



“stato della ricerca sulla sordità”



Sabato 24 maggio 2014

Prevenzione e riparazione del danno uditivo: cellule staminali e non solo

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LABORATORIO DI BIOACUSTICA
Campus Biomedico Pietro d'Abano,
via G. Orus, 2b, 35128 Padova
Prof. Alessandro MARTINI



“STATO DELLA RICERCA SULLA SORDITÀ”

Ad oggi

Impianti cocleari
Somministrazione di farmaci
Genetica diagnostica

pratica clinica
vs
ricerca biomedica



Futuro:

Cellule staminali
Sviluppo di nuovi farmaci
Nanotecnologie
Terapia genica

ricerca biomedica
vs
pratica clinica



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[Sound strategies for hearing restoration](#)

1. Géléoc GS, Holt JR.
Science. 2014 May 9;344(6184):1241062. doi: 10.1126/science.1241062.
PMID: 24812404 [PubMed - in process]
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[Regulatory system for the G1-arrest during neuronal development in Drosophila](#)

2. Tsuda L, Lim YM.
Dev Growth Differ. 2014 Apr 16. doi: 10.1111/dgd.12130. [Epub ahead of print]
PMID: 24738783 [PubMed - as supplied by publisher]
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[Multipotent mesenchymal stromal cells in otorhinolaryngology](#)

3. Skoloudik L, Chrobok V, Kalfert D, Koci Z, Filip S.
Med Hypotheses. 2014 Jun;82(6):769-73. doi: 10.1016/j.mehy.2014.03.022. Epub 2014 Mar 27.
PMID: 24726343 [PubMed - in process]
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[Molecular mechanisms and potentials for differentiating inner ear stem cells into sensory hair cells](#)

4. Liu Q, Chen P, Wang J.
Dev Biol. 2014 Jun 15;390(2):93-101. doi: 10.1016/j.ydbio.2014.03.010. Epub 2014 Mar 26. Review.
PMID: 24680894 [PubMed - as supplied by publisher]
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[Wolfram syndrome IPS cells: the first human cell model of endoplasmic reticulum disease](#)

5. Urano F.
Diabetes. 2014 Mar;63(3):844-6. doi: 10.2337/db13-1809. No abstract available.
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Neural crest stem cells and their potential application in a th [Front Biosci (Schol Ed). 2012]
Sensory cell regeneration and stem cells: what we have already achieved in [Otol Neurotol. 2008]
[Inner ear cell therapy for hereditary deafness with multipotent stem cells] [Nihon Rinsho. 2011]
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Protection of spiral ganglion neurons from degeneration using small-mole [J Neurosci. 2013]
Generation of hair cells in neonatal mice by β -catenin overexpression [Proc Natl Acad Sci U S A. 2013]
Pitpnm1 is expressed in hair cells during development but is not required [Neuroscience. 2013]
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CELLULE STAMINALI

1. Embryonic stem cells,

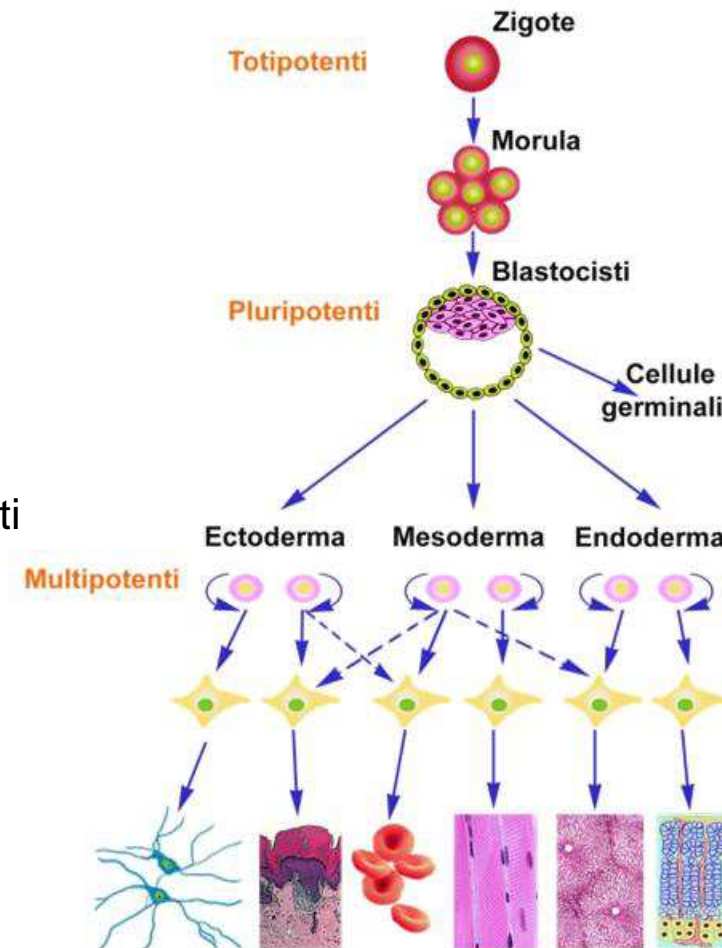
derivano dalle cellule germinative di embrioni di 4-5 gg

