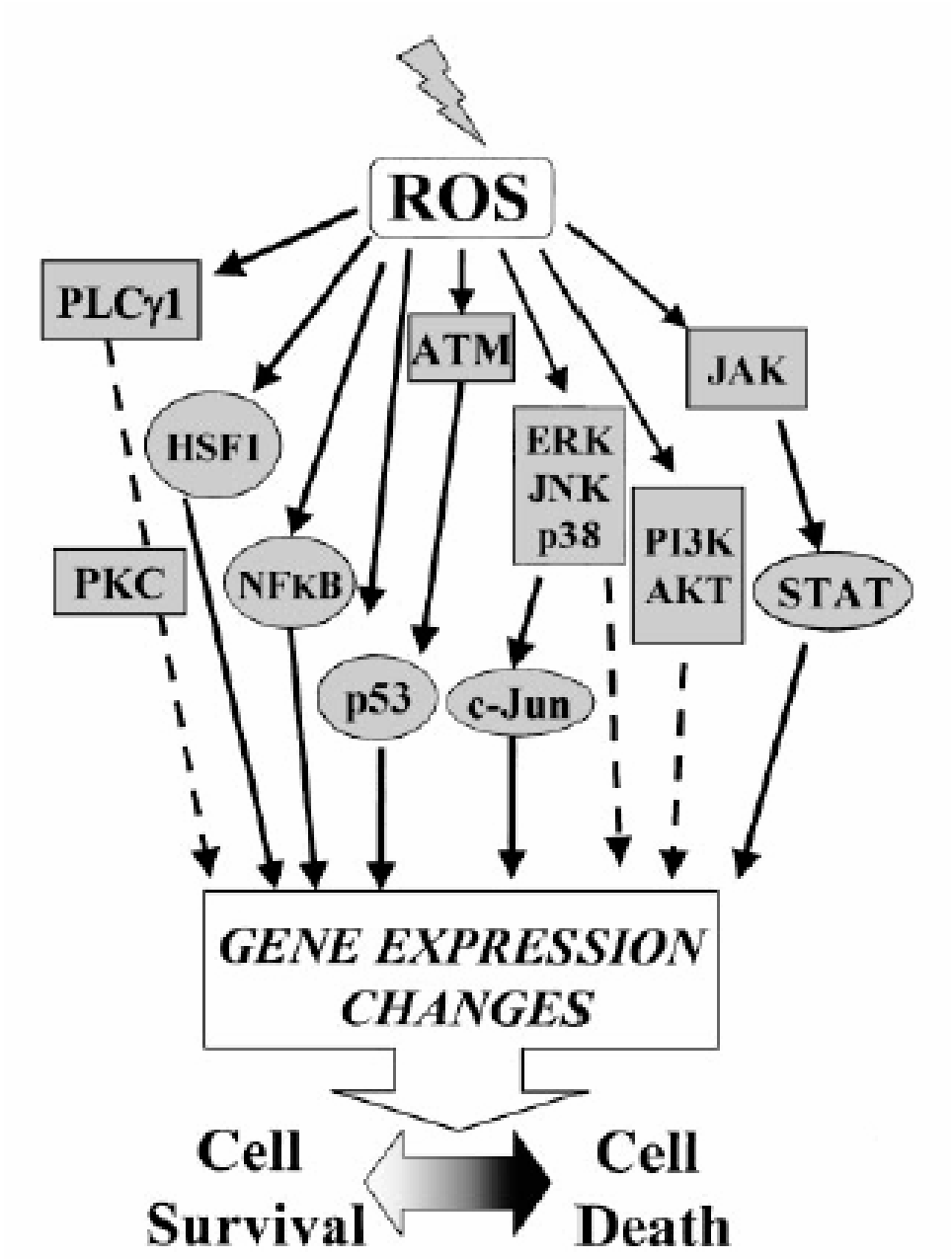
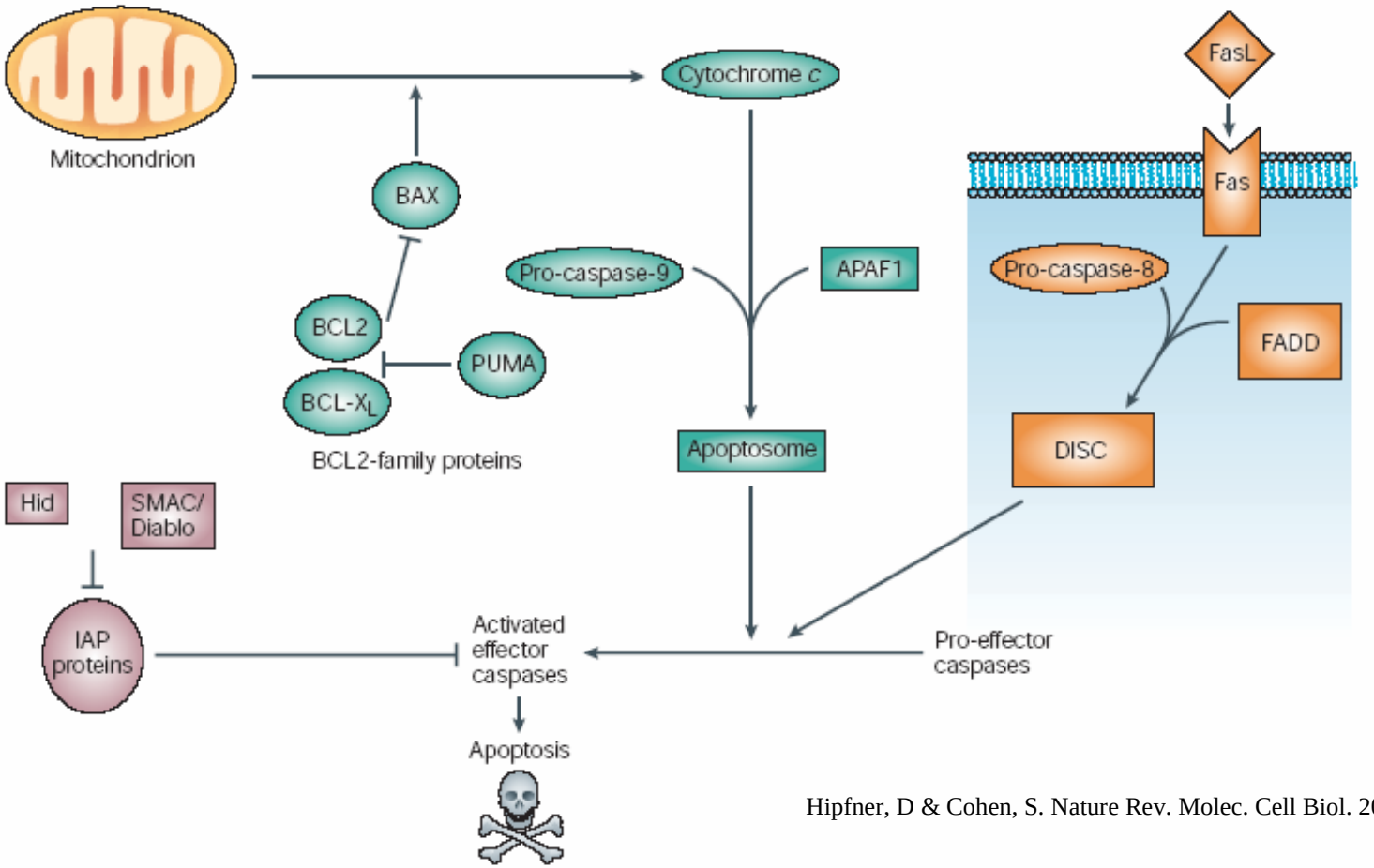
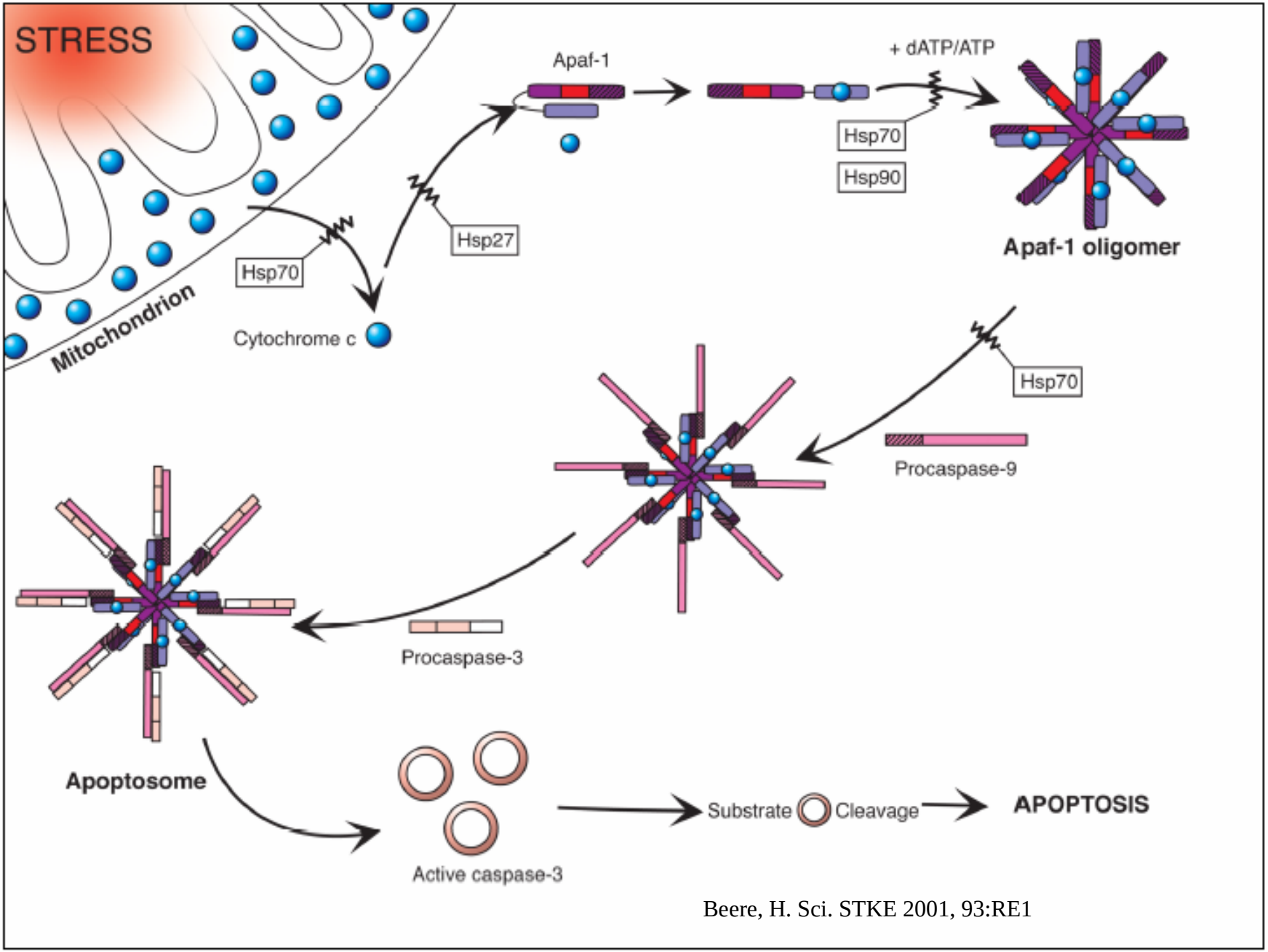

