State of the Art Symposium: Bench to Bedside

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- Los Angeles, CA, USA
Disclosure:

Yes, within the last 12 months, I have/had a financial arrangement or affiliation with commercial interests related to the content of this continuing education activity that requires disclosure.

O-Ray Pharma: CEO

No Drug has been approved by FDA for treatment of inner ear disorders

Grants, Research Support, Speakers Bureau, Consultant, Stock Shareholder, Other Financial or Material Support
Bench to Bedside

1. DISCOVERY
   - IDEA
   - BASIC RESEARCH
     The majority of the research at this stage is publicly funded at universities, colleges, and independent research institutions in every state.

2. DEVELOPMENT
   - CLINICAL TRIALS
     Once a disease target is identified, drugs are designed and tested. Both public and privately funded research are involved.
   - PHASE I
   - PHASE II
   - PHASE III

3. DELIVERY
   - REGULATORY APPROVAL
     Human trials are completed. FDA approval. Industry is responsible for bringing a drug to market. Safety and evaluation continue after approvals.

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Disease Target: Otology?

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IDEA

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PATIENT CARE
### Inner Ear Fluid Space Dimensions

#### Entire Inner Ear

<table>
<thead>
<tr>
<th>Value</th>
<th>Species</th>
<th>Source</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD 24.4, n=46</td>
<td></td>
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</tbody>
</table>

**Volume of Blood** = 5 Liters (5,000,000 ul)  
25,000 time the volume of the cochlea
Drug Delivery to the Cochlea

- Targeting of Cochlear tissue
  - How does drug get to cochlear tissue?
  - What pathway is drug targeting?

- Sustained Delivery of Drug
  - Half life of drug?
    - What is Initial dose of drug
    - How fast is drug removed?
  - Effect of drug on target pathway?
O-Ray Technology

Extended Release Particles

- Solid Drug
- Polymer Coating
- Controlled Release

**Release Rate:**

- Solubility of Drug
- Surface Area
- Permeability
- Coating

Implantation: Dry Particles

Injection: Suspension of Particles

100 micron particle
# Examples of Substances Used

<table>
<thead>
<tr>
<th>Drug Highlighted:</th>
<th>Description:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Small molecule antiviral.</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Small molecule broad spectrum antibiotic.</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Peptide used to prevent graft rejection.</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Small molecule steroid (anti-inflammatory).</td>
</tr>
<tr>
<td>Dexamethasone-Acetate</td>
<td>Small molecule steroid (anti-inflammatory).</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Small molecule used to treat Alzheimer's.</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Hormone used in contraceptive devices.</td>
</tr>
<tr>
<td>Etonogestrel</td>
<td>Hormone used in contraceptive devices.</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Small molecule steroid (anti-inflammatory).</td>
</tr>
<tr>
<td>Gentamicin Sulfate</td>
<td>Small molecule antibiotic used in the ear to treat Meniere's Disease.</td>
</tr>
<tr>
<td>Immunoglobulin G (IgG)</td>
<td>Biologic (antibody).</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Small molecule used to treat schizophrenia.</td>
</tr>
<tr>
<td>Remicade (Infliximab)</td>
<td>Biologic (antibody) used in the ear to treat autoimmune inner ear disease.</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Biologic small molecule Receptor Tyrosine Kinase inhibitor.</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Macrolide lactone molecule used to prevent graft rejection.</td>
</tr>
<tr>
<td>Tetracaine-HCl</td>
<td>Small molecule used for topical pain relief.</td>
</tr>
</tbody>
</table>
Intracochlear Delivery

- Direct administration into the cochlea through the round window membrane or in combination with device implantation
- Initial formulations – steroids
- Indications:
  - AIED
  - Cochlear Implants
  - Meniere’s Disease
  - NIHL
  - Ototoxicity (Drug Induced)
  - Sudden Hearing Loss

Intracochlear Pellet
Intra-cochlear Surgical Implant

Round Window Identified
O-Ray Pharma Surgical Implant

Sterile O-Ray Implant
Intra-Cochlear Surgical Pellet

Implant Sitting on Round Window  Round Window after insertion
Fluticasone: Intracochlear Delivery

*In vivo* Fluticasone Release and Safety

![Graph showing concentration vs time for Study 1 and Study 2.](image)

![Bar chart showing ABR LS Means for different time points.](image)
Fluticasone: Intracochlear Delivery

*In vivo* Presbycusisis Preliminary Results

Presbycusis:
- Apoptosis (hair cells and neurons) plays significant role in progression
- Reactive Oxygen Species (ROS) can play a major role in progression
- Influenced by lateral wall disfunction leading to an imbalance of metabolites
- O-Ray Steroid implant decreased age related hearing loss in animal study
Fluticasone: Intracochlear Delivery

*In vivo* Extended Release Fluticasone Efficacy: Cisplatin Otoprotection

![Graph showing ABR Threshold comparison between No Surgery and Implant groups before and after cisplatin treatment.](image-url)
Implantation of Fluticasone ER Electrode (OR-505CI) – *in vivo*, four weeks

*In vivo* OR-505CI Efficacy – Electrode Insertion

![Graph showing ABR threshold shift for different frequencies with dummy and dummy + OR-505CI conditions.]
Dexamethasone: Inner, Middle and Inner Ear

Tunable *in vitro* Extended Release:

* Other formulations 90+ days *in vitro*
Histology (SEM):
Scanning electron microscopy of inner ear hair cells following intracochlear OR-406 (dexamethasone)

Results: No difference in cochlear hair cells with dexamethasone present
O-Ray Pharma

- Target Disease: Steroid responsive AIED
- Autoimmune Inner Ear Disease
- Orphan Status for AIED
- IND submission
- Phase 1 trial to begin Q4 2019 or early 2020