1. Induced pluripotent stem cells,

tessuti cellulari che sono stati ingegnerizzati per regredire allo stato di cellula staminale

1. Adult stem cells,

derivano dai tessuti adulti

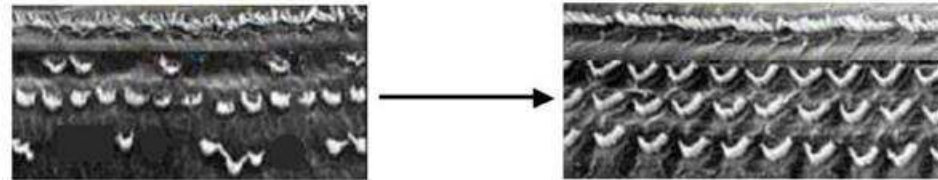


CELLULE STAMINALI

1. Cellule staminali sono state identificate nell'organo vestibolare di ratto
2. E nel nervo cocleare di Guinea pigs e uomo



Possibili scenari per la rigenerazione dell'epitelio ciliato



1. trapiantare di cellule staminali nella coclea



2. "risvegliare" cellule staminali endogene, se presenti



3. transdifferenziare cellule di sostegno in ciliate



CELLULE STAMINALI

Cell Transplantation, Vol. 17, pp. 665–678, 2008
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0963-6897/08 \$90.00 + .00
E-ISSN 1555-3892
www.cognizantcommunication.com

Cochlear Repair by Transplantation of Human Cord Blood CD133⁺ Cells to *Nod-Scid* Mice Made Deaf With Kanamycin and Noise

Roberto P. Revoltella,* Sandra Papini,* Alfredo Rosellini,* Monica Michelini,*
Valeria Franceschini,† Andrea Ciorba,‡ Lucia Bertolaso,‡ Sara Magosso,‡ Stavros Hatzopoulos,‡
Guiscardo Lorito,‡ Pietro Giordano,‡ Edi Simoni,‡ Emanuela Ognio,§ Michele Cilli,§ Riccardo Saccardi,¶
Serena Urbani,¶ Rosemary Jeffery,# Richard Poulson,# and Alessandro Martini‡

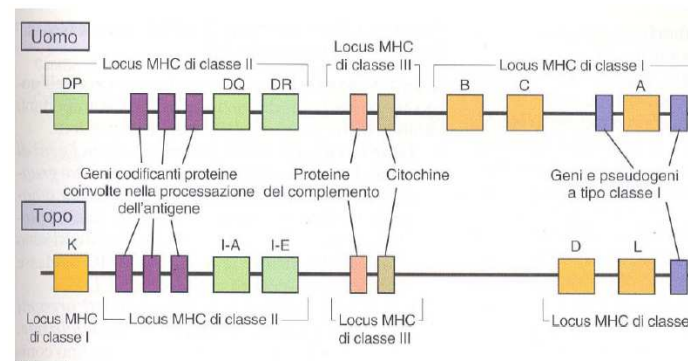
- 1) MODELLO ANIMALE: 70 **topi NOD-SCID** di 2 mesi di età
(Charles Rivers, Laboratories Clinical, UK)
- 2) DANNO : **RUMORE** (105 dB SPL; 4 hrs)
AMINIGLICOSIDI (Kamicina: 700 mg/kg\48 hrs x14gg)
- 3) SOMMINISTRAZIONE SISTEMICA **(IV)**
DI CELLULE STAMINALI (HCBSCS)