ROS
PLCγ1
ATM
JAK
HSF1
ERK
JNK
p38
PI3K
AKT
PKC
NFκB
STAT
p53
c-Jun
GENE EXPRESSION
CHANGES
Cell
Survival
Cell
Death



Hipfner, D & Cohen, S. Nature Rev. Molec. Cell Biol. 2004,5:805-815

Figure 2 | **Simplified model of intrinsic and extrinsic apoptosis pathways.** The intrinsic death pathway (left, green) is activated by the release of cytochrome *c* from mitochondria in response to various stresses and developmental-death cues. These death-inducing signals are sensed by BH3-ONLY-DOMAIN PROTEINS of the BCL2 family (for example, PUMA), which, in turn, bind to pro-survival family members (such as BCL2 and BCL-X_L) and prevent them from interacting with pro-apoptotic family members (such as BAX). When not bound to BCL2, BAX functions, at least in part, by perturbing mitochondrial membrane permeability, thereby promoting cytochrome-*c* release. Cytosolic cytochrome *c* triggers the formation of the apoptotic-protease-activating factor-1 (APAF1) and caspase-9-containing 'apoptosome' as well as activation of caspase-9. Once activated, caspase-9 triggers the effector-caspase cascade, which leads to cell death. The EXTRINSIC DEATH PATHWAY (right, orange) is activated by the binding of secreted ligands such as Fas ligand (FasL) to 'death receptors' of the tumour-necrosis-factor-receptor family, such as Fas. Receptor aggregation recruits other proteins, including the adaptor protein Fas-associated death-domain protein (FADD) and pro-caspase-8, into the 'death-inducing signalling complex' (DISC). Cleavage and activation of caspase-8 in the complex triggers the effector-caspase cascade, which leads to cell death. Caspases are inactivated by inhibitor of apoptosis (IAP) proteins, which can bind to and block the active site on the caspase. IAPs are targeted for degradation by the activity of pro-apoptotic proteins like second mitochondria-derived activator of caspase (SMAC)/Diablo and its functional homologues in flies, which include Grim, Reaper and Hid.



Beere, H. Sci. STKE 2001, 93:RE1

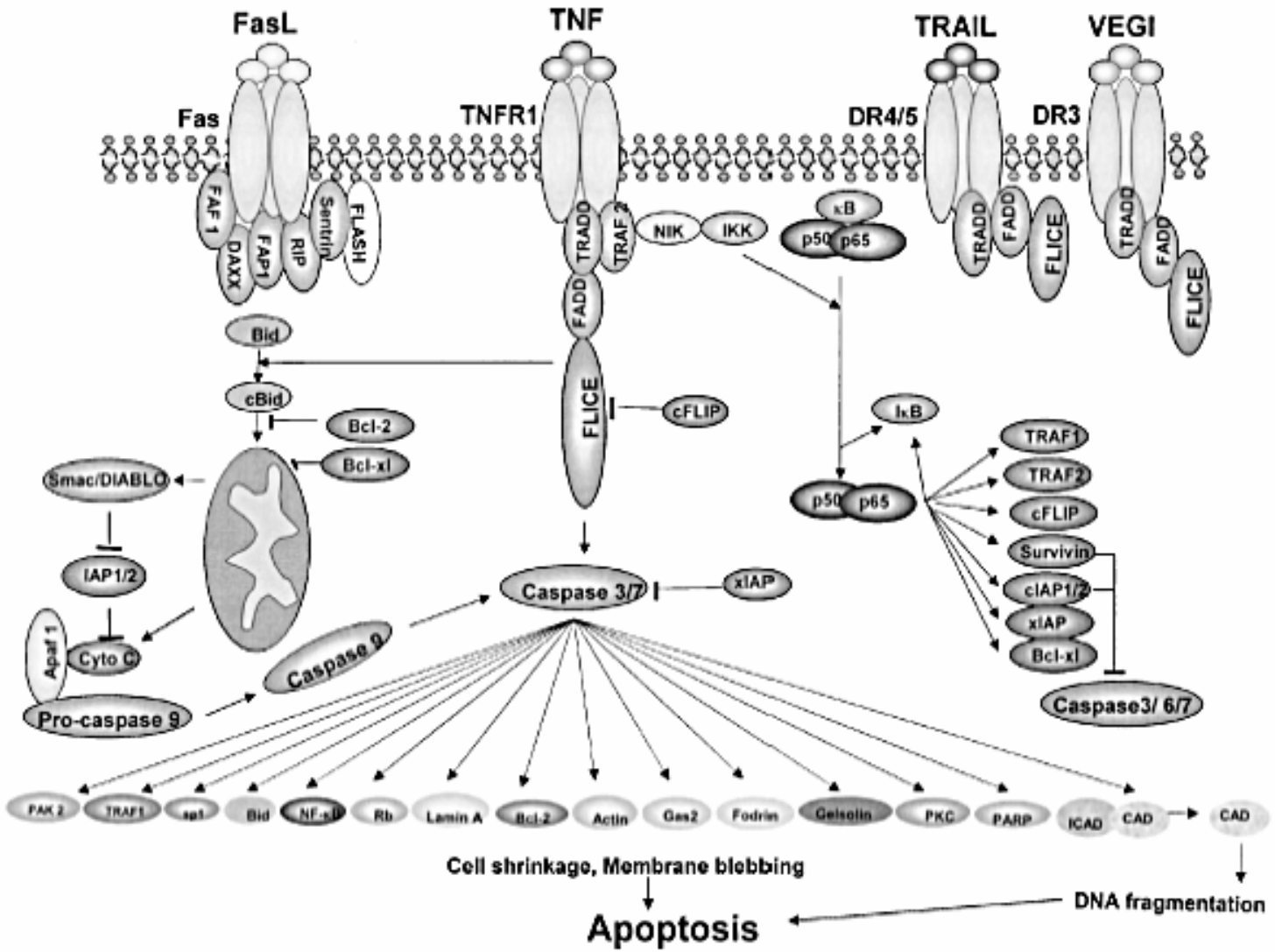


Fig. 2. Induction and regulation of apoptosis by various death ligands.

