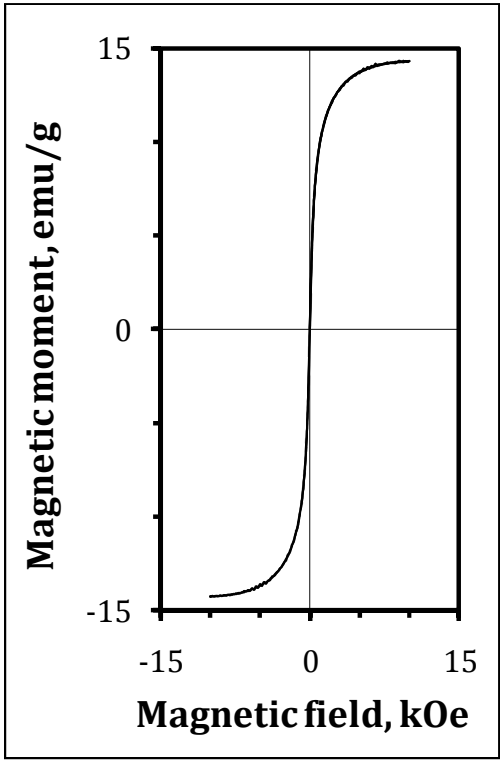
TEM



DLS



AGM

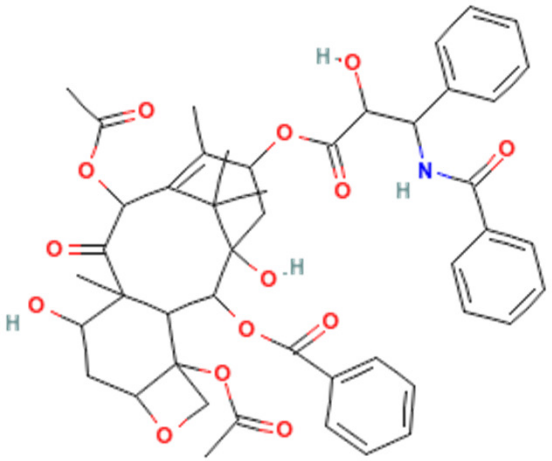


PACLITAXEL: a candidate drug for MNP-mediated restenosis treatment

- ***Potent antineoplastic drug***
- ***Proven antirestenotic efficacy***
- ***Prevents cell division by promoting the assembly of abnormally stable microtubules resisting depolymerization***

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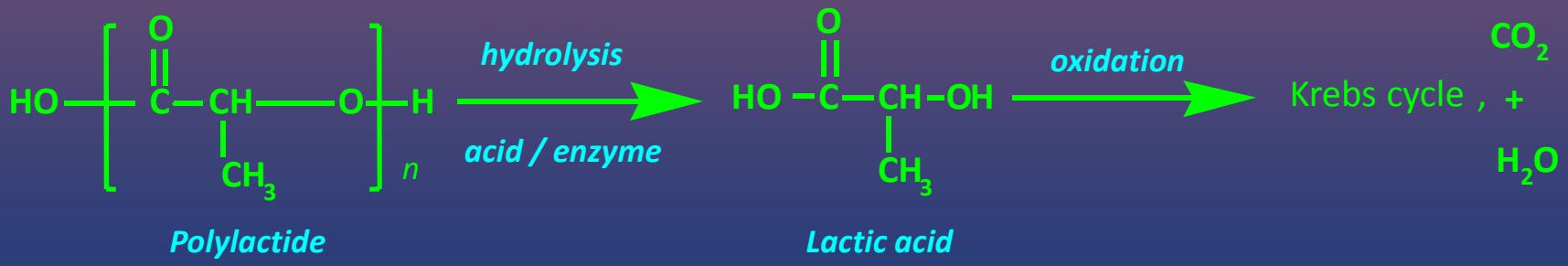
Molecular Weight: 853.9

Solubility: Soluble in organic solvents. Highly insoluble in water and aqueous buffers.

Polylactide

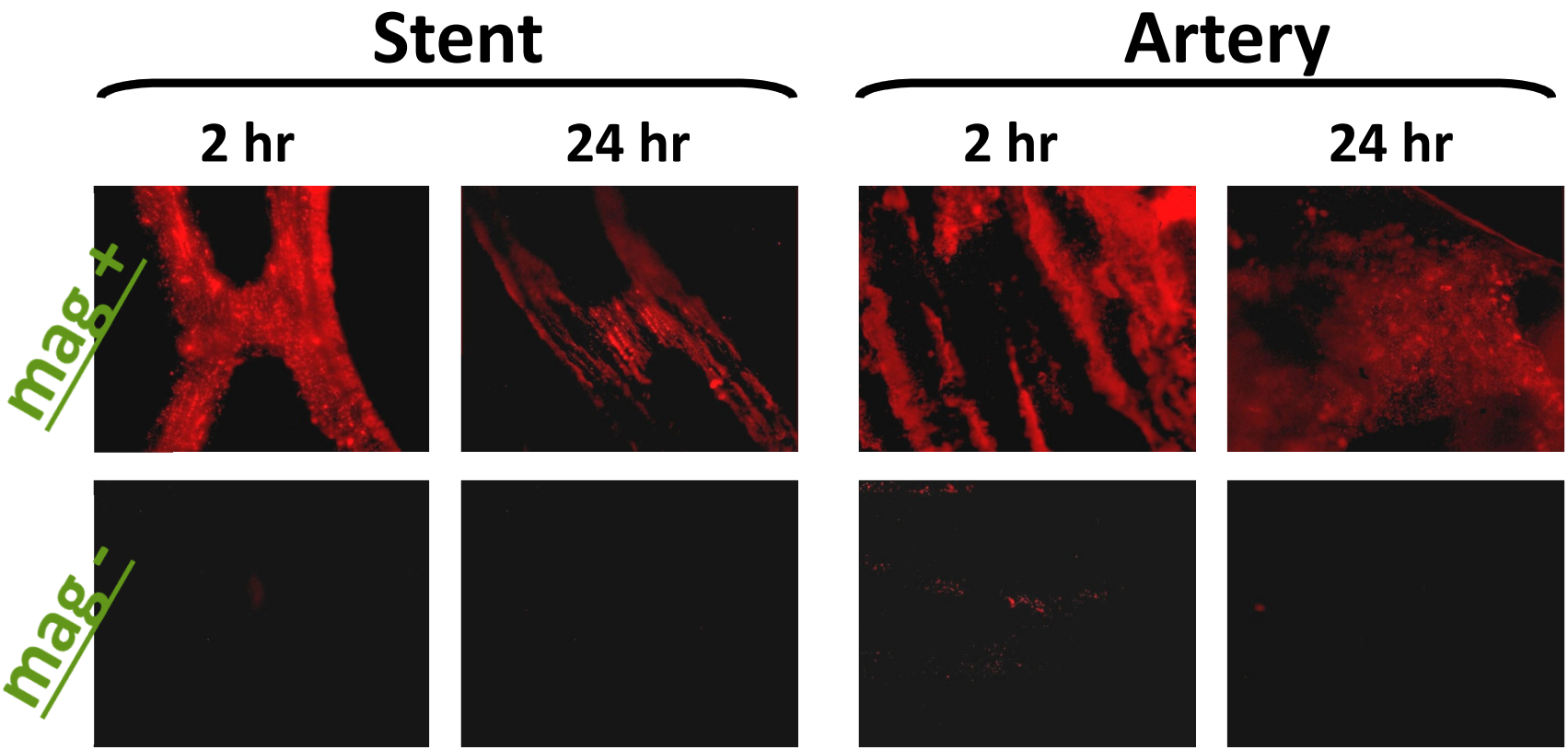
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Polymer biodegradation:



Magnetic guidance to stented arteries

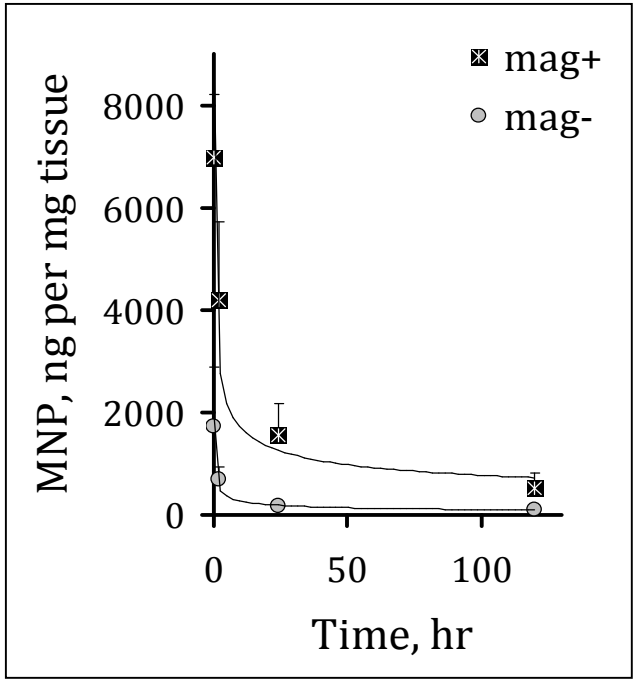
(rat carotid stenting model)



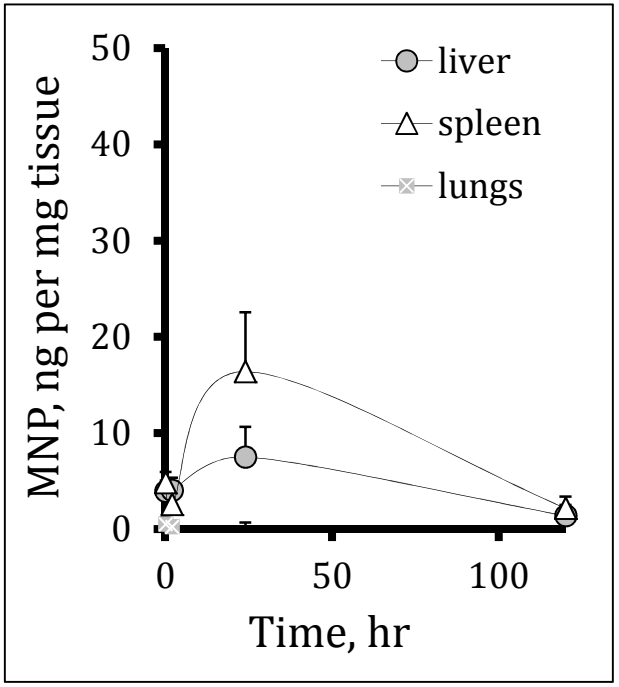
Magnetic guidance to stented arteries

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carotid artery



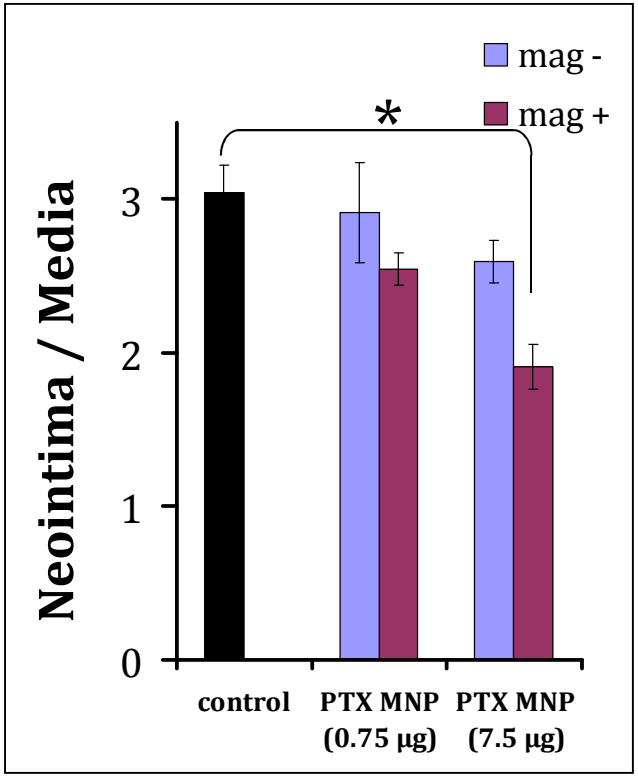
peripheral tissues

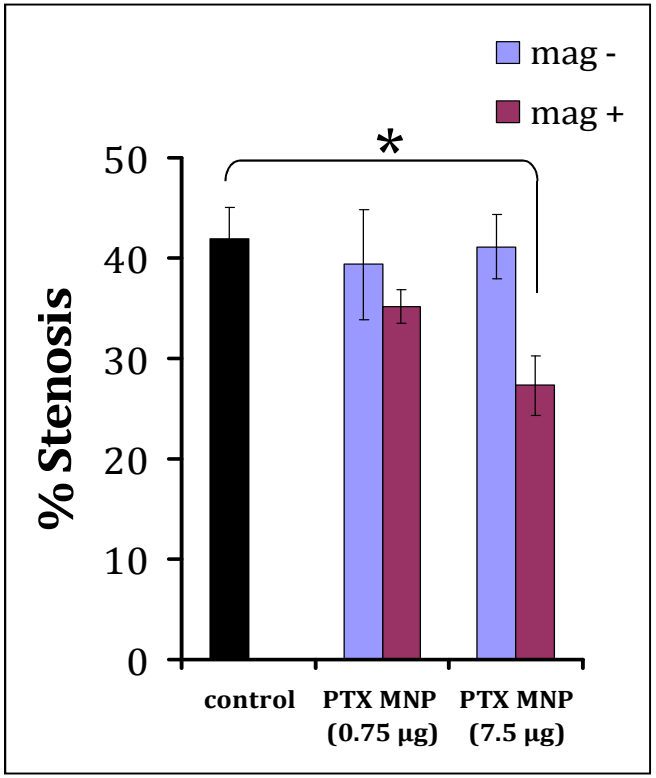


Magnetic guidance to stented arteries

(rat carotid stenting model)

