



Preclinical Otic Models at CBI

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COMPARATIVE BIOSCIENCES, INC.
A TRANSLATIONAL APPROACH TO PRECLINICAL RESEARCH

COMPARATIVE BIOSCIENCES, INC.

Premier Preclinical Contract Research Organization

- **Focus on Ears and Eyes**
- Over 20 years of experience
- Conveniently located in the heart of Silicon Valley, amidst many biotech companies
- State of the art, purpose-built facility
- Approximately 30 employees
- Highly experienced staff
- GLP, OECD, FDA, USDA, OLAW
- AAALAC Accreditation

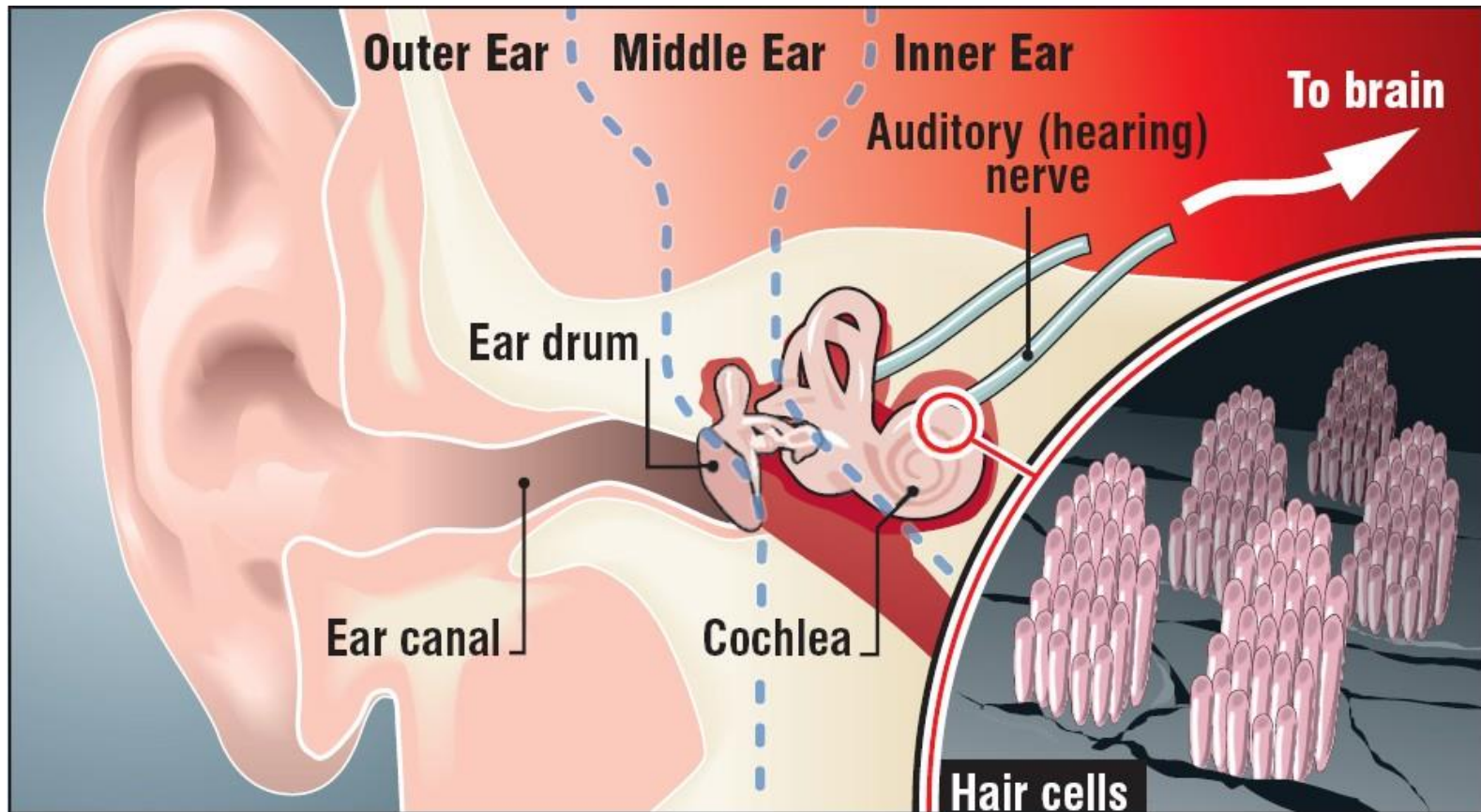


Otic Studies at CBI

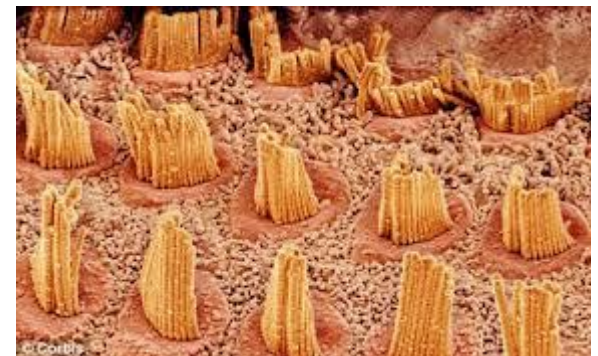
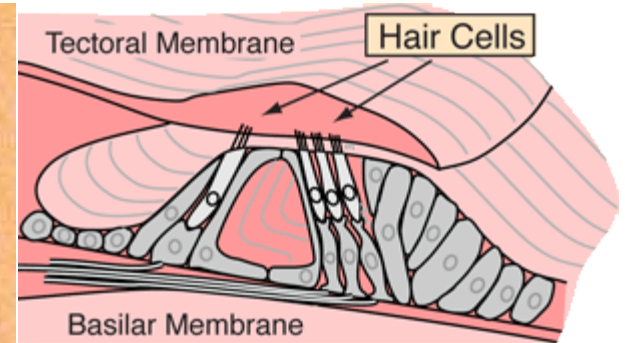
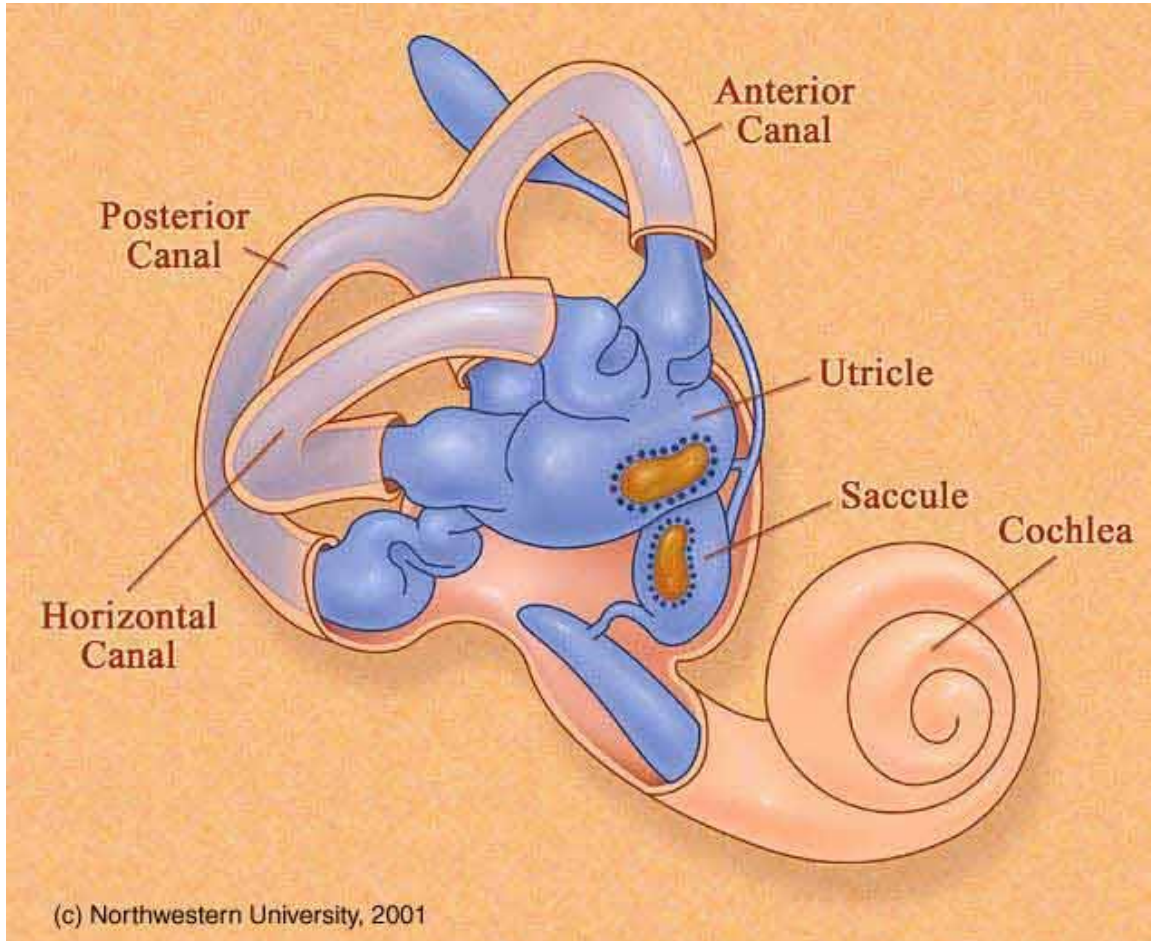
- CBI is one of the few CROs which provide specialized otic preclinical studies
 - Research studies
 - GLP, IND enabling studies
 - Efficacy, pharmacokinetics, and toxicology
 - Histopathology
 - Multiple species-rodents, guinea pigs, chinchillas, pigs, dogs, cats