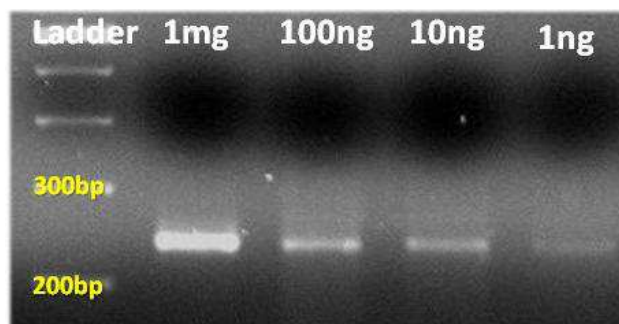
CELLULE STAMINALI

Analisi Molecolare (PCR) : HLA-DQ

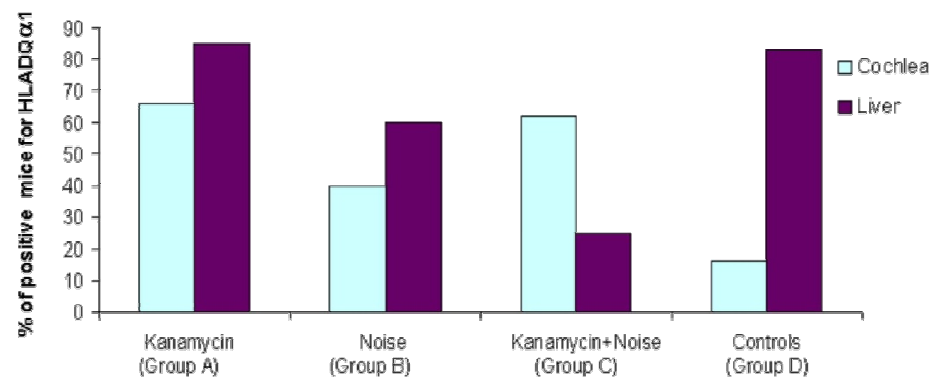
MHC di II° classe sono espressi in alcuni precursori mieloidi, in alta percentuale nei monociti/macrofagi, in cellule di langerhans della cute



Sensibilità della PCR HLA-DQa1:

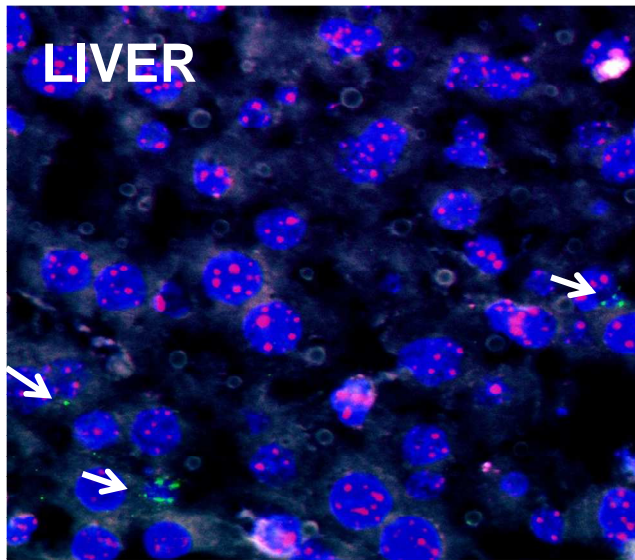


Analysis of the engraftment in Cochlea and Liver in different groups of mice

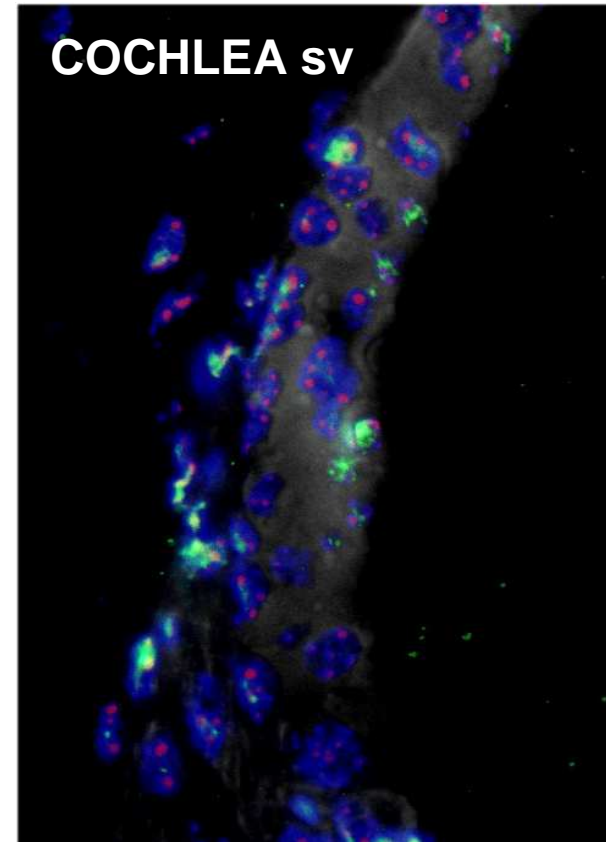


CELLULE STAMINALI HOMING E INTEGRAZIONE NEL TESSUTO

FISH (DUAL-COLOR)



Centromeri
murini
Centromeri
umani



"STATO DELLA RICERCA SULLA SORDITÀ"

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1. [Attenuation of Cisplatin Ototoxicity by Otoprotective Effects of Nanoparticulated Curcumin and Dexamethasone in a Guinea Pig Model.](#)
Salehi P, Akingpelu OV, Waissbluth S, Peleva E, Meehan B, Rak J, Daniel SJ.
Otol Neurotol. 2014 May 16. [Epub ahead of print]
PMID: 24841915 [PubMed - as supplied by publisher]
[Related citations](#)

2. [Hearing preservation and clinical outcome of 32 consecutive electric acoustic stimulation \(EAS\) surgeries.](#)
Usami SI, Moteki H, Tsukada K, Miyagawa M, Nishio SY, Takumi Y, Iwasaki S, Kumakawa K, Naito Y, Takahashi H, Kanda Y, Tono T.
Acta Otolaryngol. 2014 May 19:1-11. [Epub ahead of print]
PMID: 24834839 [PubMed - as supplied by publisher]
[Related citations](#)

3. [Effects of hearing aid settings for electric-acoustic stimulation.](#)
Dillon MT, Buss E, Pillsbury HC, Adunka OF, Buchman CA, Adunka MC.
J Am Acad Audiol. 2014 Feb;25(2):133-40. doi: 10.3766/jaaa.25.2.2.
PMID: 24828214 [PubMed - in process]
[Related citations](#)

