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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

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

Damage and death to heart tissue shown in purple
Angioplasty for obstructive vascular disease
Angioplasty for obstructive vascular disease
Angioplasty with stent placement for obstructive vascular disease

1. Plaque build up in the coronary artery blocking blood flow and oxygen to the heart.
2. Damage and death to heart tissue shown in purple.
3. Balloon catheter is inserted into the artery.
4. Balloon is inflated to expand the stent.
5. Balloon is deflated.
6. Catheter is removed. Stent remains to hold open artery.
Angioplasty with stent placement for obstructive vascular disease

*In-stent restenosis*
Angioplasty with stent placement for obstructive vascular disease

In-stent restenosis
Angioplasty with stent placement for obstructive vascular disease

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In-stent restenosis

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

- Effective in patients with non-complex lesions (risk of ISR < 10%)
Drug Eluting Stents (DES): a clinically used treatment modality for ISR

- **Effective in patients with non-complex lesions (risk of ISR < 10%)**

- **Considerably less effective in complex settings (“off-label” use) with high rates of DES-ISR**
  - *Left main, bifurcation, small vessels, vein grafts, chronic total occlusions, acute coronary syndromes, diabetic patients, etc.*
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• **DES-ISR is less manageable and more challenging than BMS-ISR.**
  – *Clinical recurrences after DES-ISR treatment 2 × those of BMS-ISR*
  – *No established treatment; approached by a “stent sandwich technique”*
Drug Eluting Stents (DES): a clinically used treatment modality for ISR

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  - Clinical recurrences after DES-ISR treatment $2 \times$ those of BMS-ISR
  - No established treatment; approached by a “stent sandwich technique”
- **Prevent proper endothelial healing**
  - Promote stent thrombosis and neointimal hyperplasia
Drug Eluting Stents (DES): a clinically used treatment modality for ISR

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

- Drug choice is defined, the dose and release profile are fixed and cannot be adjusted to the blood vessel anatomy or disease status of specific patients
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Drug Eluting Stents (DES): a clinically used treatment modality for ISR (cont.)

- Drug choice is defined, the dose and release profile are fixed and cannot be adjusted to the blood vessel anatomy or disease status of specific patients
- Clinically used DES cannot be “reloaded” to replenish exhausted drug payload
- **Safety issues**
- **Suboptimal efficacy in real-world patients**
- **Lack of flexibility**
Magnetically Targeted Therapy

Potential advantages as a therapeutic strategy
Potential advantages as a therapeutic strategy

- site-specificity ↔ improved therapeutic index
  (higher local levels, reduced dissemination)
**Magnetically Targeted Therapy**

**Potential advantages as a therapeutic strategy**

- **site-specificity** ↔ **improved therapeutic index**  
  *(higher local levels, reduced dissemination)*

- **flexibility:**
  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
  – Submicronial size
  – Highly magnetically responsive
  – No magnetic memory (remanent magnetization = 0)
Magnetically Targeted Therapy

- Magnetic field source
Magnetically Targeted Therapy

- Magnetic field source
Magnetically Targeted Therapy

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Magnetically Targeted Therapy

- Magnetic field source
Magnetically Targeted Therapy

- Magnetic field source

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

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- **Magnetic field source**
  - Strong, far-reaching magnetic field
  - High magnetic field gradient at the target site
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Two-source magnetic guidance
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- **Two-source magnetic guidance**
  **Primary source**: uniform, deep-penetrating magnetizing field
  (e.g. MRI scanner, magnetic navigation systems or paired electromagnets)

  1. **Magnetizing MNP, Making Them Responsive to Magnetic Force**
Magnetically Targeted Therapy

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• **Two-source magnetic guidance**
  - **Primary source**: uniform, deep-penetrating magnetizing field (e.g. MRI scanner, magnetic navigation systems or paired electromagnets)
    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

Stainless steel stent

Magnetic carrier

Artery

Magnetizing uniform field
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.