Schematic of human ear. The ear is a complicated structure and is subject to a variety of disorders.



Schematic of Complex Anatomic Structures Within The Ear



Comparison of skeletal anatomy of guinea pig vs rat



Figure 1. A) Guinea pig's skull base showing the tympanic bullas (lower view) (millimeter scale); B) Rat's skull base showing the tympanic bullas (lower view) (millimeter scale); C) Lateral left-side view of a young guinea pig's skull (millimeter scale); D) Lateral left-side view of a young-adult rat's skull - (millimeter scale). 1 - Bulla; 2 - External auditory canal; 3 - Squamous bone; 4 - Posterior air Sinus notch; 5 - Anterior air sinus; 6 - Para-occipital apophysis.



Gross and Correlative Histology of Cochlea

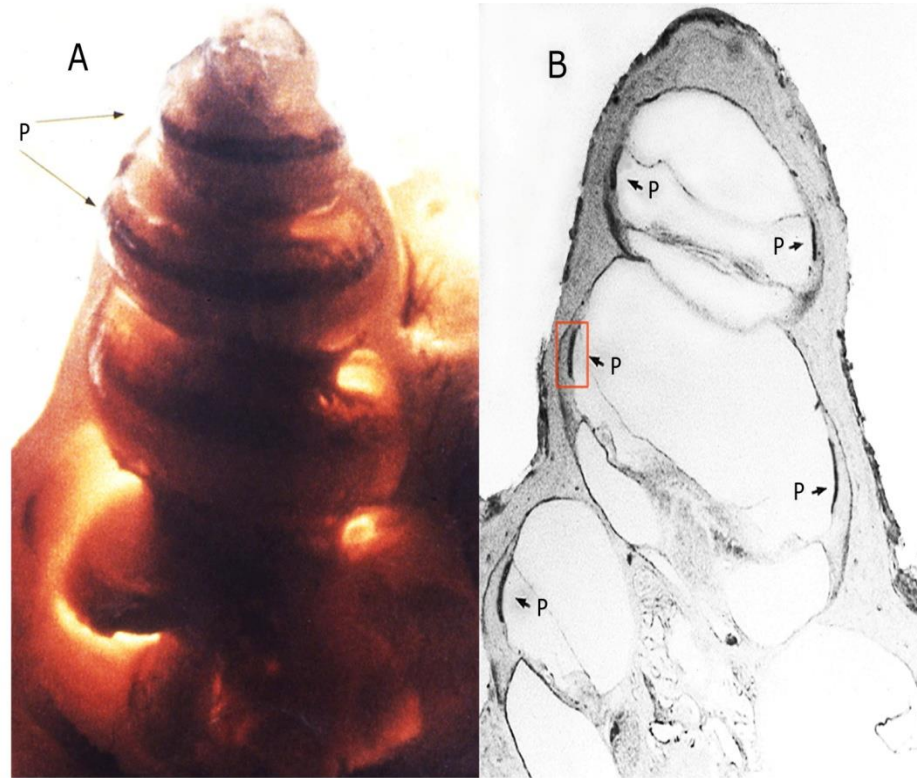
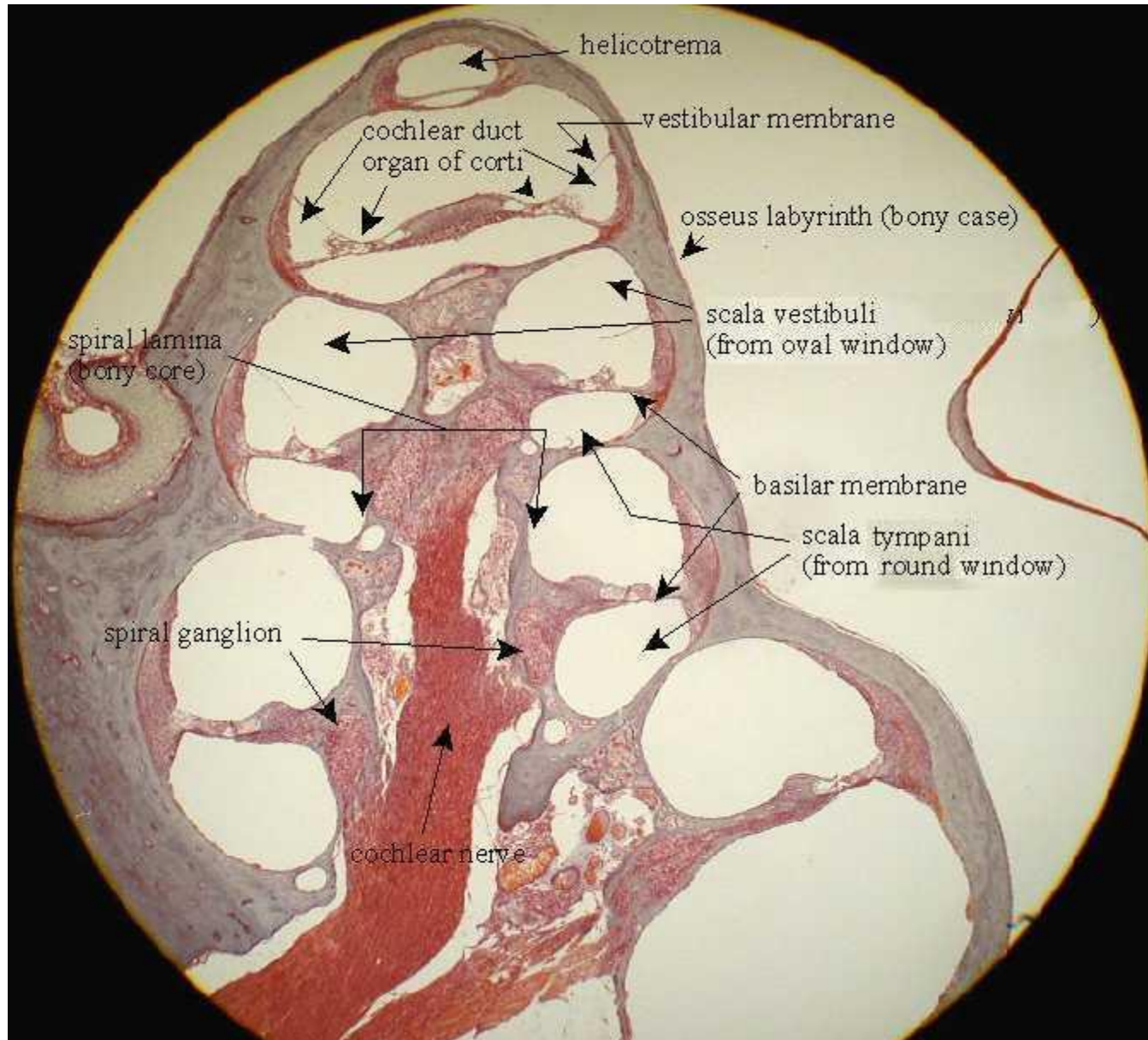


Figure 22. Decalcified guinea pig cochlea (A) and sagittal section (B) through a guinea pig cochlea show deposition of melanin pigment (P) in stria vascularis. Red boxed area enlarged in Figure 23.





