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Responsive Biomaterials

- Oral Protein Delivery
- Oral siRNA Delivery
- Oral Chemotherapeutic Delivery
- Molecular Recognition
- Biotechnology
Bionanotechnology

Externally Responsive Nanoparticles

Gold-polymer nanoparticles
- Laser irradiation leads to polymer collapse and release of therapeutic

Fe3O4 nano-composites
- Temperature sensitive
- Thermal-IR imaging

Nanoparticle localization
- IV injection leads to localization due to leaky vasculature
- Surface chemistry manipulation can improve localization
- Drug carriers can be improved by modification of polymer chemistry

Targeted Delivery and Theranostics

Molecularly decorated, intelligent nanoparticles take advantage of unique phenotypic features of diseased tissues and cells in order to deliver a particle or drug to the site of action.

Targeting Ligands:
- Small Molecules
- Aptamers
- Folate, Transferrin
- Antibodies
- Peptides
- Oligonucleotides

Dual-Delivery Systems

Drug-Resistant Cancer:
- Efflux pumps
- Anti-apoptotic pathways

Drug Delivery System:
- Injectable
- Amine methacrylates
- pKa ~6
- Simultaneous delivery

- siRNA
- Chemotherapeutic
- Poly (ethylene glycol) graft
- Cationic pH responsive polymer
**Background**

**Major Disease Targets and Therapeutics**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Therapeutics</th>
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<tbody>
<tr>
<td>Multiple Sclerosis</td>
<td>Interferon-β</td>
</tr>
<tr>
<td>Crohn's Disease</td>
<td>&quot;High Isoelectric Point Drugs&quot;</td>
</tr>
<tr>
<td>Cancer</td>
<td>Chemotherapeutic Agents, siRNA, Interferon-α</td>
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<tr>
<td>Ulcerative Colitis</td>
<td>siRNA</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>siRNA</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Calcitonin</td>
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<tr>
<td>Hemophilia</td>
<td>Hemophilic Factor IX</td>
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<tr>
<td>GHD, Turner's Syndrome, Prader-Willi Syndrome</td>
<td>Human Growth Hormones</td>
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</tbody>
</table>

**Highlight of Recent Patents**

**Hemophilia**

Treatment of hemophilia B, a bleeding disorder, relies on i.v. injections/infusions of blood clotting protein, factor IX.

**Goal:** To improve hemophilia B treatment by offering a convenient, needle-free, and accessible protein replacement therapy.

**Objective:** To develop a pH-sensitive polymeric carrier for the oral delivery of factor IX.

**Carrier System:** P(MAA-g-EG) Crosslinked poly(methacrylic acid)-grafted-poly(ethylene glycol)

**Stomach (pH 2)**

**Intestine (pH 7)**

**Oral Delivery of High Molecular Weight Proteins**

- Insulin 5.8 kDa
- Factor IX 57 kDa

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**Osteoporosis**

Proteins exhibiting a high isoelectric point present delivery challenges due to charge interactions with our carriers.

- **Salmon Calcitonin**
  - Osteoporosis medication
  - Cationic in small intestine
  - Anionic hydrogels

Nearly half of all proteins exhibit high isoelectric point, as do many best-selling drugs.

**Notable High \( p_I \) Drugs:**

- Humira
- Enbrel
- Remicade
- Avastin
- Herceptin
- Lucentis

**> $72 Billion sales**

Using P(IA-co-NVP) hydrogels, we can deliver therapeutic levels of salmon calcitonin, in 1 daily capsule.

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**Growth-Related Disorders**

**Human Growth Hormone**

Replacement therapies can aid in the treatment of the following pediatric disorders:

- Growth hormone deficiency
- Turner's Syndrome
- Prader-Willi Syndrome

**Research Goal:** To develop a pH-responsive polymeric system for the oral delivery of hGH to replace once daily injections.

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**Methacrylic Acid**

**N-vinyl pyrrolidone**

**Tethered mucosal adhesive molecules**

**Poly(ethylene glycol) Dextran**

**Tetra- or polyethylene glycol dimethacrylate**

**Increased Residence Time**

**Swelling Behavior**

**pH-response**

**Hydrophilicity**
**Oral siRNA and Chemotherapeutics Delivery**

**Chemotherapeutics**

**Goal:** To improve treatment efficacy and patient quality of life by increasing the solubility and permeability of hydrophobic therapeutics.

**Oral delivery platform:** Grafted, copolymer network for delivering hydrophobic therapeutics (e.g., doxorubicin).

**siRNA**

<table>
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<th>Preserving biological activity in harsh pH and enzymatic conditions</th>
<th>Facilitating intracellular uptake and endosomal release</th>
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<td>Mitigating off-target gene silencing</td>
<td>Effective RNAi-mediated gene silencing</td>
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</table>

**Challenges to the oral delivery of siRNA**

**Two-Part Oral Delivery of siRNA**

1. **Intestinal Delivery**
   - Microgels protect nanogels and siRNA
   - Microgels swell, undergo enzymatic degradation, and release nanogels

2. **Intracellular Delivery**
   - Polycationic nanogels facilitate cellular uptake, siRNA release, and endosomal escape into the cell cytosol.
   - Right: Nanogels (green) internalized by RAW 264.7 cells.
Oral Vaccine Delivery

- Improve vaccine safety
- Controlled release biomaterials
- Controlled release of antigens
- Increase "pathogen-like" properties
- Protein-based antigens
- Stability and tailored release of antigens
- Appropriate antigen processing and presentation
- Induce systemic and mucosal immunity via oral delivery
- Enhancement, modulation of immune response

Proposed Solution: Dual system for targeted oral vaccine delivery

Polyanhydride nanoparticles as antigen carriers

Degradable anionic microgels for oral delivery
Molecular Recognition

Functional monomers are polymerized in the presence of a biomolecule of interest. Following purification, these polymers have recognition moieties. Applications include \textit{low cost biosensors and drug delivery systems}.

Imprinted particles preferentially bind template proteins.

Specificity is achieved through numerous non-covalent interactions between templates and functional monomers.

Bulk Imprinting: Small molecules for SMART drug delivery

Core-Shell Imprinting: Proteins for diagnostic applications

Surface Imprinting: Cells for applications in regenerative medicine
System-Responsive Therapy:  A Bright Future

- Need for advanced intelligent materials, more reliable devices, miniaturized systems
- Society asks for improved treatment of disease, advanced detection and therapy, and cost effective processes
- Improvement of quality of life is important