Antirestenotic effect

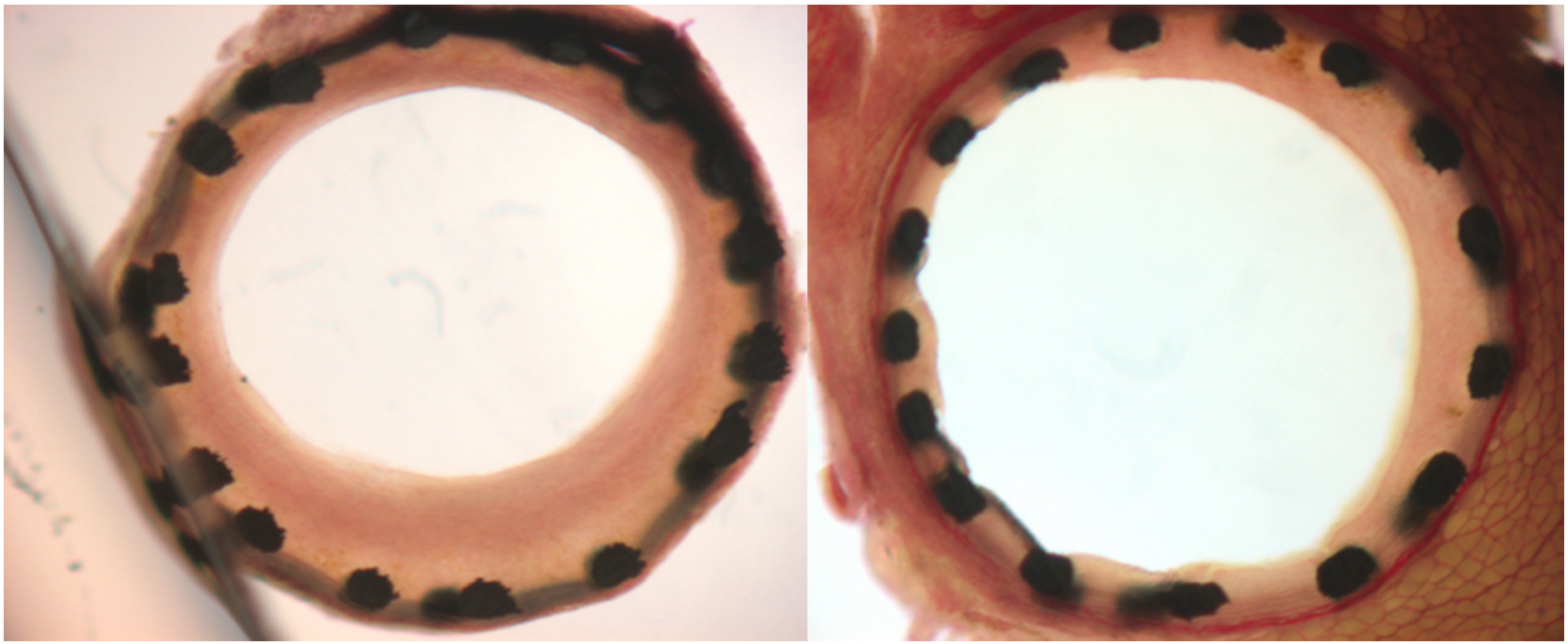




Magnetic guidance to stented arteries

(rat carotid stenting model)

Antirestenotic effect



Stenting only (control) ***MNP(PTX) / mag+***

Gene delivery for site-specific antirestenotic therapy

RATIONALE:

Gene therapy can target a variety of molecular pathways and potentially offer a safer and more effective alternative to antiproliferative drugs for preventing restenosis

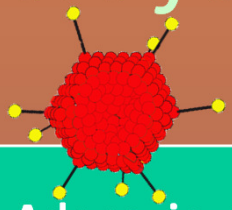
Restenosis as a therapeutic target

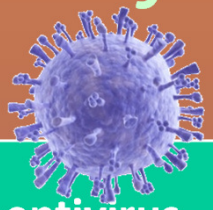
Antirestenotic therapy: when, where and how ?

- *the precise moment of onset is known (time).*
- *the intervention site is exactly where reobstruction develops (location).*
- *arterial segment is accessed at the same time when the pathological process is triggered (accessibility).*

- ***Pathological process triggered by early events***
  (endothelial denudation, platelet deposition and activation, inflammatory cell recruitment)
  - ***Early intervention and sustained but rapidly developing effect***
- ***Vulnerability period is usually well-defined***
  (several weeks to months, depending on the vessel type)
  - ***Acute condition, does not require a life-long treatment***

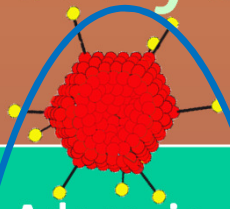
Viral Vectors for Vascular Gene Transfer

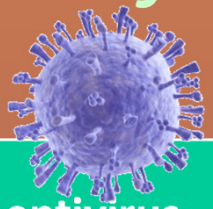


	Adenovirus	Adenoassociated virus	Retrovirus	Lentivirus
Capacity	up to 30 Kbp	up to 5 Kbp	up to 8 Kbp	up to 9 Kbp
Tissue specificity	↓	↑	↓	↑
Transgene expression (peak levels, duration, onset)	Episomal, Early onset, Strong transient expression	Episomal and integrating, Late onset, Long-lasting expression	Integrating, Early onset, Stable expression	Integrating or episomal, Early onset, Stable or transient expression
Quiescent cell transduction	+	+	--	+
Immunogenicity and toxicity	↑	↓	↓	↓
Stability	↑	↑	↓	↓
Scalability, ease of production	↑	↑	↑	↓↑

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Adenovirus (Ad) as a gene vector

- ✓*Efficient nuclear entry*
- ✓*Early onset of transgene expression*
- ✓*Gene transfer in both quiescent and dividing cells*
- ✓*Transgenes of up to 30 kb*
- ✓*No integration, transient expression*