4. [Identification of a novel splice site variant of OTOF in the Korean nonsyndromic hearing loss population with low prevalence of the OTOF mutations.](#)
Jin YJ, Park J, Kim AR, Rah YC, Choi BY.
Int J Pediatr Otorhinolaryngol. 2014 Apr 24. pii: S0165-5876(14)00182-7. doi: 10.1016/j.ijporl.2014.03.033. [Epub ahead of print]
PMID: 24814232 [PubMed - as supplied by publisher]
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5. [Safety, Efficacy, and Hearing Preservation Using an Integrated Electro-Acoustic Stimulation Hearing System.](#)
Mahmoud AF, Massa ST, Douberty SL, Montes ML, Ruckenstein MJ.
Otol Neurotol. 2014 May 2. [Epub ahead of print]
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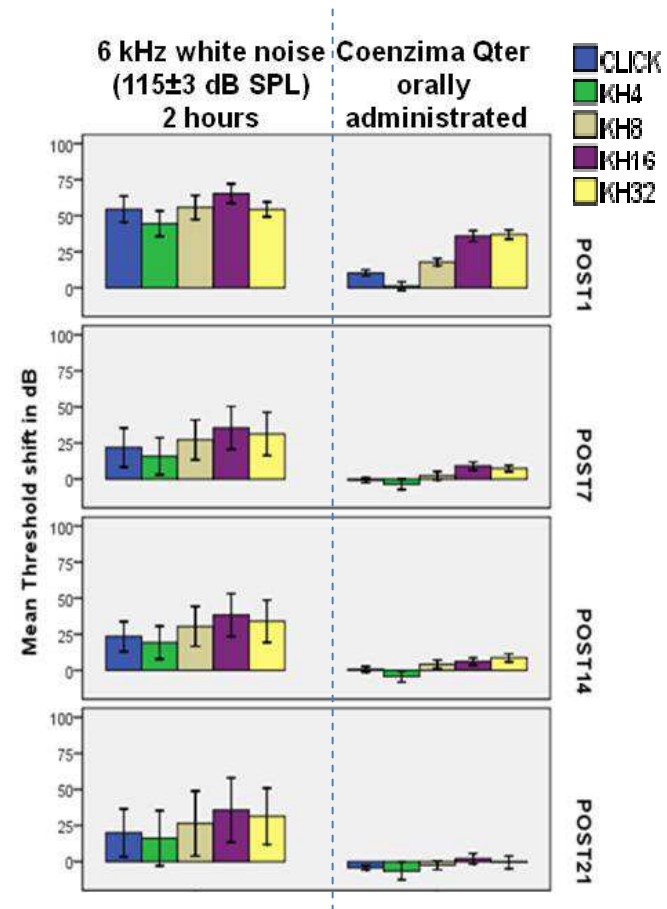
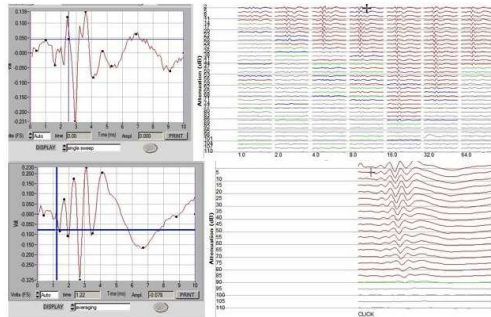
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PREVENZIONE DAL DANNO DA RUMORE