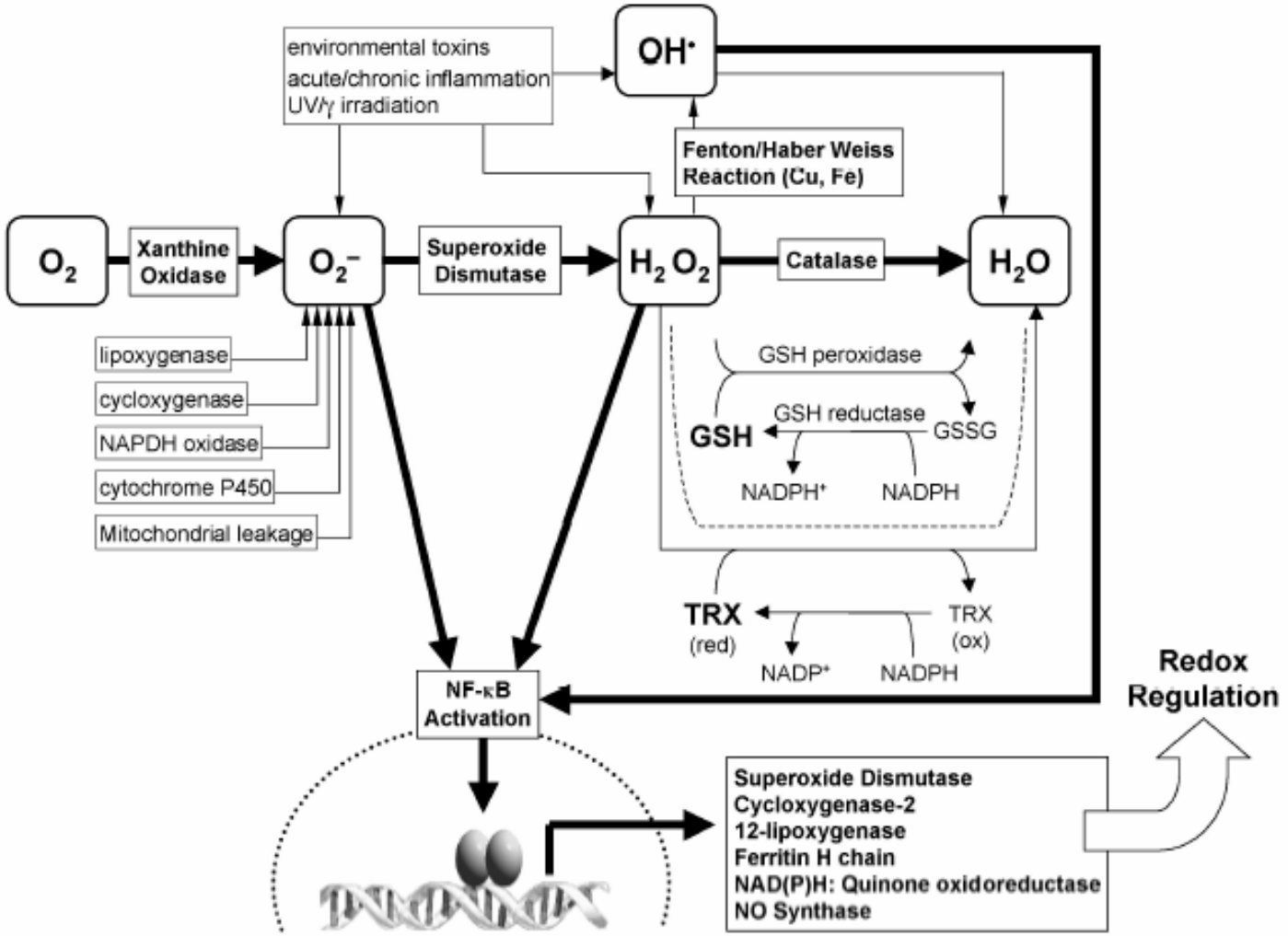
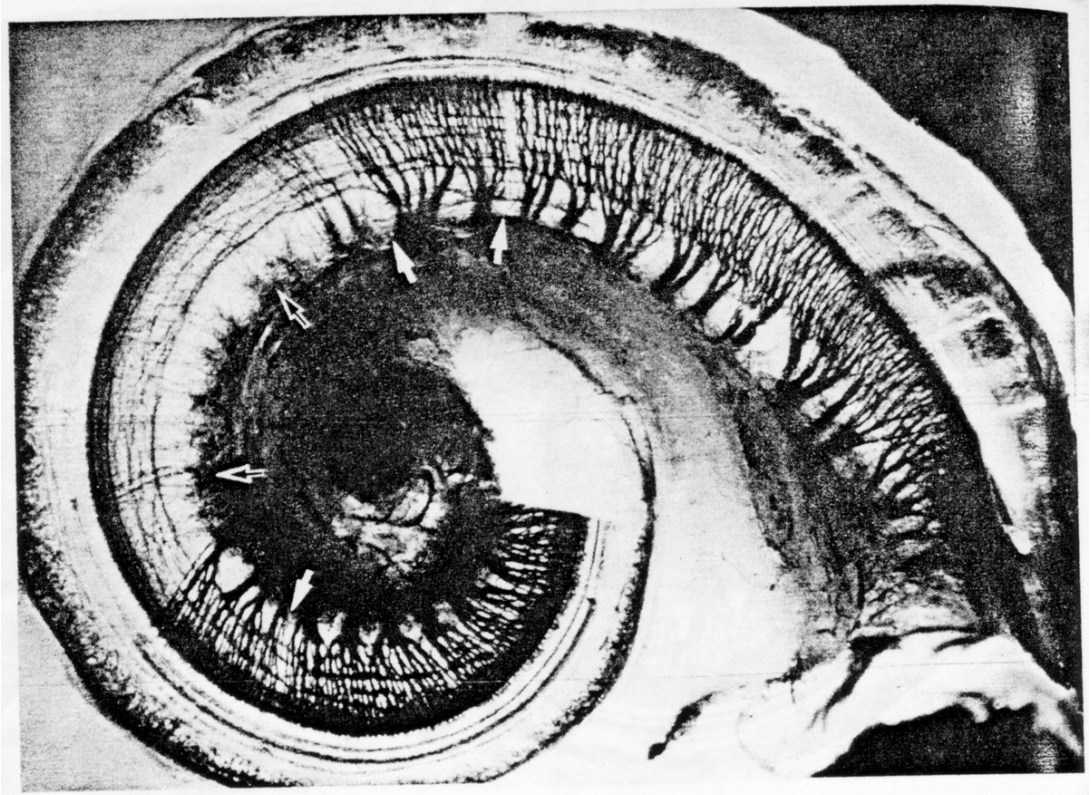
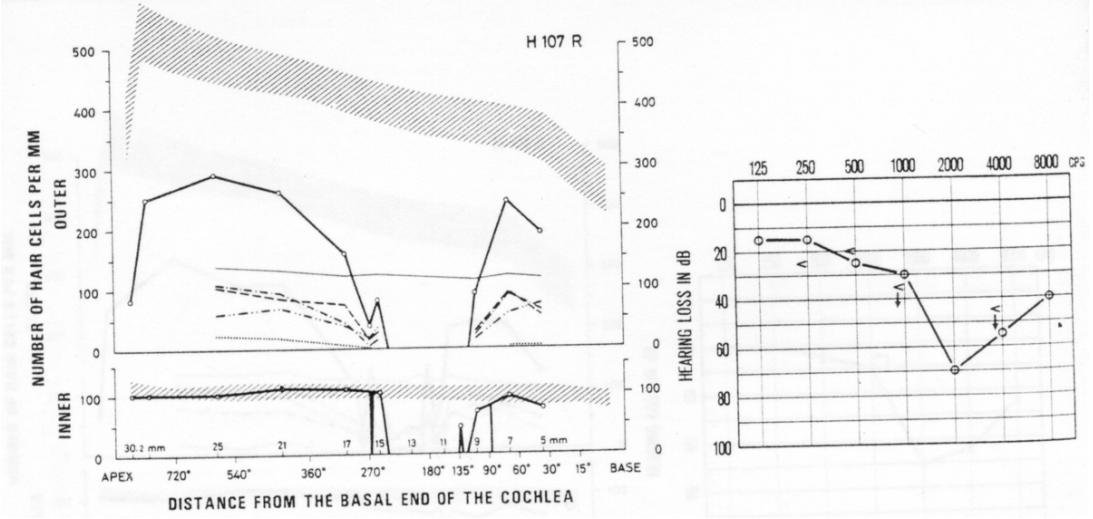
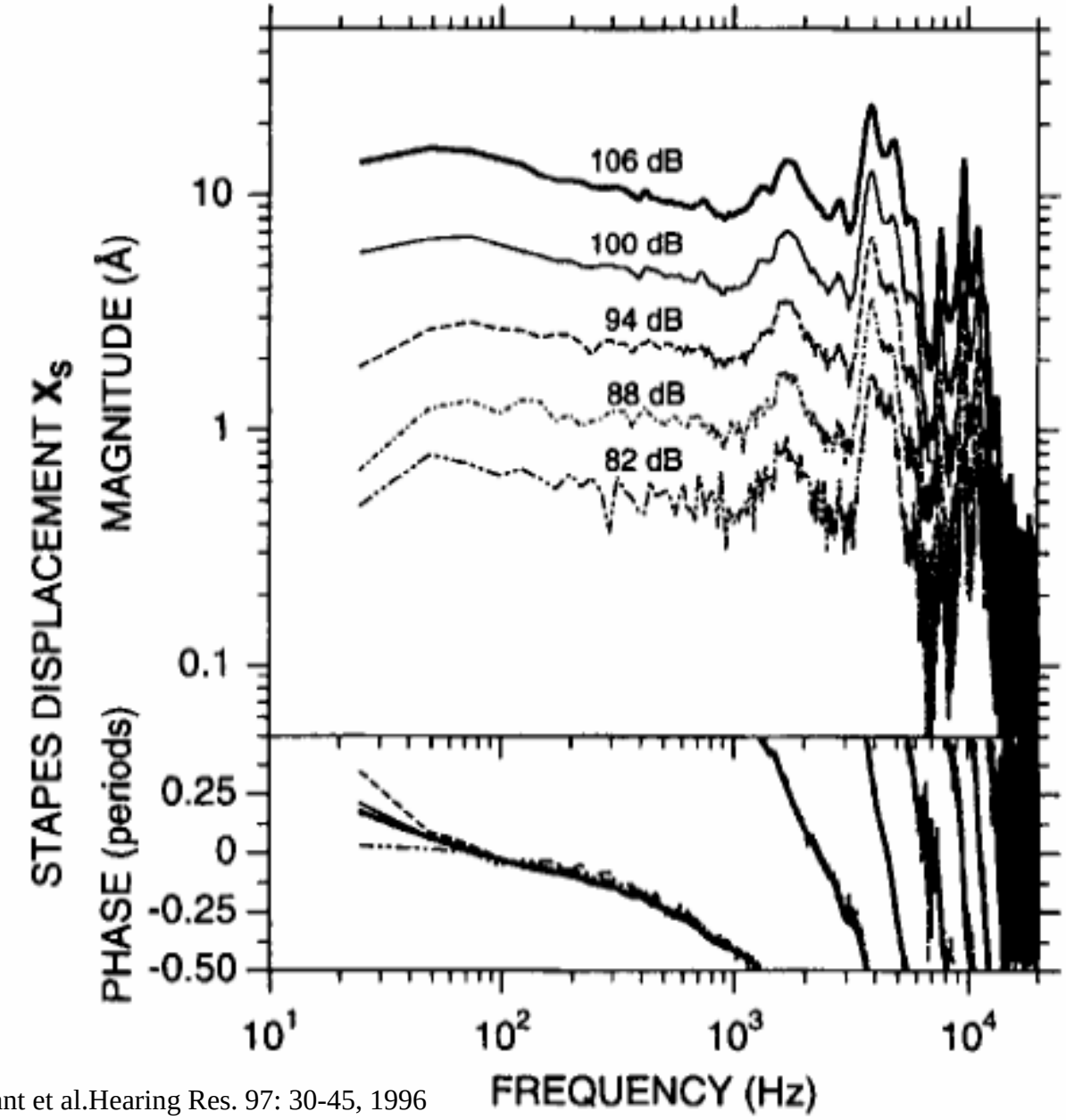