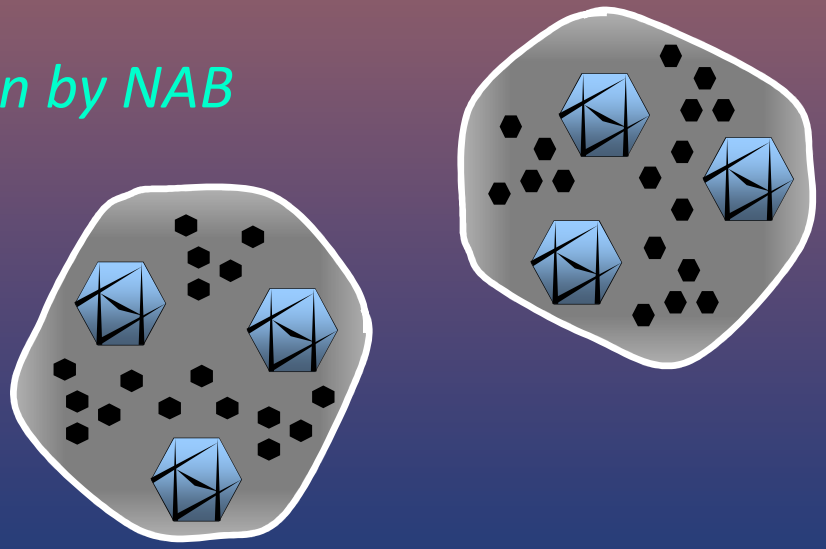
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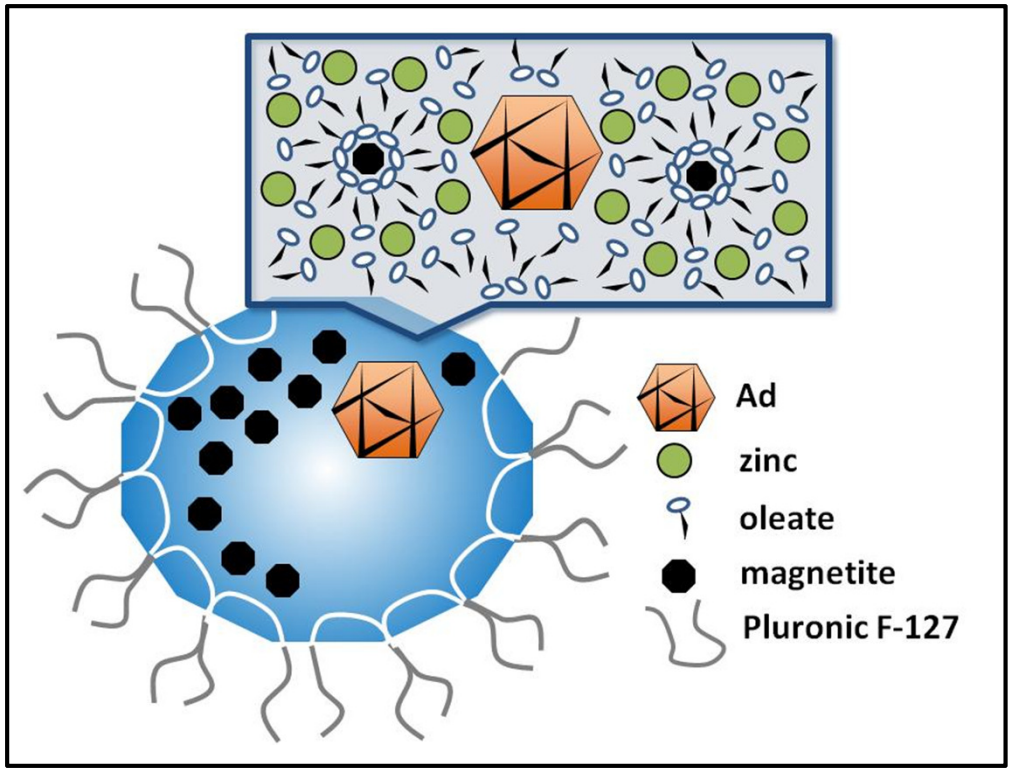
- × *Side effects due to*
  - *distribution to non-target tissues*
  - *low transduction specificity*
- × *Rapid inactivation by neutralizing antibodies*

Nanoparticles for Ad delivery

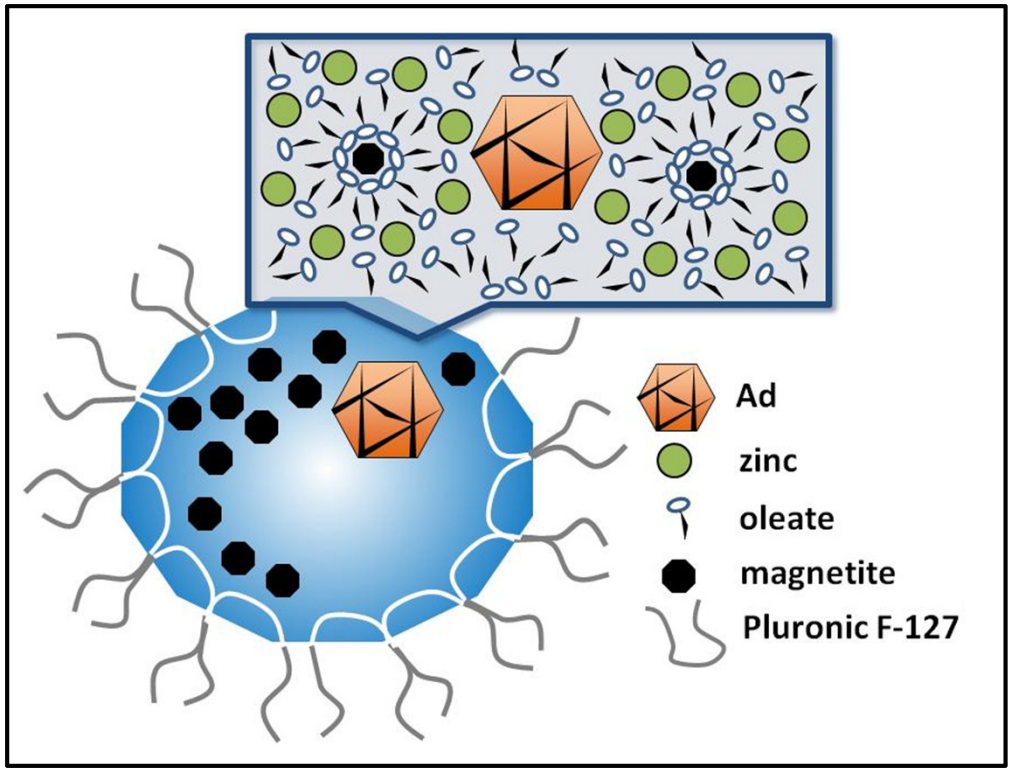
- *Lower toxicity due to minimized vector dissemination and immune response*
- *Improved therapeutic efficacy due to higher local vector concentrations in the target tissue*
- *Protection from inactivation by NAB*