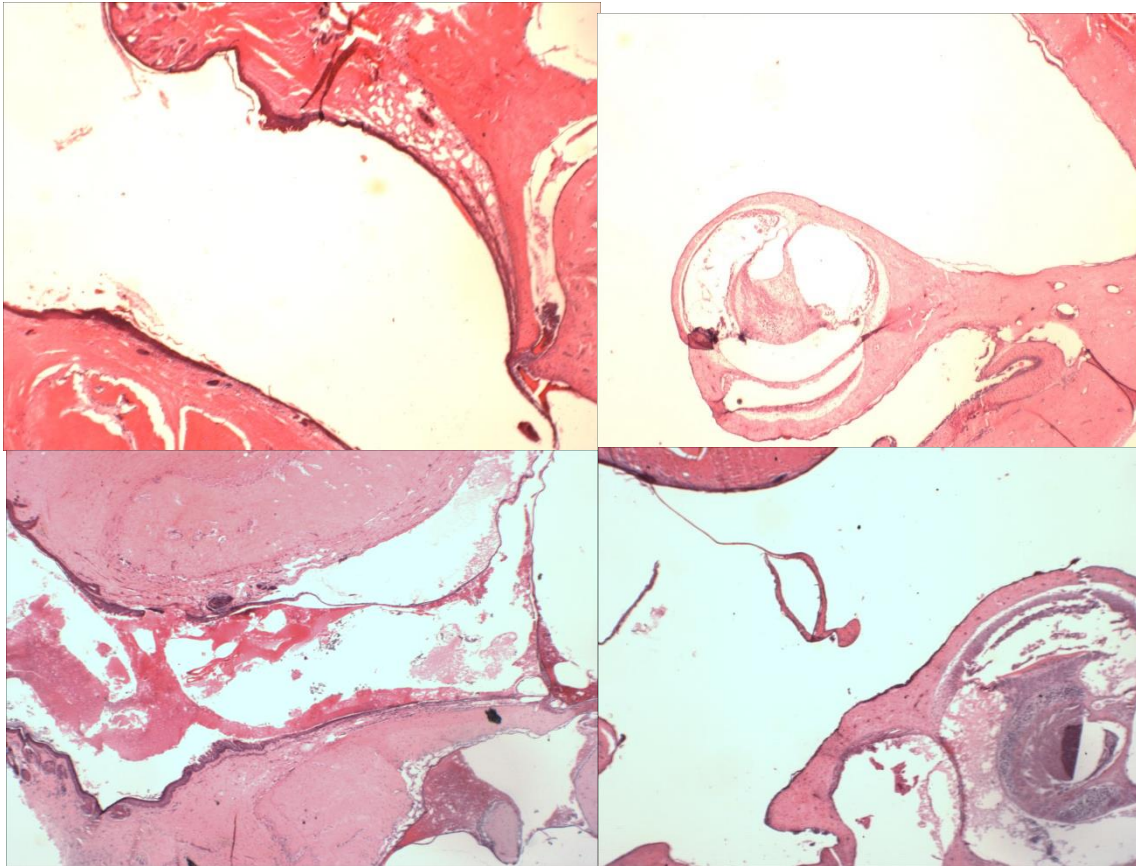
Otic Pharmacology

CBI offers otic toxicology, pharmacokinetic and pharmacology capabilities

- Wide range of otic pharmacology and efficacy studies
- Inflammation
- External ear effects, irritation, infection, parasitism
- Tympanic membrane perforation
- Infection of the external or internal ear
- Middle and inner ear damage, acoustical damage
- Otic implants
- Custom studies



External and Middle Ear Inflammation



- Top: normal ear canal and middle ear
- Lower: inflamed ear canal, ruptured ear drum and middle ear inflammation



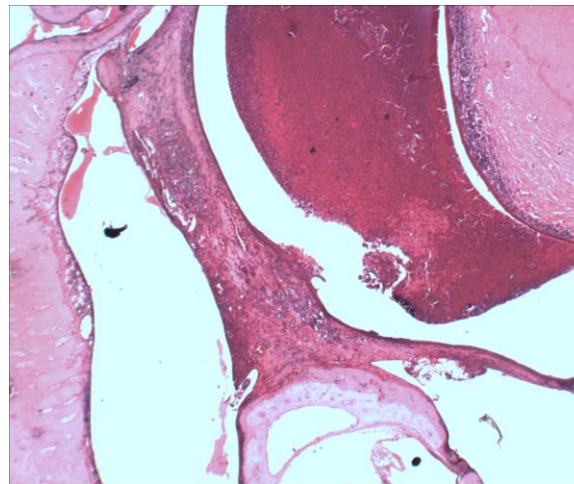
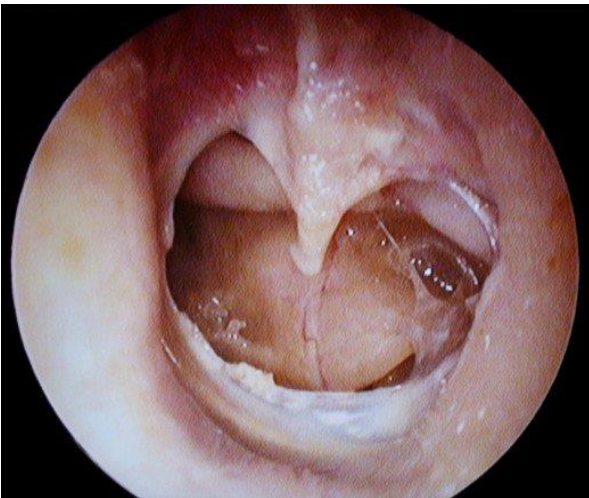
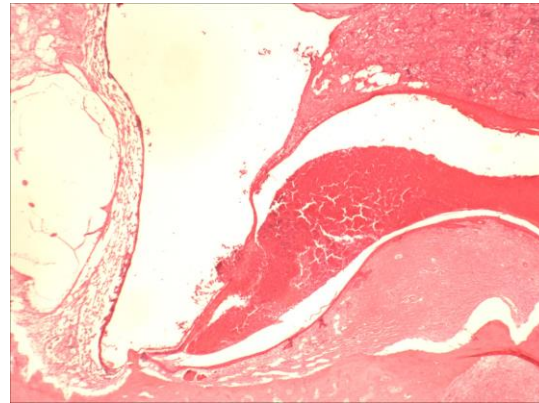
Ear Drum Perforation