Figure 2 Schematic representation of reactive oxygen intermediate generation systems and mechanisms of activation of NF-κB




H 107 R
NUMBER OF HAIR CELLS PER MM
OUTER
INNER
500
400
300
200
100
0
30.2 mm
25
21
17
15
13
11
9
7
5 mm
APEX
720°
540°
360°
270°
180°
135°
90°
60°
30°
15°
BASE
DISTANCE FROM THE BASAL END OF THE COCHLEA
HEARING LOSS IN dB
125
250
500
1000
2000
4000
8000
CPS
0
20
40
60
80
100



Merchant et al.Hearing Res. 97: 30-45, 1996

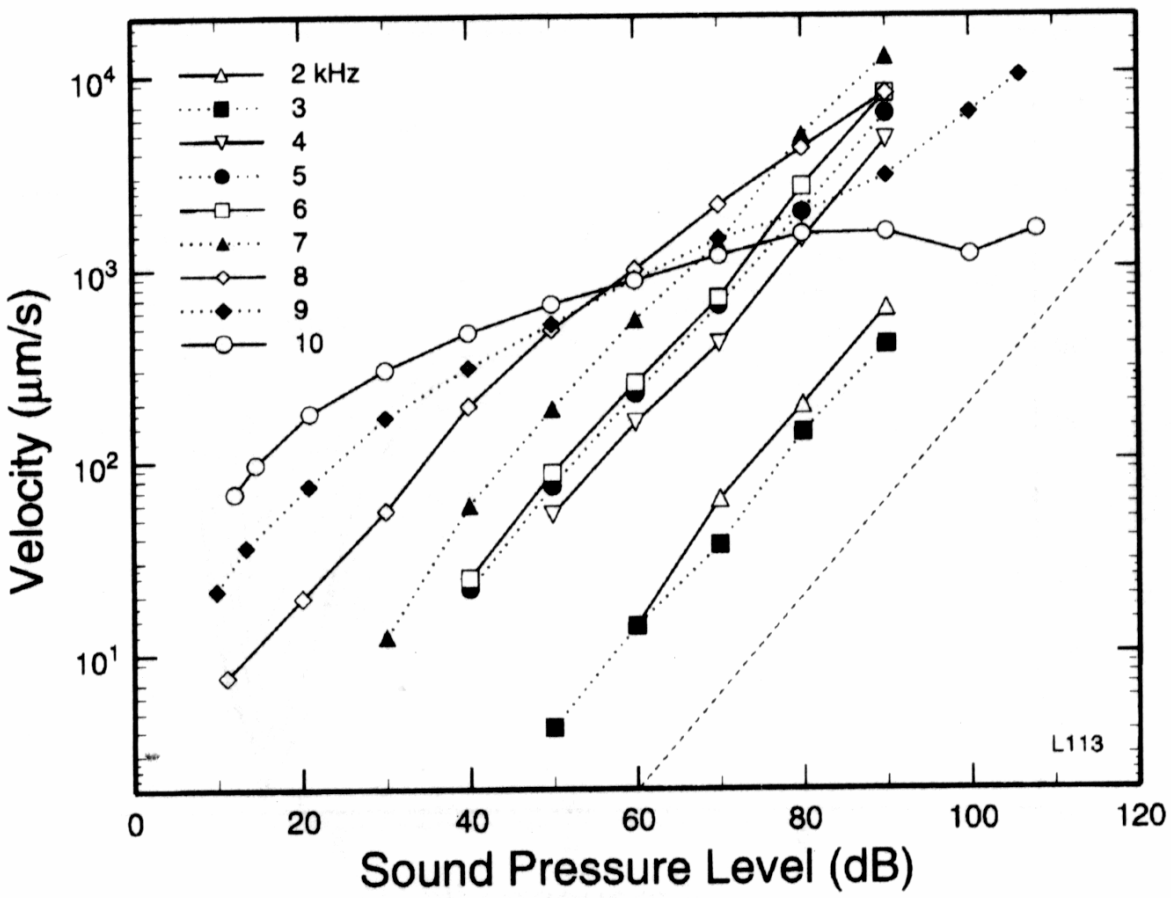
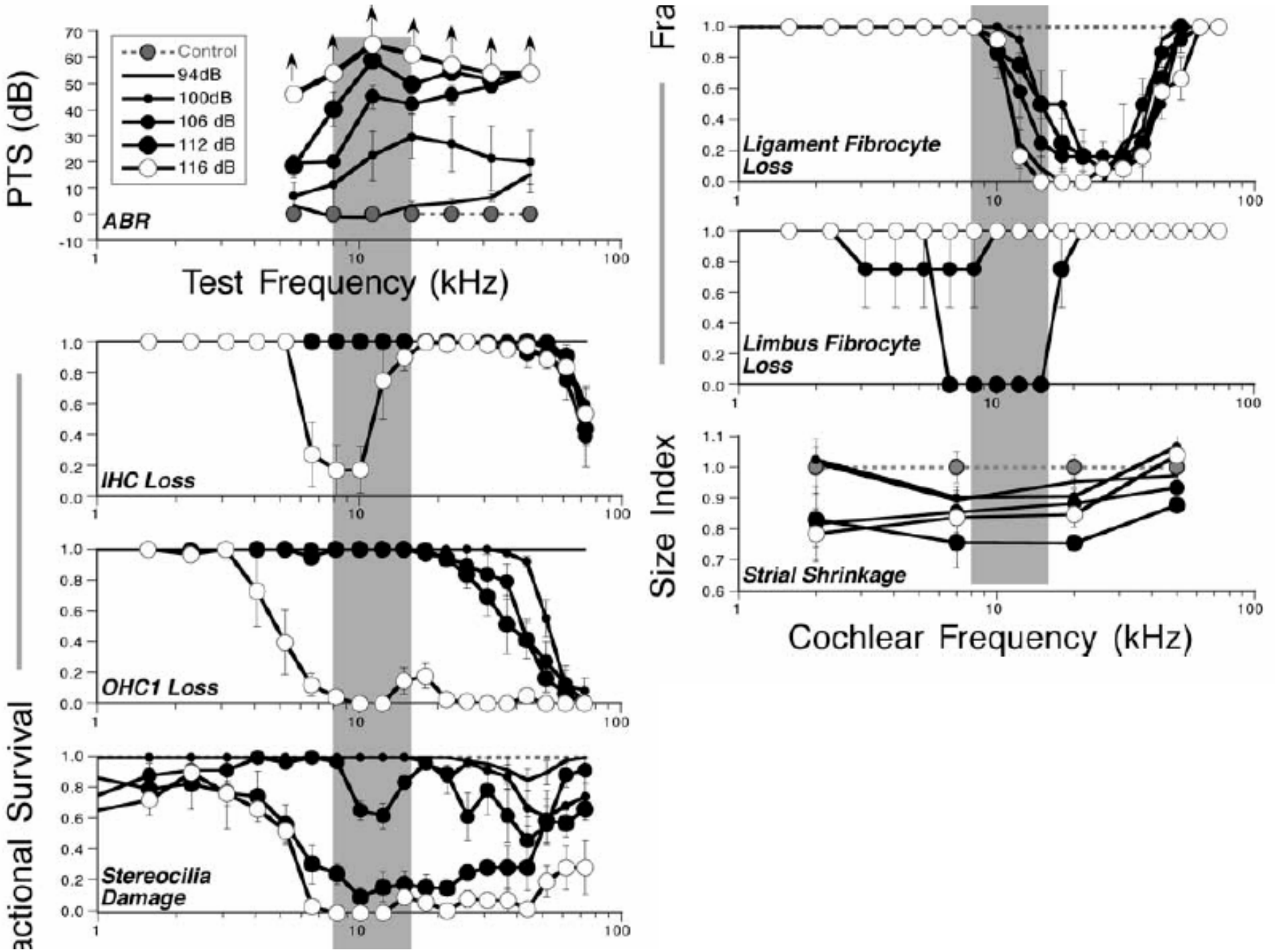
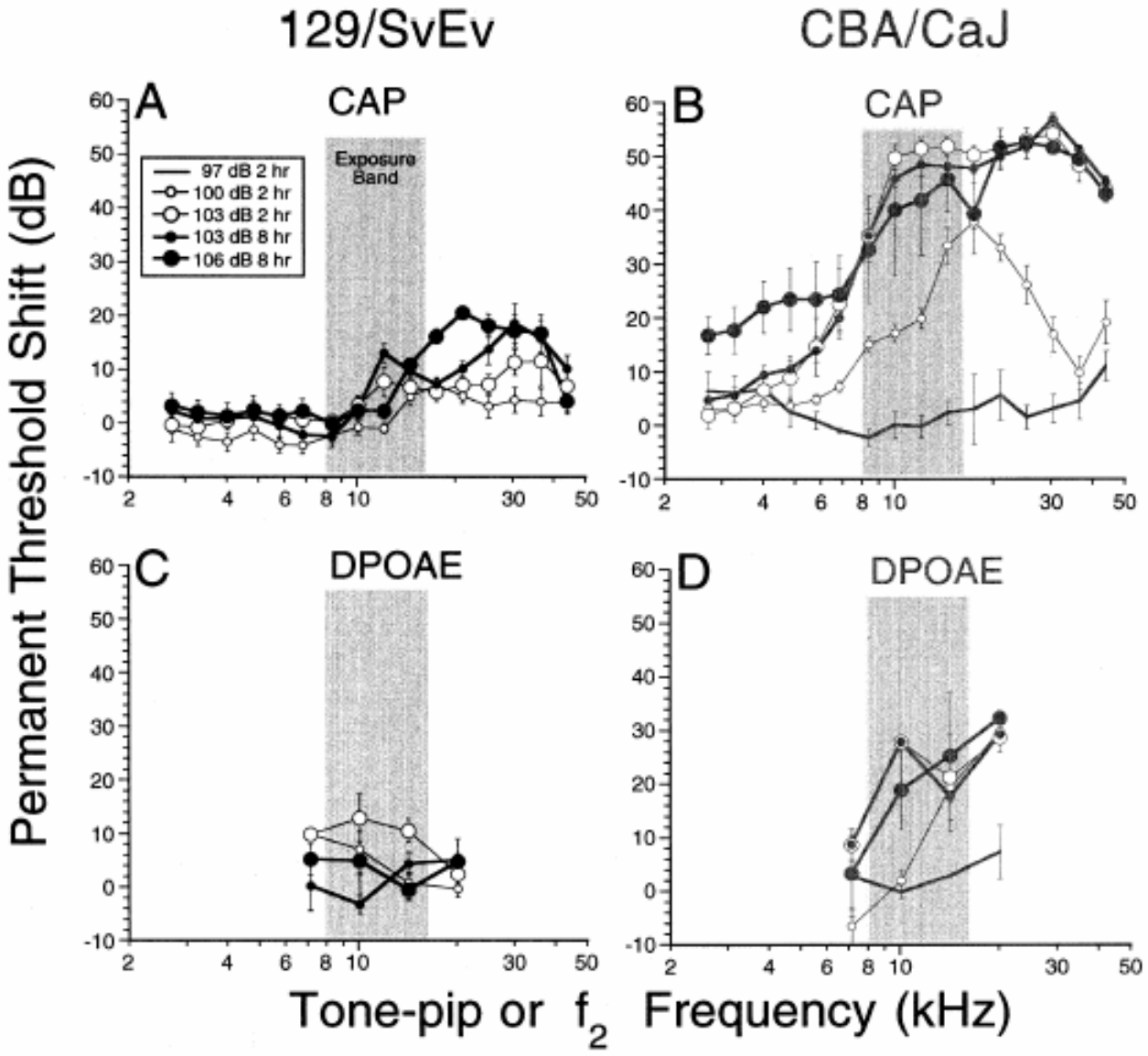
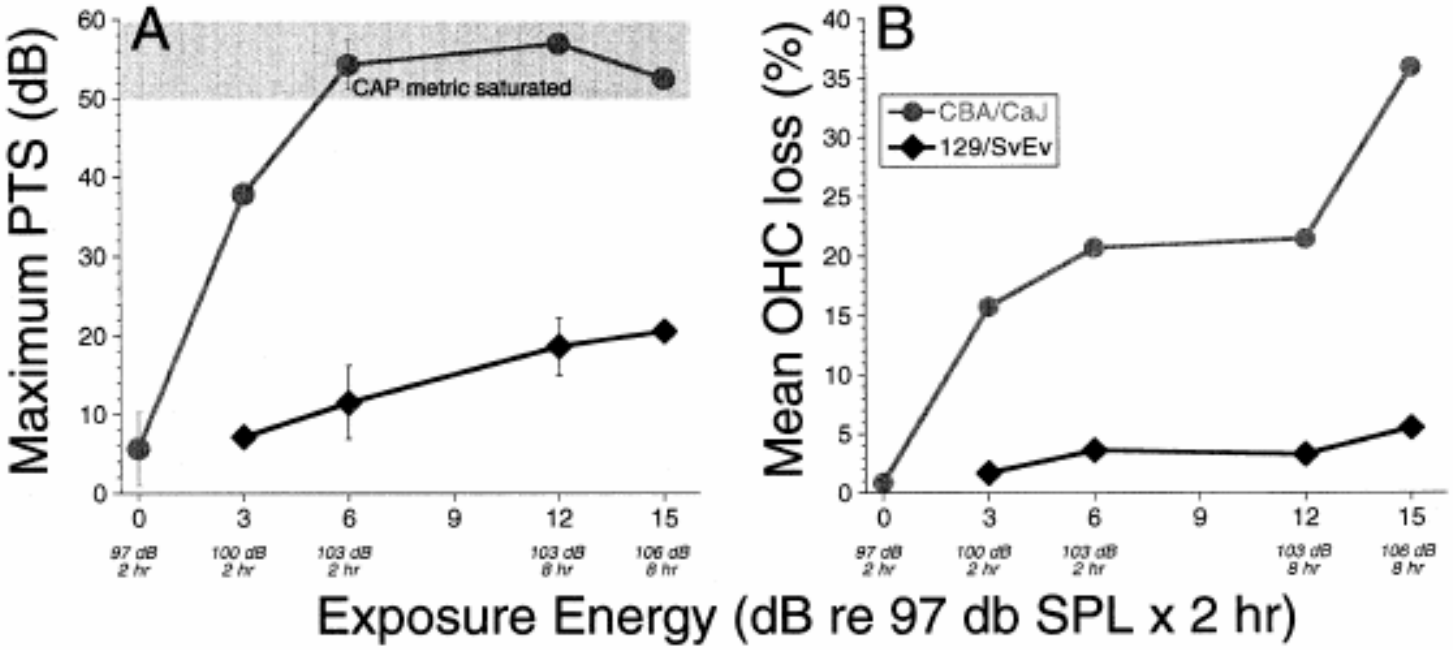