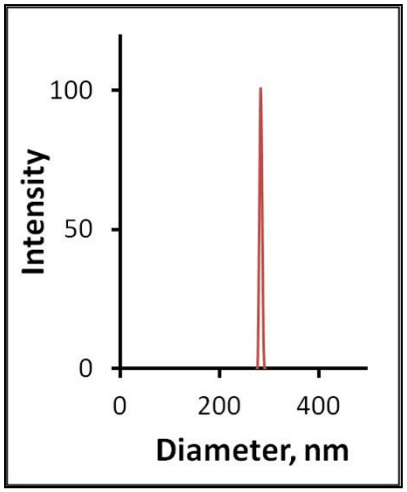


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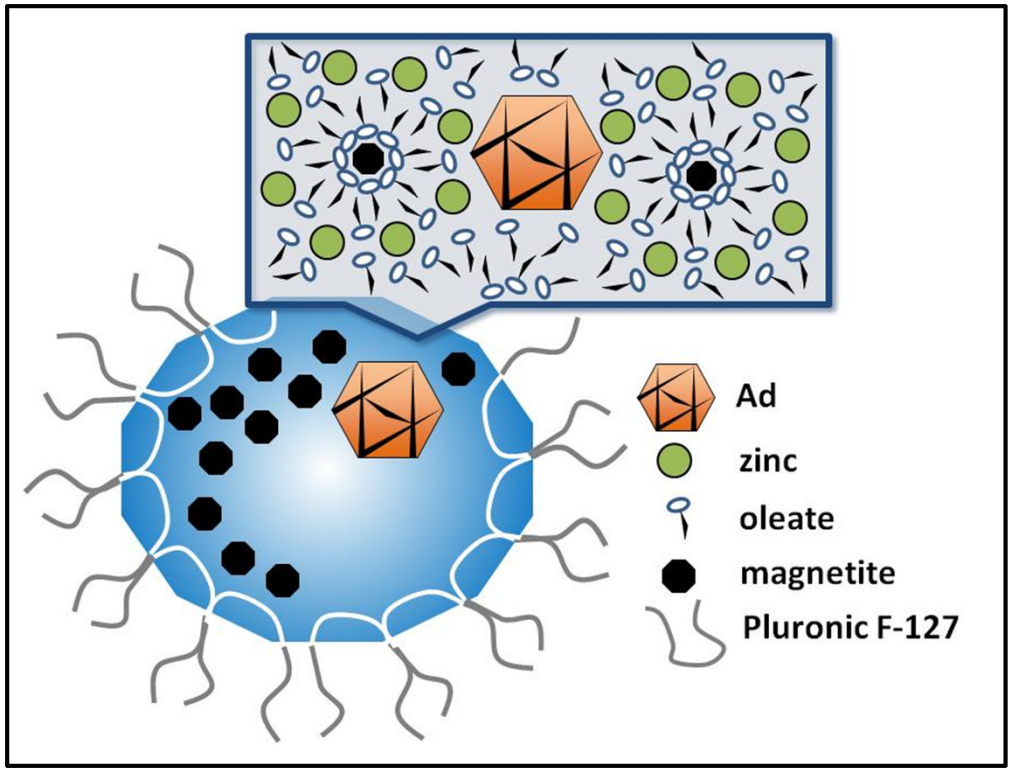


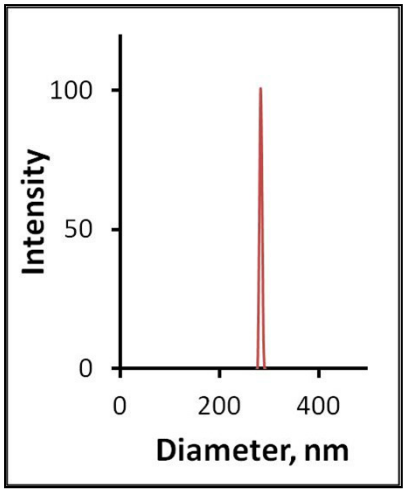
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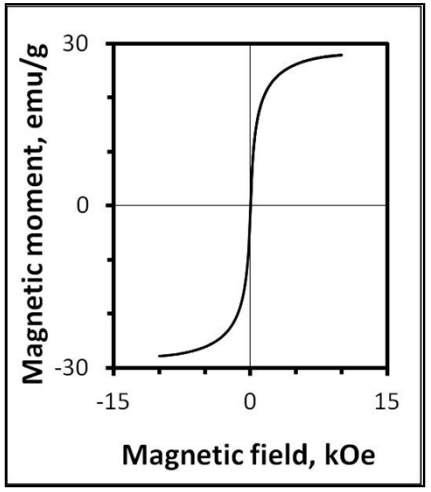




Nanoparticles for Ad delivery

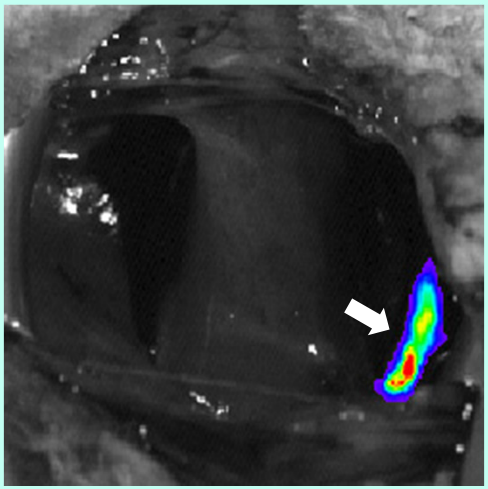




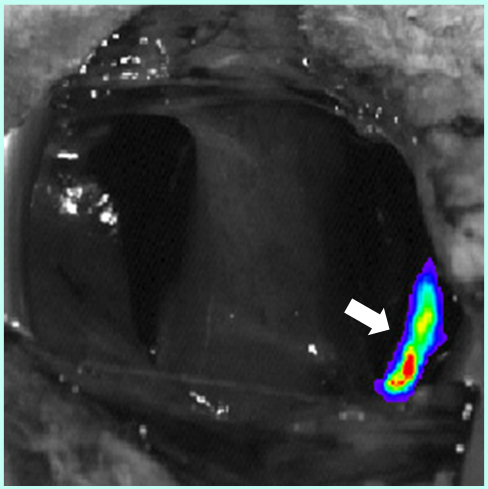


Stent-targeted Ad delivery

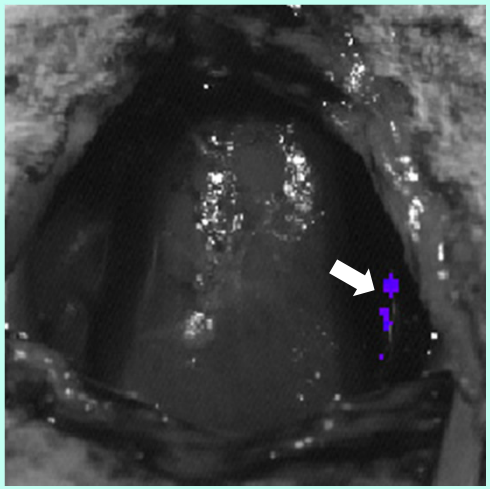
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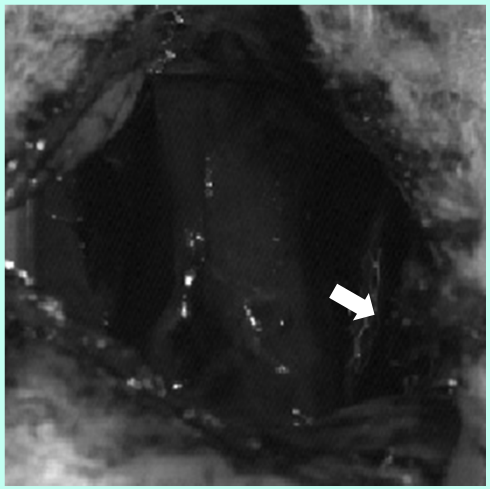
Stent-targeted Ad delivery