- Chinchilla or Guinea pig are common species
- Tympanic membrane is perforated surgically
- Tympanic membrane may be visualized with otoscope
- Auditory Brain Response Test indicates sudden complete loss of hearing
- Heals over several weeks and ABR improves
- Test article effects and tolerability may be tracked and evaluated



Ear Drum Perforation

DATE: 19. 04. 07 TITLE:
TIME: 13. 54



- Top left: normal
- Lower left: perforated ear drum
- Top right: acute puncture with hemorrhage
- Lower right: 2 weeks repair of ear drum



Otic Pharmacokinetics

CBI offers otic toxicology, pharmacokinetic and pharmacology capabilities

- Otic and other routes of delivery
- Special otic assessments
- Perilymph collection
- Bioanalytical method development and transfer
- Tissue and fluid collection from different subparts of the ear
- Complete, prompt reports



Perilymph Collection

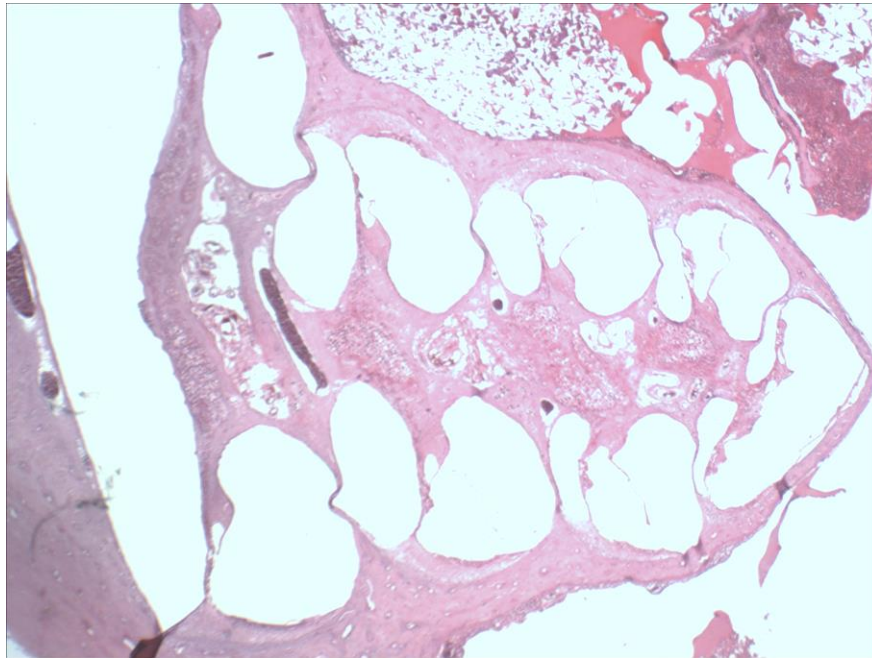
- Collection of the perilymph is part of otic pharmaco-and toxicokinetics
- The cochlea is punctured with a fine point and the fluid is aspirated with a micropipette of capillary tube
- The fluid is analyzed as per protocol
- CBI has a 90% success rate in collection of perilymph fluid



Perilymph collection: The cochlea is exposed, and a cannula is introduced into the cochlea and fluid collected



Histology of Cochlea During Perilymph Collection.



Left-normal cochlea. Right-puncture of tip of cochlea to allow for collection of perilymph.