MODELLO ANIMALE: RATTO



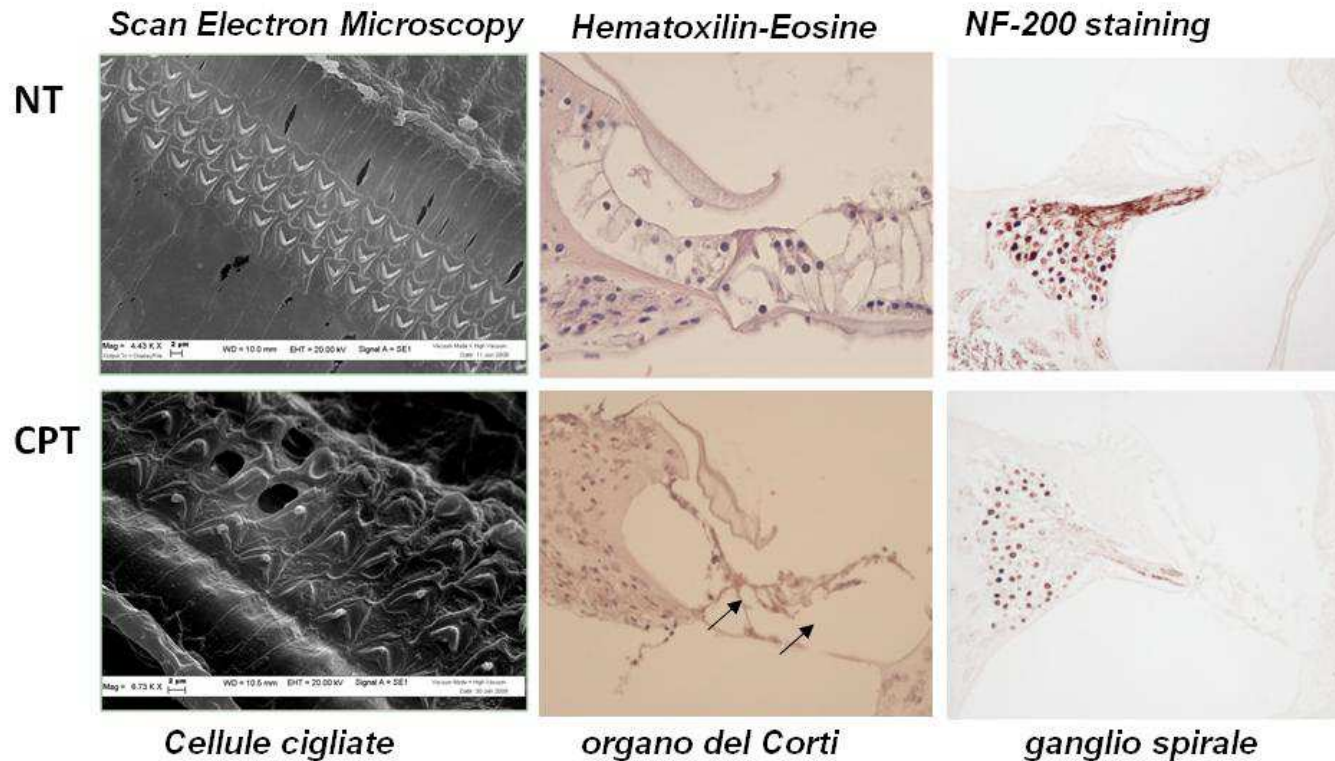
VERIFICA DELLA FUNZIONE Uditiva:
ABR thresholds