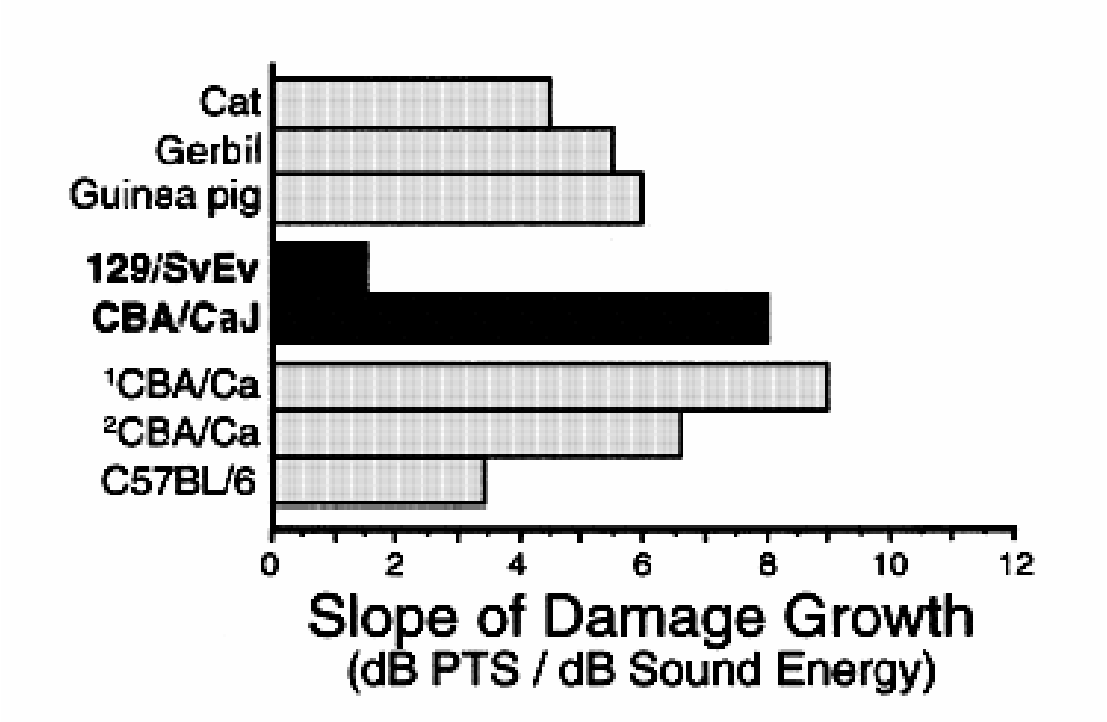
FIG. 7. Velocity-intensity functions of basilar-membrane responses to tones with frequency equal to and lower than CF (10 kHz). The straight dashed line at right has a linear slope (1 dB/dB). The data were recorded in the same cochlea (L113) represented in Fig. 6.

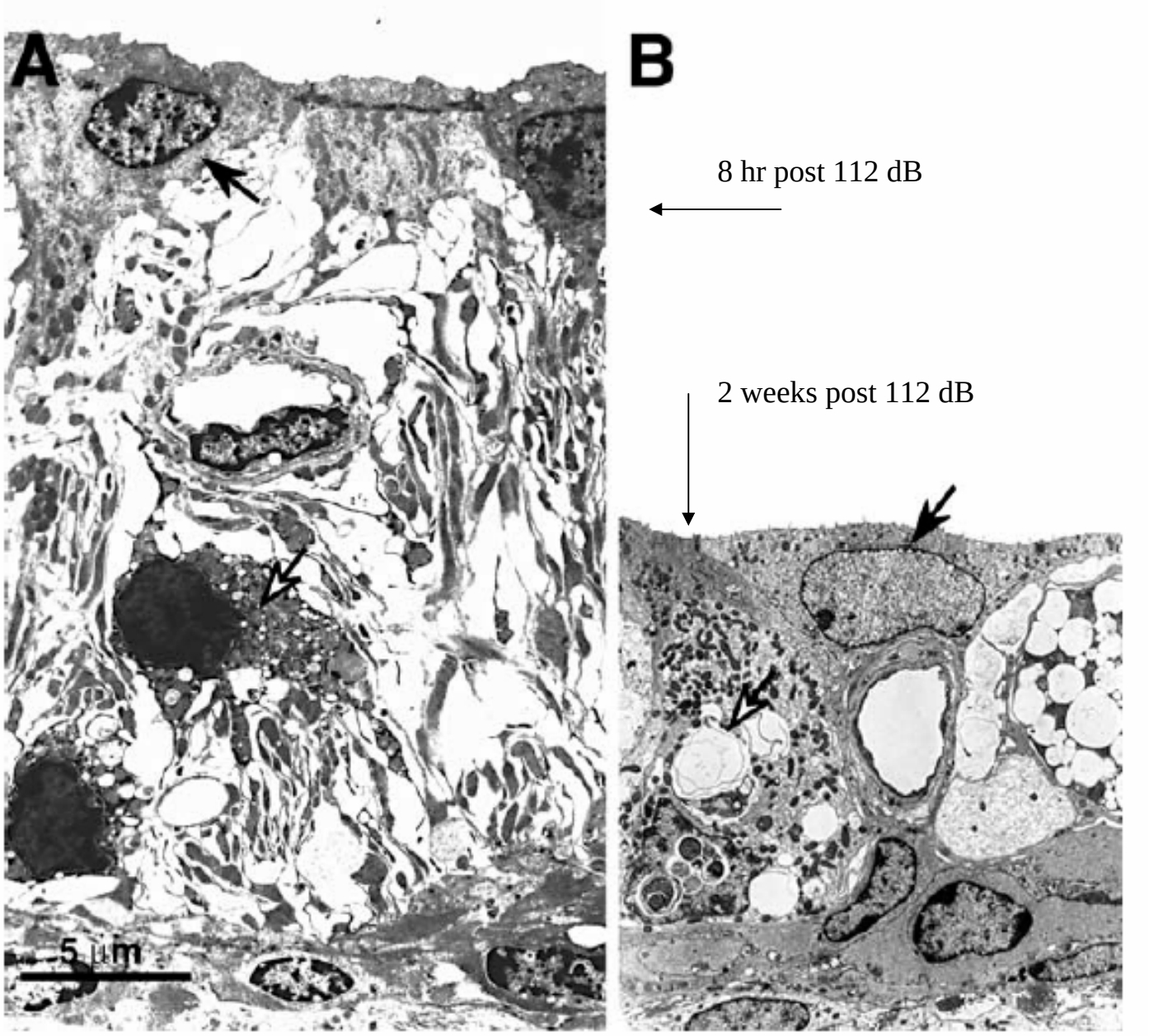
Ruggero et al. JASA 101: 2151-2163, 1997