Otic Toxicology

CBI offers otic toxicology, pharmacokinetic and pharmacology capabilities

- Acute, subacute and chronic toxicology studies
- Discovery and investigative toxicology studies
- Ototoxic compounds and treatment of ototoxicity
- Ototoxic effects of test articles
- Specialized routes of delivery
- Special otic assessments
- Complete, prompt reports



Assessment of Ototoxicity by Test Compounds

- Some classes of compounds damage the ear as a part of their general toxicity
 - Anti-infectives-Aminoglycosides (kanamycin, gentamycin)
 - Chemotherapeutic agents (carboplatin and cis platin)
 - NSAIDS
 - Cardiovascular drugs
 - Neurologic drugs



Assessment of Compounds for Ototoxicity

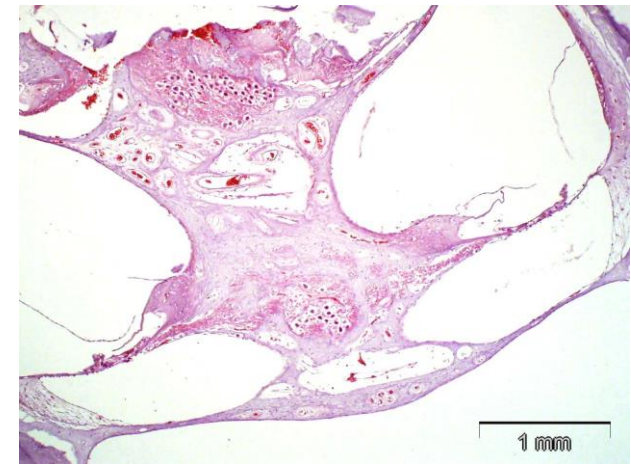
- Dose response of ototoxic effects
- Positive controls include aminoglycosides
- Assessments include ABR, clinical signs, histopathology, hair cell analysis



Histopathology of the Ear

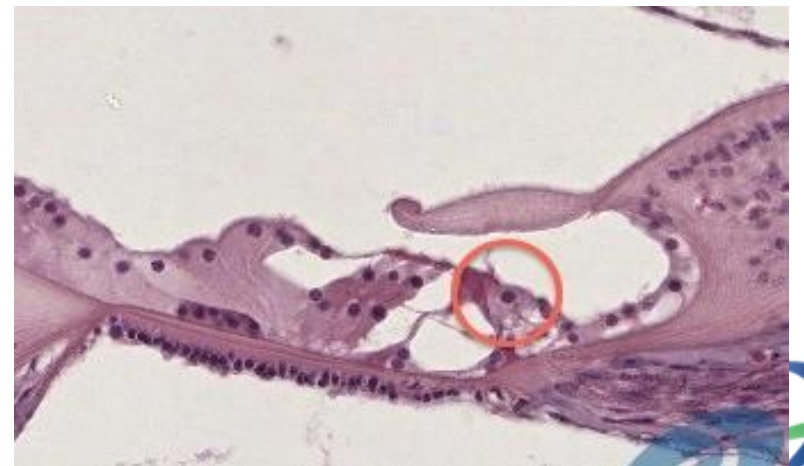
CBI offers otic histopathology, immunohistochemistry and histomorphometry

- Complete in house histopathology laboratory
- Experience in preparing entire ears, and cochlea
- Special stains and immunohistochemistry
- Histomorphometry
- Cytocochleograms
- Hair cell assessments
- ACVP Board Certified Pathologist