Fluorescent conjugates of PLA with BODIPY fluorophores were synthesized for MNP uptake and distribution studies.
Magnetic nanoparticles
design and characterization

TEM

100 nm
Magnetic nanoparticles
design and characterization

**TEM**

**DLS**

- TEM image showing two magnetic nanoparticles with a scale bar of 100 nm.
- DLS graph showing normalized fraction against diameter in nanometers (nm).
Magnetic nanoparticles

design and characterization

TEM

DLS

AGM

Normalized fraction

Magnetic moment, emu/g

Diameter, nm

Magnetic field, kOe

100 nm
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
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

Molecular Weight: 853.9
Solubility: Soluble in organic solvents. Highly insoluble in water and aqueous buffers.
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.

Polymer biodegradation:
Magnetic guidance to stented arteries

*(rat carotid stenting model)*

<table>
<thead>
<tr>
<th></th>
<th>Stent</th>
<th>Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 hr</td>
<td>24 hr</td>
</tr>
<tr>
<td>mag+</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>mag-</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
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</tbody>
</table>
Magnetic guidance to stented arteries

*rat carotid stenting model*

carotid artery

<table>
<thead>
<tr>
<th>Time, hr</th>
<th>MNP, ng per mg tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8000</td>
</tr>
<tr>
<td>50</td>
<td>2000</td>
</tr>
<tr>
<td>100</td>
<td>0</td>
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peripheral tissues

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- mag+
- mag-

- liver
- spleen
- lungs
Magnetic guidance to stented arteries
*(rat carotid stenting model)*

**Antirestenotic effect**

![Graph showing Neointima / Media and % Stenosis](image)
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

<table>
<thead>
<tr>
<th></th>
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<th>Adenoassociated virus</th>
<th>Retrovirus</th>
<th>Lentivirus</th>
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<tbody>
<tr>
<td><strong>Capacity</strong></td>
<td>up to 30 Kbp</td>
<td>up to 5 Kbp</td>
<td>up to 8 Kbp</td>
<td>up to 9 Kbp</td>
</tr>
<tr>
<td><strong>Tissue specificity</strong></td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Transgene expression (peak levels, duration, onset)</strong></td>
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<td>Episomal and integrating, Late onset, Long-lasting expression</td>
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<td>Integrating or episomal, Early onset, Stable or transient expression</td>
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<td><strong>Quiescent cell transduction</strong></td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
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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
Adenovirus (Ad) as a gene vector

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

- 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
Nanoparticles for Ad delivery
Nanoparticles for Ad delivery
Nanoparticles for Ad delivery
Stent-targeted Ad delivery
Stent-targeted Ad delivery
Stent-targeted Ad delivery

- MNP(Ad), mag +
- MNP(Ad), mag -
- Free Ad
Stent-targeted Ad delivery

*MNP(Ad), mag +*  |  *MNP(Ad), mag -*  |  *Free Ad*

![Images of stented artery, liver, and spleen with different conditions: MNP(Ad), mag +, MNP(Ad), mag -, and Free Ad.](image)

Bar graph showing luminescence levels in different tissues:
- Stented artery: MNP(Ad), mag +
- Liver: MNP(Ad), mag +
- Spleen: MNP(Ad), mag -

Luminescence, $\times 10^3$ RLU/mg
Cell therapy for preventing restenosis

**Endothelial cells**
- Form a barrier separating the arterial wall from blood
- Secrete factors necessary for maintaining vascular homeostasis
Cell therapy for preventing restenosis

**Endothelial cells**
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- Angioplasty causes disruption of the endothelium
- Drugs used in DES (drug eluting stents) prevent endothelium regeneration
  - in-stent restenosis
  - thrombosis
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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)

Internalized MNP, µg/well

MNP dose, µg/well

mag -

mag +

Graph showing the uptake efficiency of endothelial cells with magnetic nanoparticles across different doses.
Loading endothelial cells with magnetic nanoparticles

**Uptake efficiency (24 hr)**

- **Internalized MNP, µg/well**
  - □ mag -
  - ▲ mag +

**Magnetic properties**

- **Magnetic field, kGauss**
  - Magnetic moment, nemu/cell
- MNP-loaded cells
- Non-loaded cells
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)
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
Genetically modified cells: targeted delivery feasibility
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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!!!!!!!
Let Us Meet Again

We welcome you all to our future conferences of OMICS International

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http://www.conferenceseries.com/clinical-research-conferences.php