PTS (dB)
Control
94dB
100dB
106 dB
112 dB
116 dB
ABR
Test Frequency (kHz)
IHC Loss
OHC1 Loss
Stereocilia Damage
Fractional Survival
Ligament Fibrocyte Loss
Limbus Fibrocyte Loss
Strial Shrinkage
Size Index
Cochlear Frequency (kHz)

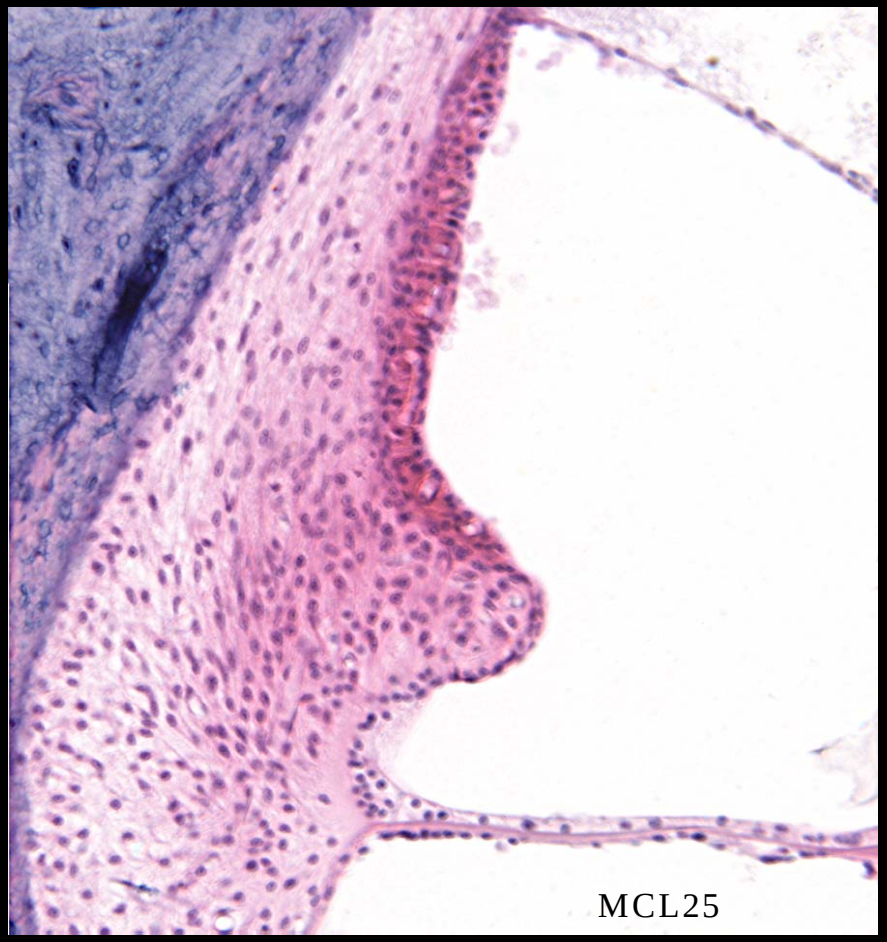

129/SvEv
CBA/CaJ
A
CAP
B
CAP
C
DPOAE
D
DPOAE
97 dB 2 hr
100 dB 2 hr
103 dB 2 hr
103 dB 8 hr
106 dB 8 hr
Exposure Band
Permanent Threshold Shift (dB)
Tone-pip or f2 Frequency (kHz)


A
CAP metric saturated
Maximum PTS (dB)
60
50
40
30
20
10
0
0
3
6
9
12
15
97 dB 2 hr
100 dB 2 hr
103 dB 2 hr
103 dB 8 hr
106 dB 8 hr
B
Mean OHC loss (%)
40
35
30
25
20
15
10
5
0
CBA/CaJ
129/SvEv
Exposure Energy (dB re 97 db SPL x 2 hr)

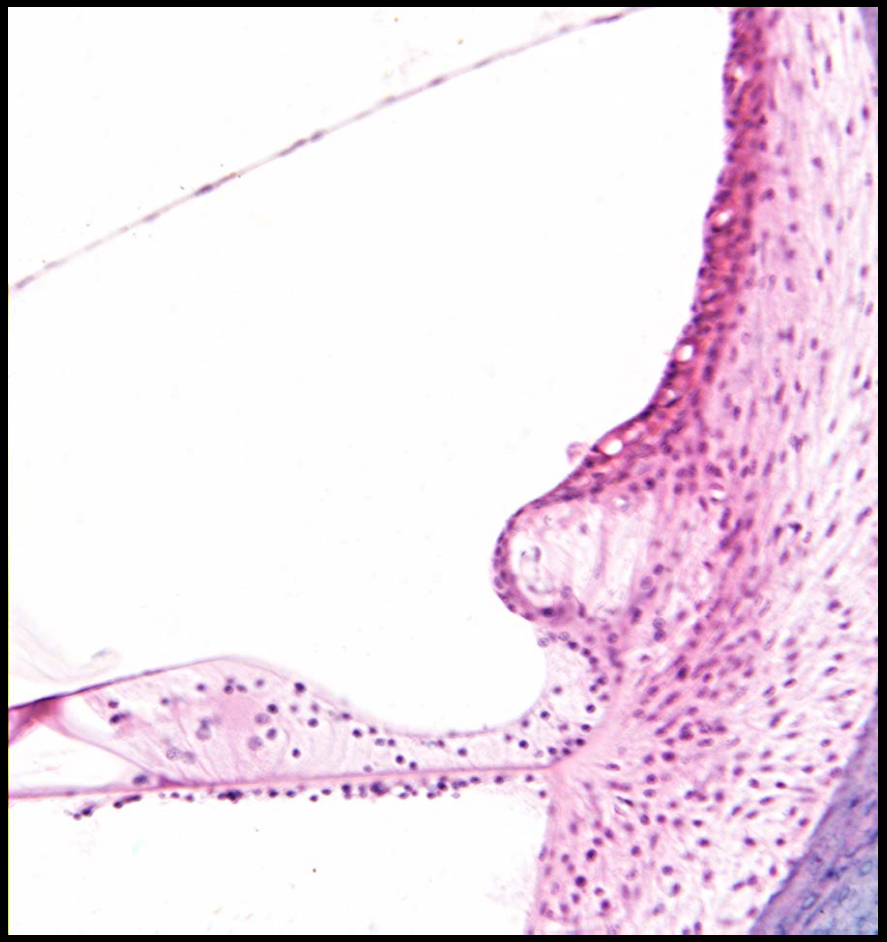

Cat
Gerbil
Guinea pig
129/SvEv
CBA/CaJ
[1]CBA/Ca
[2]CBA/Ca
C57BL/6
0
2
4
6
8
10
12
Slope of Damage Growth
(dB PTS / dB Sound Energy)