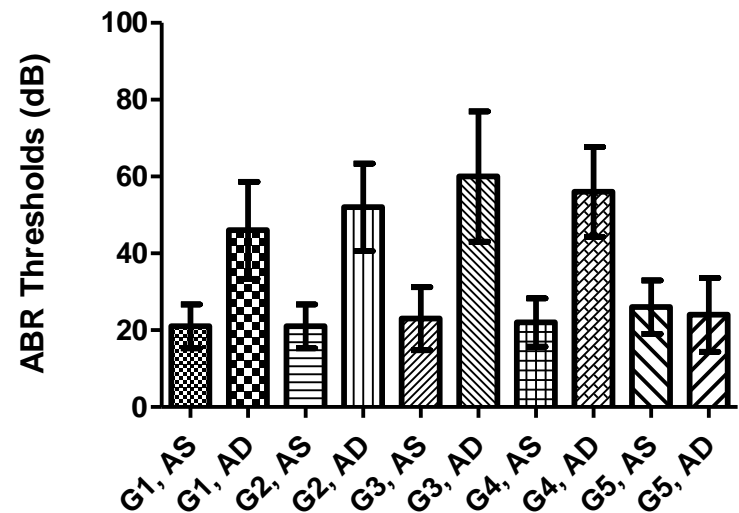
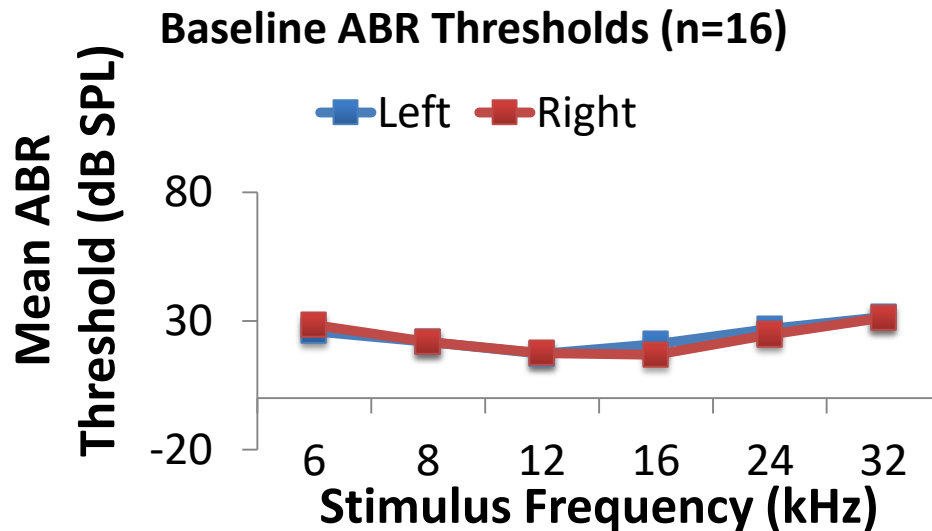
Specialized Techniques

- Auditory Brainstem Response (right)
- Perilymph collection
- Hair cell analysis
- Cytocochleograms
- Surgical techniques
- Specialized histopathology
- Organ of Corti (right)



Auditory Brainstem Response: A modified EEG to determine if the animal is able to hear-measures a brain response to a sound stimulus.

Left: Base line ABR thresholds. Right: Bar Graph: For the thresholds, the left ear is normal and the right ear has undergone a puncture of the ear drum (Gr 1-4)



Typical Endpoint Assessments for Otic Studies at CBI

- Clinical observations
- Visual otoscopic examination of the external ear and drug
- Auditory Brain Response
- Cytocochleogram
- Histopathology and Immunohistochemistry
- Photomicroscopy and Histomorphometry



Typical Routes of Administration for Otic Studies at CBI

- Topical application to ear canal-tympanic membrane
- Middle and inner ear cannulization
- Infusion into middle and inner ear
- Standard systemic routes



Species Commonly Used in Otic Studies

- Typical species for most toxicology studies
- Guinea pigs and chinchillas are common otic species due to ear anatomy
- Pigs, rabbits and dogs for external ear studies



Service and Quality

- **The people at CBI**—from the executive team to the study directors to the research associates expect to have to earn your trust and business.
- **Our ratio of scientists to non-scientists** is one of the highest in the industry. We believe in sound science and every study director is a PhD-level scientist
- **Thoroughness in planning and execution** is key to a successful study. All protocols are vetted and approved by multiple personnel. Our QAU has a rigorous training program. All non-GLP studies are conducted in the spirit of GLP with the same SOPs.
- **We believe in communication:** timely responses to your inquiries and frequent updates on your study are mandatory.
- **Rapid initiation and adjustments;** with the collective expertise of must larger organizations but the flexibility of a smaller more nimble group.
- **You are always welcome** at CBI to meet the staff, tour the laboratory and discuss the progress and results of your study.



Our Staff

- **Study Directors**

- PhD level scientists
- Appointed by management for each job
- Serves as single point of control and is responsible and accountable for study conduct and scientific interpretation
- Experienced attentive and communicative
- Rapid study initiation and report preparation

- **Research Associates**

- Bachelor Level Scientists
- Extensive technical training

- **Quality Assurance**

- Full time, dedicated
- Rigorous training program

- **CBI Management**

- Experienced senior scientific management-with large and small pharma experience



Summary

- **With a focus on quality, CBI provides state of the art:**
 - Toxicology
 - Pharmacokinetics
 - Efficacy
 - Pharmacology
 - In house histopathology
- **Experienced attentive and communicative study directors**
- **Rapid study initiation and report preparation**
- **Established, stable business**
- **Regulatory compliance**
- **Favorable pricing structure**

