Challenges in Development

1. Is the drug designed to protect hearing from aminoglycoside-, cisplatin/carboplatin-, or noise-induced ototoxicity?
2. What are the financial considerations? What is the intellectual property status?
3. How will it be delivered?
4. In which species is it safe and effective?
5. Has it been used in humans?
6. Is it approved by the FDA for other purposes? Are similar drugs approved?
7. Which clinical trial populations are available?
8. What is the timeline for development?

Which Ototoxic Indication?

The most common indications are aminoglycoside, cisplatin/carboplatin, or noise-induced ototoxicity.

Each indication has its special considerations and challenges. In some cases, it may be desirable that an otoprotective drug work across all areas. For example, an immunosuppressed patient on chemotherapy may need an aminoglycoside for a resistant strain hospital infection. Or a soldier with NIHL may also require an aminoglycoside for an infection. Some patients on chemotherapy may be noise exposed at work or recreationally.

A drug that protects against NIHL but exacerbates aminoglycoside induced hearing loss may not be the best drug for all patients.
Challenges for Aminoglycoside Otoprotection Development

• If given systemically, extensive testing is needed in vivo and usually in vitro to determine if the drug interacts with the aminoglycosides in bacteria. This testing must be done for each aminoglycoside and for a wide variety of target pathogens. The tests are very expensive and time consuming and require specialized labs for infectious agents.
• If the protective agent is given directly to the round window, will it be effective in the presence of otitis media, common in infectious disease populations?
• Aminoglycosides are frequently given over a period of weeks and stay in the cochlea for prolonged periods. How long will the otoprotective agent need to be administered?
• The highest rate of aminoglycoside induced ototoxicity is in impoverished countries. Pharmaceutical companies have little incentive to develop products for the market and may not be able to recover their development costs.
• Clinical trials in developing countries are challenging. The stringent infrastructure for clinical trials may not be present.
• One area has been to develop new aminoglycosides with less toxicity to reduce the need for a protective agent.

Challenges for Cisplatin/Carboplatin Otoprotection Development

• If given systemically extensive testing is needed to ensure that the protective agent does not reduce or inhibit the tumor kill for the target tumors. Are sufficient numbers of patients available? Are enrolled patients already committed to studies for other agents? Do you need to go through a cooperative study group?
• If the protective agent is given directly to the round window, will it be effective in the presence of otitis media, common in immunosuppressed populations and children in general?
• These patients can be fragile. Side effects must be minimal. Palatability is critical in nauseated patients.
• Markets could be high. The FDA has incentives for orphan drugs and for pediatric approvals.
• US Clinical trial sites exist, including networks if you can access them.

Challenges in Development for Long Term Noise Induced Hearing Loss

• For many noise exposed populations, the exposure continues for years. Therefore the drug must be safe over a period of years for that type of exposure. Safety data and clinical trials over long periods of time can be expensive and time consuming. Attrition can be high. Patent clocks run out.
• Other factors affecting hearing are likely to impact results over long time periods.
• Same issues for age related hearing loss.
Challenges in Development for Short Term Noise Induced Hearing Loss

- For most of these populations the focus is on reducing exposure and increasing protection as it should be.
- For blast injury, the populations have highly variable and unexpected exposures rendering it difficult to compare treated and control groups or even to access the population.
- Protective agents are more likely to prevent or treat metabolic rather than mechanical damage.
- Clinical trials in the military have an extra layer of rules and regulations.
- TTS clinical trials may or may not predict PDS protection but even if they do, they may not be sufficient for PDS approval.
- TTS clinical trials inducing TTS for study are controversial.

Systemic Versus Round Window Delivery

- Systemic:
  - May have beneficial effects throughout the body such as nephrotoxicity for cisplatin or aminoglycosides.
  - If oral, the drug must survive the digestive system and first pass through the liver. Oral bioavailability may be limited by formulation.
  - If given iv, extensive testing is needed for compatibility with all materials and possible injection site reactions.
  - Greater likelihood of systemic side effects.
  - Greater likelihood of interfering with patient’s other medical conditions or medications.

Round Window or Transtympanic Delivery

- If injected through the round window, how will the amount of drug actually administered to each round window be measured? Round window access can vary from animal to species and be variable by individual.
- If a longer term administration is given, by gel, by pump, or other system, will it stay in place? Will the drug migrate through the Eustachian tube affecting other body areas? Could it be swallowed?
- Can it be placed when and in the patient it is needed? (e.g., battlefield injury, at sea, in a small child)
- Does the drug irritate mucosal tissues of the middle ear? Will repeated injections or placement damage the tympanic membrane?
- What happens in the presence of otitis media?
- Will placement mechanically reduce hearing?
- Will placement in the target population require sedation?
- Who is qualified to place it? (e.g., medical versus otolaryngologist)
Which species?

- For noise induced hearing loss studies, chinchillas are frequently used because, unlike most rodents, their hearing is very similar to humans. But they have poor renal function and are therefore not suitable for cisplatin or other drugs which require renal clearance.
- Rats are hardy and used for many cisplatin studies and some noise studies but have a much higher frequency range of hearing than humans.
- Guinea pigs are the most common model for aminoglycosides but pigmented guinea pigs are no longer available for research, which makes it difficult for them to be used in clinical studies.
- Mice have the most defined genetics but the histology is more difficult and a wide variety of strains must be considered for each application.
- If a drug is safe and effective in multiple species, that is a good sign. But you never want to waste animals.
- Animal models are essential and form the basis for virtually all of the effective medicines we all use every day.