MNP(Ad), mag +

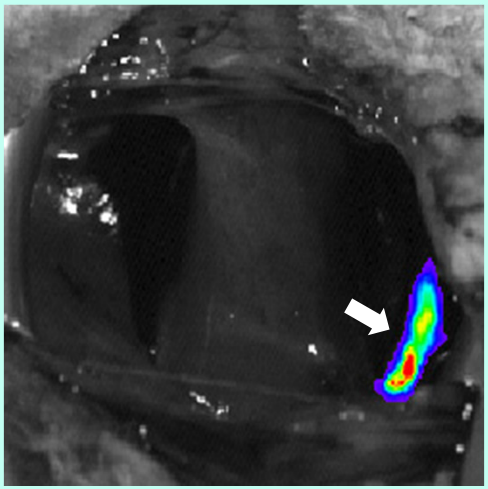


MNP(Ad), mag -

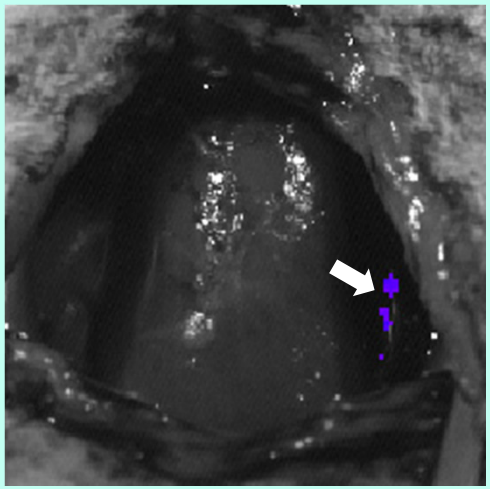


Free Ad

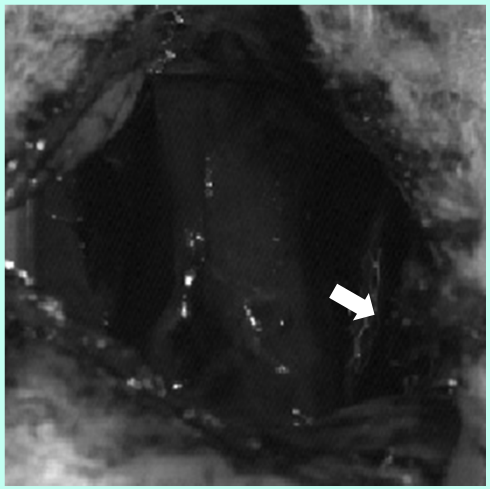
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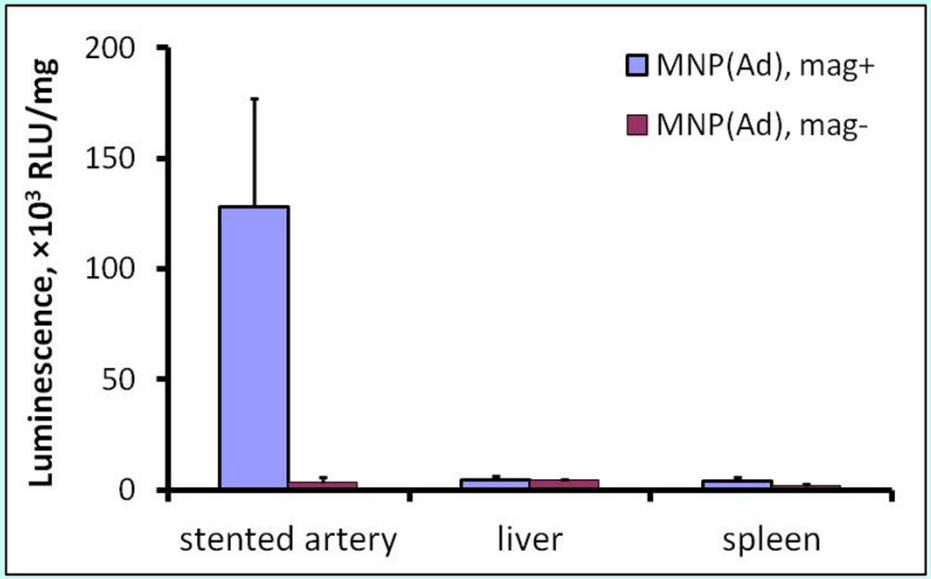
MNP(Ad), mag +



MNP(Ad), mag -



Free Ad



Cell therapy for preventing restenosis

Endothelial cells

- *Form a barrier separating the arterial wall from blood*
- *Secrete factors necessary for maintaining vascular homeostasis*

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Cell therapy for preventing restenosis

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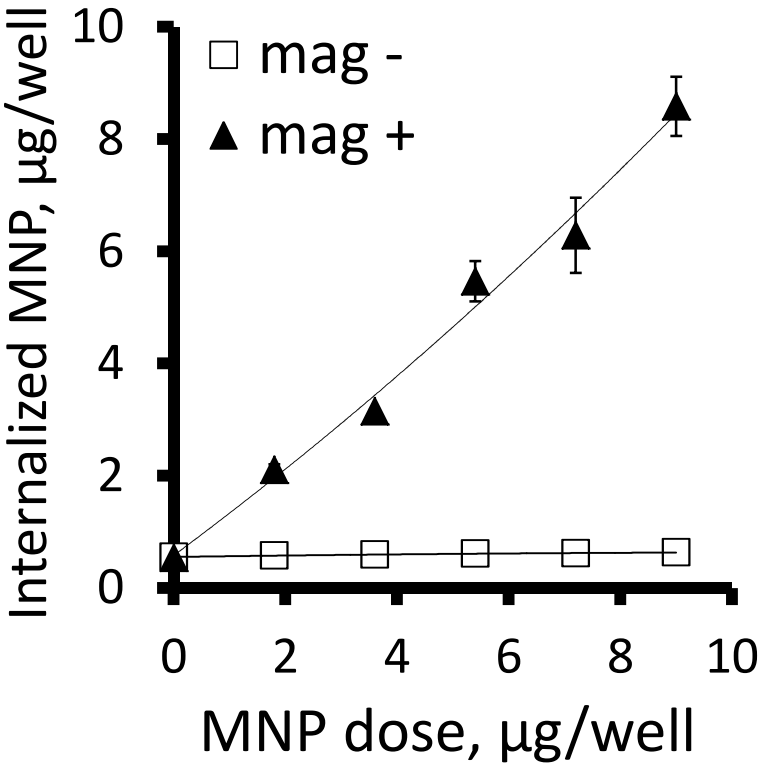
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Rapid restoration of endothelium can prevent restenosis without the side effects caused by DES