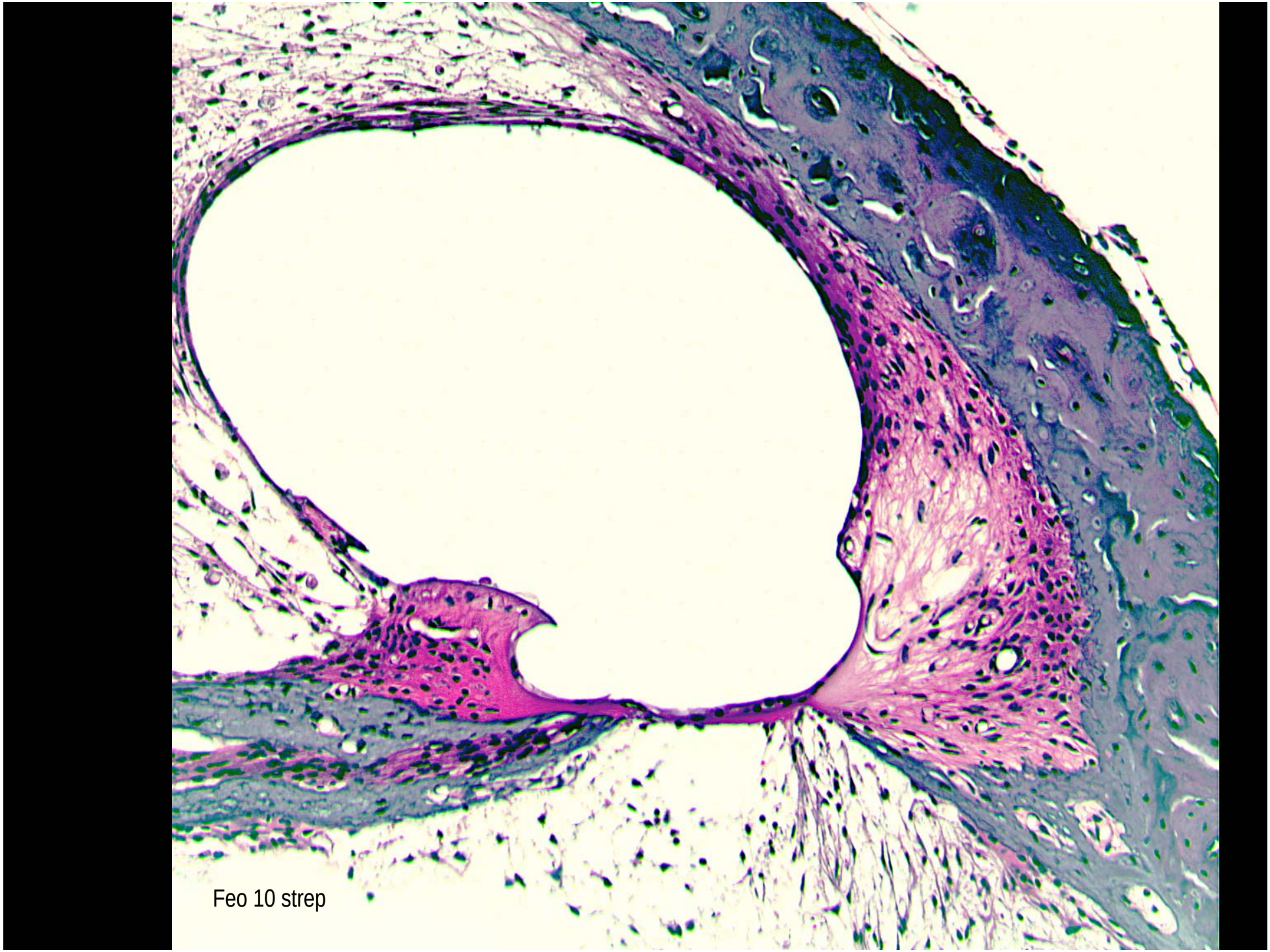


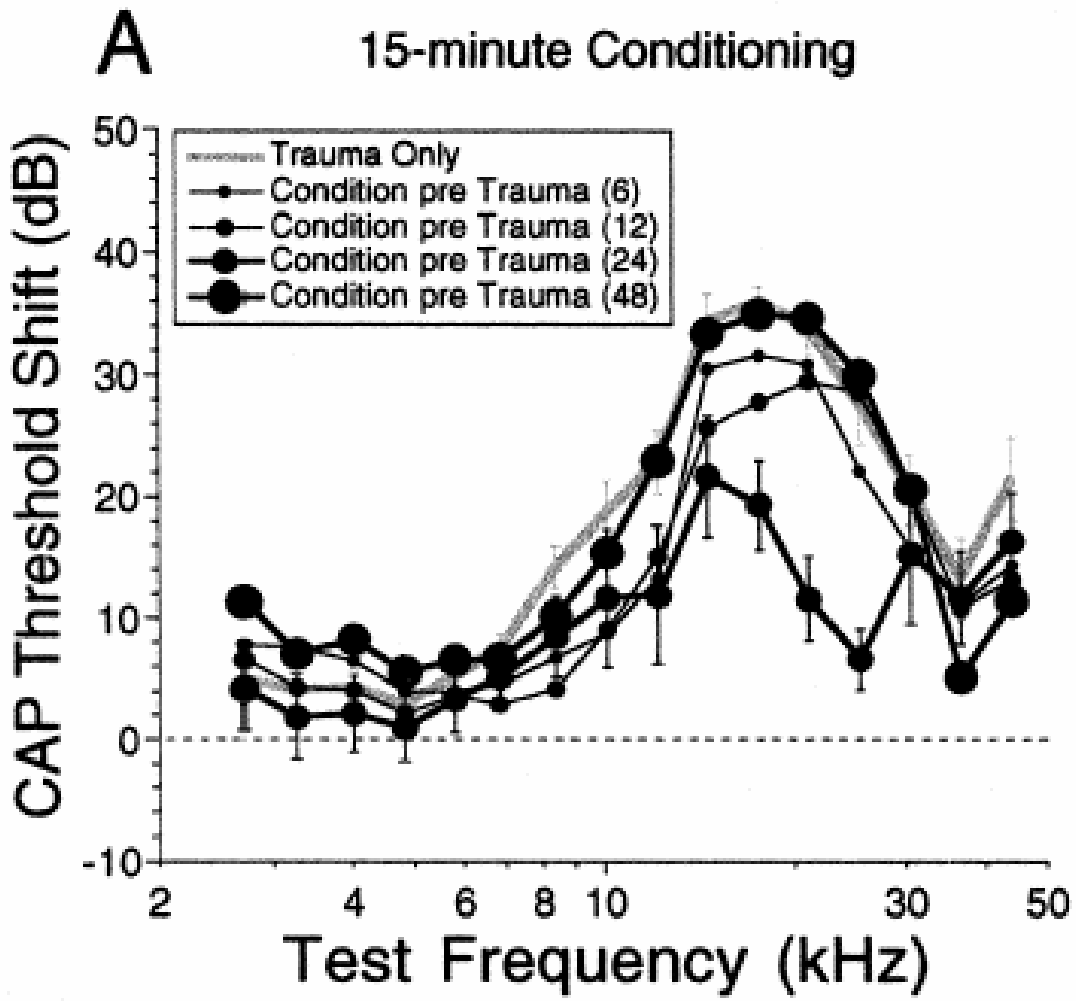
Hirose & Liberman JARO 4:339-352, 2003



MCL25




Feo 10 strep


A
15-minute Conditioning
Trauma Only
Condition pre Trauma (6)
Condition pre Trauma (12)
Condition pre Trauma (24)
Condition pre Trauma (48)
CAP Threshold Shift (dB)
50
40
30
20
10
0
-10
2
4
6
8
10
30
50
Test Frequency (kHz)

Prevention of cochlear cell degeneration

1. meningitis :

   a. block inflammatory response prior to antibiotic treatment
   b. antioxidants

2. acoustic trauma:

   a. conditioning (acoustic, heat, surgery, restraint stress, ? ischemia)

   b. growth factors (GDNF, BDNF)

   c. neurotrophins (NT3, NT 4-5)

   d. antioxidants (D-methionine, allopurinol, CuZn SOD, adenosine, glutathione, acetylcysteine)

   e. block caspases, calpains

   f. block JNK signaling (, D-JNKI-1, CEP-1347, grape seed proanthocyanidin)

3. aminoglycosides, cisplatin: nearly the same as acoustic trauma