Has the Study Drug Previously Been Used in Humans? Is it FDA Approved for Another Purpose?

- If a drug has previously been used in humans, that provides an enormous advantage because information in the target species exists.
- If the drug is an FDA approved drug for any purpose, that means that both safety and efficacy, at least for one purpose have met the rigorous FDA standards.
- The clinical development program for an FDA approved drug is much easier, even if the drug is for a new purpose. That does not mean that an FDA approved drug can automatically be promoted or used for another purpose but it does mean that the development program for the new application can draw from the extant information.

Is the New Drug Similar to Other Drugs?

- If the drug is of a similar class to other approved drugs, that does not mean it is the same as an approved drug.
- The class of drug may help guide the types of testing needed for the new drug.
- For example, a new aminoglycoside or platinum based chemotherapeutic may be required to test for hearing loss in clinical trials even if the pre-clinical animal studies did not show ototoxicity.
What is the Timeline for Development?

- Patents only last 20 years (although some extensions may be available in some cases)
- Considering that developing a new drug through FDA approval may cost more than $2 billion dollars, a sufficient number of patent years need to remain for the company to not just recover its cost and make a profit. The profits will probably also need to cover the drugs they developed that did not get approved.
- Therefore clinical trials extending over many years may not be viable. The time pressure can be high.

Clinical Trials Process

Phase I: Checking for Safety

- Small Group (usually 20-80) of healthy volunteers
- First few patients
- Single dose or three or more repeated doses
- Single or double-blind design
- Not be randomized or stratified
- Determine pharmacokinetics (how the body affects the drug) and pharmacodynamics (how the drug affects the body)
- Explore drug concentration and drug measurements
- Safety studies
- If a study is extended to a larger population it is referred to as a Phase II study and the phase 1 study is called a Phase I pilot.
Phase O - Microdosing

- Some clinical trials may include a Phase O.
- Small group (10-15) of healthy volunteers
- Single micro-dose
- Determine if PK and PD profiles are as predicted from pre-clinical research
- Enable researchers to quickly decide which drug candidates will undergo further development
- Little or no safety or efficacy data
- Speeds the development of drugs

Adapted from: SOCRA (Society of Clinical Research Associates) presentation, Chicago 2011

Phase 2: Checking for Efficacy

- Small group (usually 100 – 300) of patients
- Open-label or blinded; usually randomized
- PK studies to assess behavior of drug in patients with target disease
- Assess therapeutic efficacy in patients with target disease
- Define safety profile in patients
- Determine dosage schedules for subsequent studies
- Provide basis for confirmatory studies

Adapted from: SOCRA (Society of Clinical Research Associates) presentation, Chicago 2011

Phase 3: Confirm Findings in Large Patient Population

- Large group (usually 1000 – 3000) of patients with the target indication
- Comparative study with placebo or similar drugs already on the market
- Nearly always blinded or randomized
- Confirm efficacy
- Establish safety profile
- Establish dose/response relationship
- Provide basis for risk/benefit assessment
- Provide support for planned marketing claims

Adapted from: SOCRA (Society of Clinical Research Associates) presentation, Chicago 2011
Phase 4: Testing Long Term Safety in a Diverse Patient Population

- Start this phase after FDA approval
- Real-life patients in a clinical environment
- To optimize the use of the drug with the approved indication
- Evaluate the efficacy and tolerability in this larger very diverse group of patients
- Also called 'Post-Marketing Surveillance Studies'

Adapted from: SOCRA (Society of Clinical Research Associates) presentation, Chicago 2011

Purpose of an IND

- It affirms a body of knowledge about the manufacturing, pharmacology, and toxicology of the drug to support its use in human testing
- Requires that the clinical investigation be performed in accordance with Good Clinical Practice (GCP)
- Provides an additional level of protection through FDA oversight. The FDA's review focuses on safety of human subjects and ensuring that the studies will produce useful information to assess safety and efficacy of the test product

Source: Translational Research Program | www.childrenshospital.org/trp

When an IND is Required?

- New drug or biologic product
- New use of an approved drug or biologic
- New use of a combination of an approved drugs or biologics
- Combination products in which the components are physically, chemically or otherwise combined and the primary mode of action is due to the drug or biologic

Adapted from: Louise Johnson, M.S. INVESTIGATIONAL NEW DRUG APPLICATION (IND) Requirements for Filing and Contents May 18, 2010
When an IND is not Required for Drugs and Biologics

- Study of placebo
- Study of approved drug or biologic used under the approved label
- When it falls under the DSHEA Act

DSHEA (Dietary Supplement and Health Education Act) of 1994

- Enacted to "preserve the consumer's freedom to choose dietary supplements"
- Defines dietary supplements as food and not drugs
- Defines permissible labeling claims and places the burden of proof on the FDA to show that a product is unsafe
- Just because a product is in a health food store does NOT mean it is healthy
- Things that are safe in low doses may NOT be safe at high doses
- Drug interactions with systematic other medications are ignored
- Some herbs can interact with some drugs
- The DSHEA act does not require any labeling statements on dietary supplement products
- The DSHEA act does not allow a supplement to be promoted to treat or prevent any disease (including hearing loss)

Questions and Comments