- *Autologous endothelial cells / endothelial progenitor cells*
- *Cell-based gene delivery as a combined therapeutic strategy*

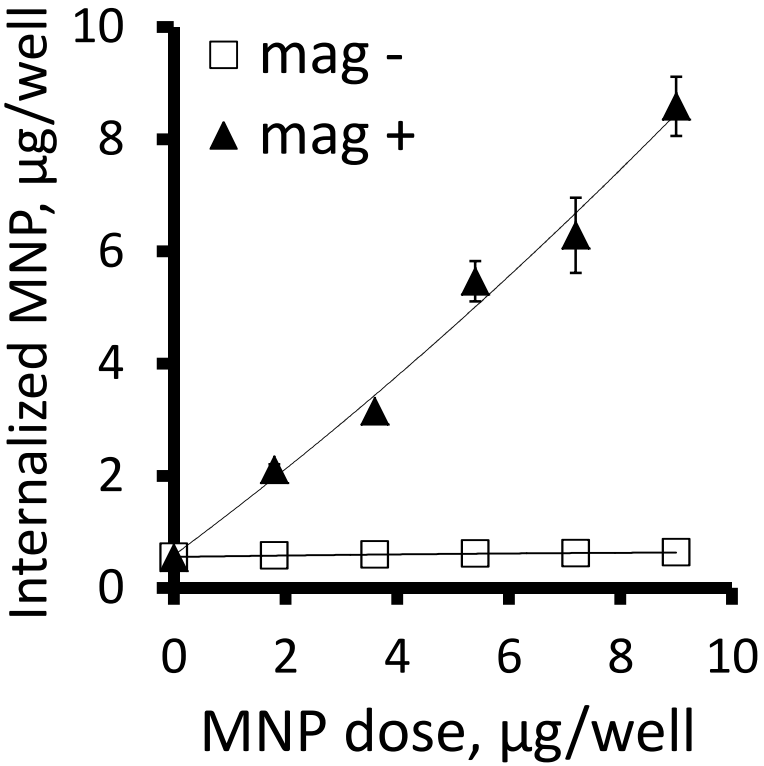
Loading endothelial cells with magnetic nanoparticles

Uptake efficiency (24 hr)

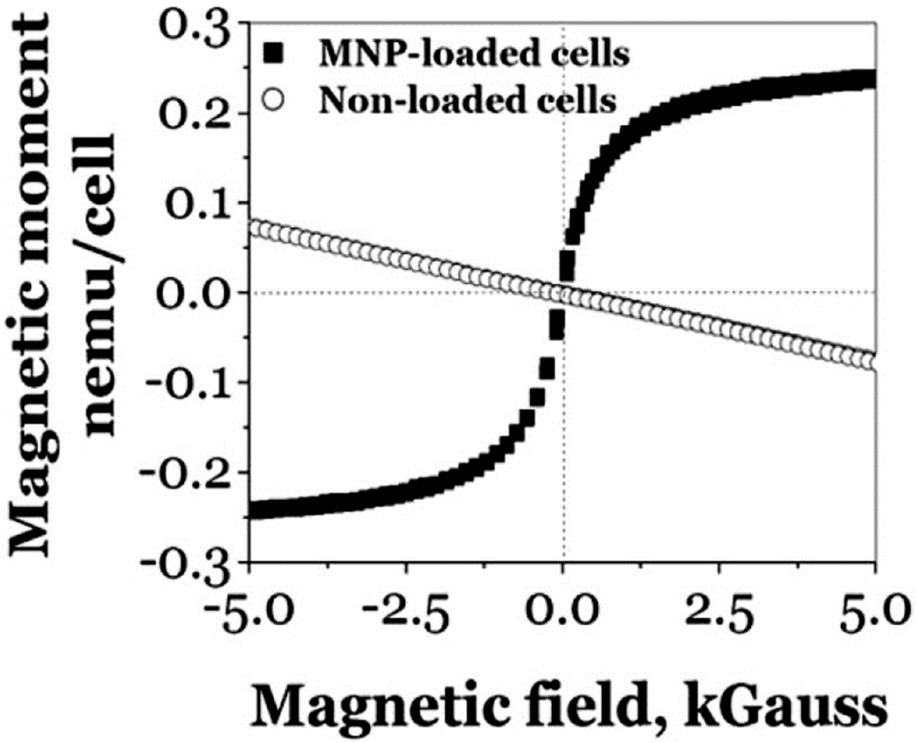


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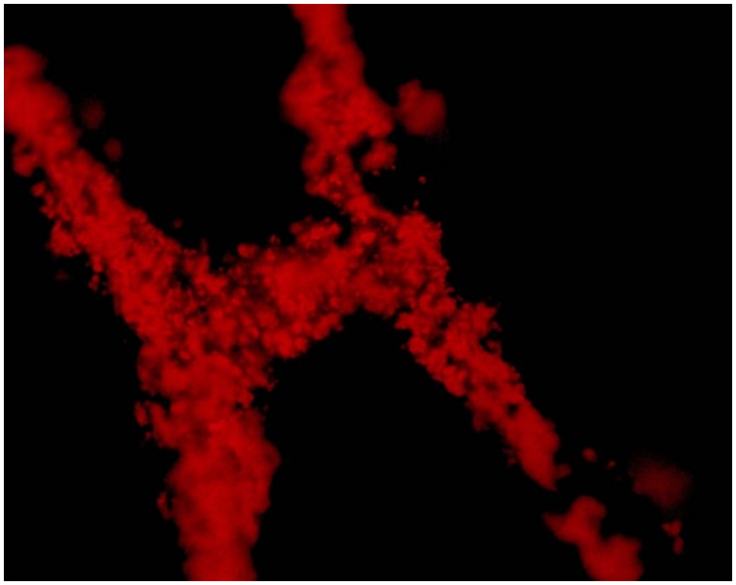
Magnetic properties



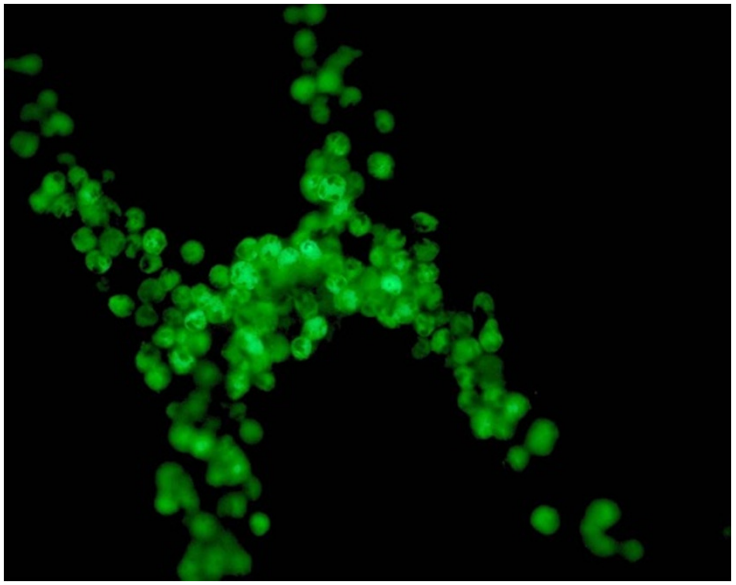
Magnetic targeting of endothelial cells to stents

In vitro **cell capture under flow conditions, 30 ml/min (uniform field, 1000 G, 30 min)**

MNP



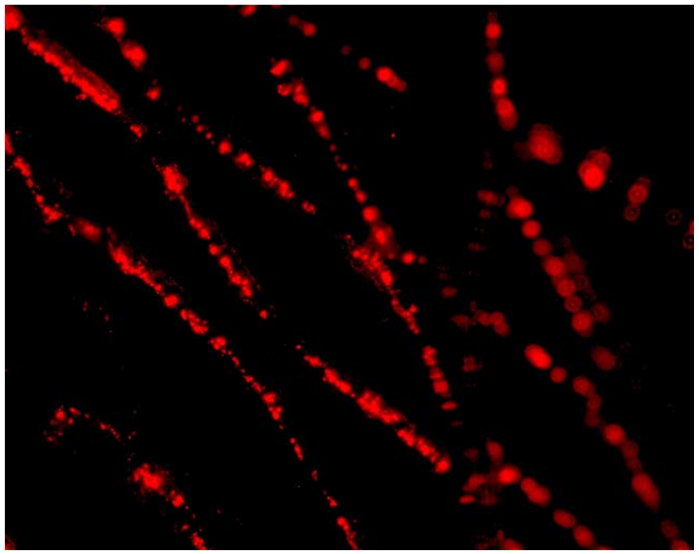
Calcein
(cell viability marker)



Magnetic targeting of endothelial cells to stents

In vivo **cell targeting (rat carotid stenting model) (uniform field, 1000 G, 5 min)**

Mag +



Mag -



Genetically modified cells: targeted delivery feasibility

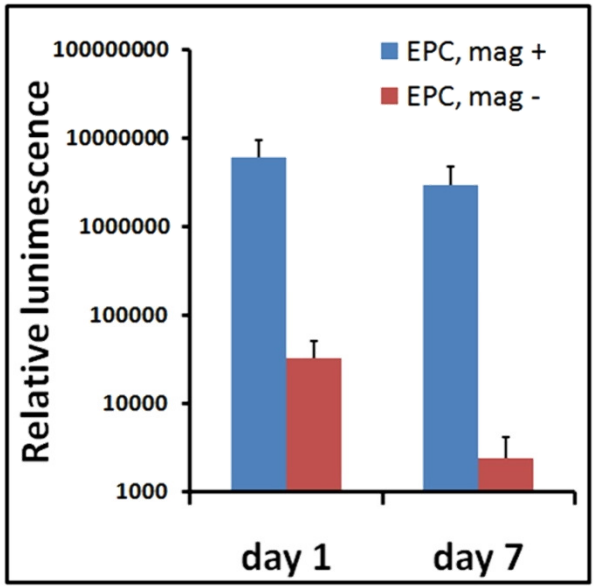
rat carotid stenting model

- Rat endothelial progenitor cells stably expressing luciferase reporter
- 10^5 cells administered via the aortic arch
- Uniform field (1,200 G) maintained over 5 min
- Bioluminescence assayed on days 1 and 7

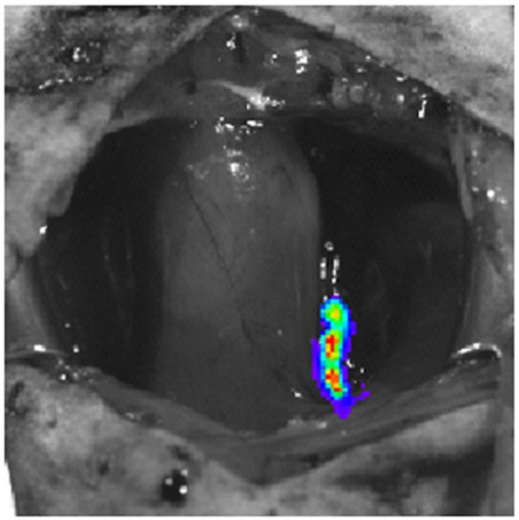
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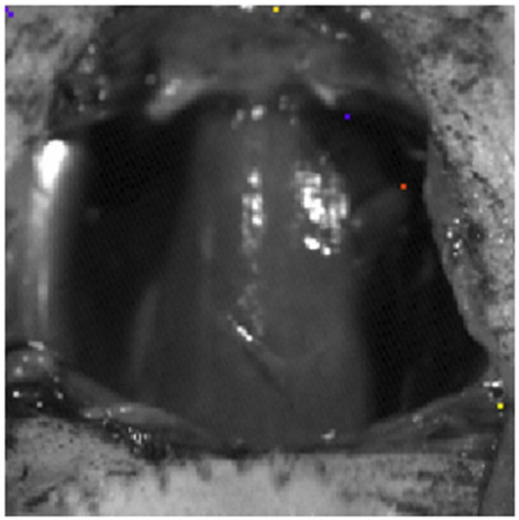
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Mag -



Summary

- *Gene delivery has the potential to provide new treatment strategies for vascular disease and address limitations of currently used therapeutic modalities.*
- *Non-viral or viral gene vectors with different gene expression profiles, tissue specificities and transgene capacities are available. New generations of gene vectors with improved performance and reduced risk of side effects are being continuously developed.*
- *The choice of a vector (or vectors) best-suited for a specific application depends on the spatiotemporal pattern and pathophysiological mechanisms of the condition to be treated.*
- *Further optimization of vascular gene delivery can be achieved through the use of hybrid systems, such as nanoparticle-vector complex formulations and targeted delivery strategies.*

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Thanks' for your kind attention!!!!!!



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