OTOTOSSICITÀ DEL CISPLATINO

MODELLO ANIMALE: RATTO

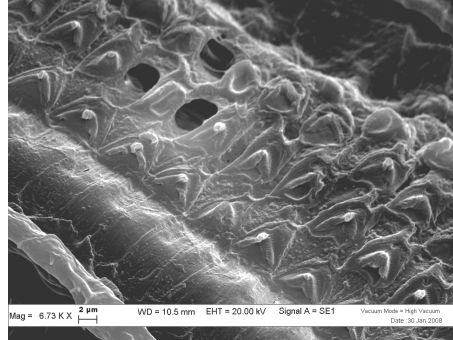
TRATTAMENTO: IP 16 mg/kg



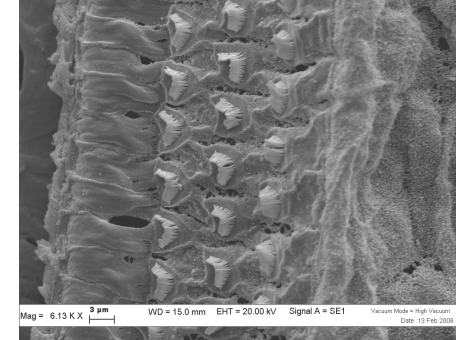
PREVENZIONE DAL DANNO OTOTOSSICO

Effetto **PROTETTIVO**
del **DEXAMETASONE**
nei confronti del
CISPLATINO

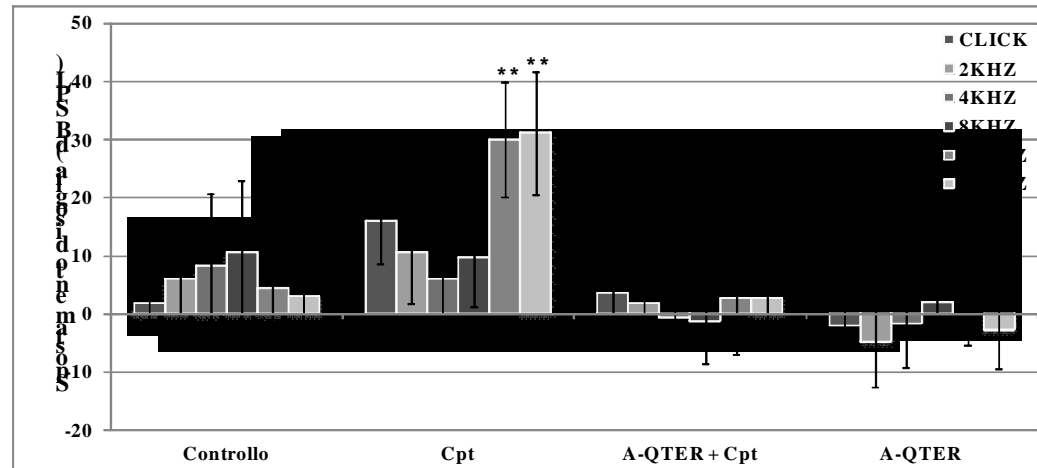
CISPLATINO (CONTROLLO POSITIVO)



DEXAMETASONE + CISPLATINO



Effetto **PROTETTIVO**
del **Coenzima Q10**
nei confronti del
CISPLATINO

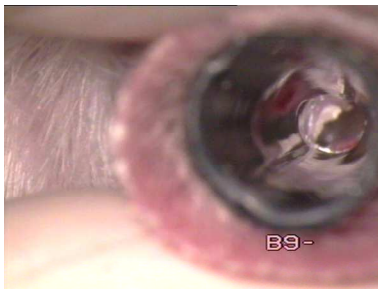


COME APPLICARE I FARMACI

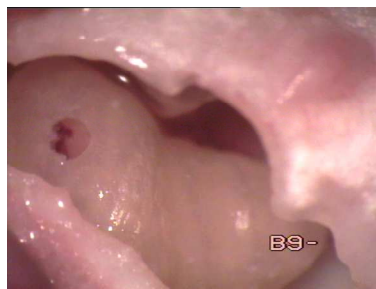
@ APPLICAZIONE DIRETTA

@ CONIUGATI A NANOPARTICELLE

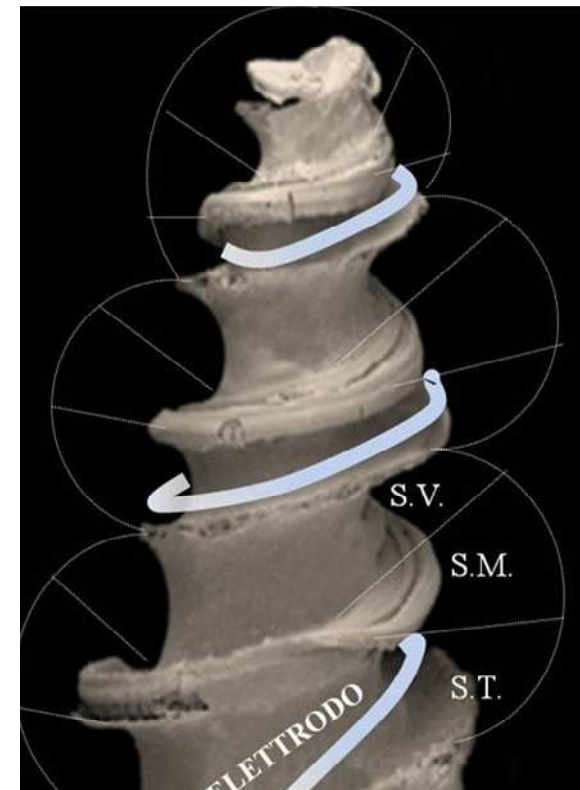
via INTRA-TIMPANICA



via INTRA-COCLEARE



IMPIANTO COCLEARE



APPLICAZIONE DIRETTA e IMPIANTI COCLEARI

Progetto:

EVALUATION OF THE CAUSES OF COCHLEAR DAMAGE AFTER IMPLANTATION AND THE PROTECTIVE CAPACITY OF A DEXAMETHASONE-RELEASING ELECTRODE

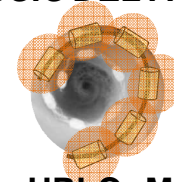


MODELLO ANIMALE



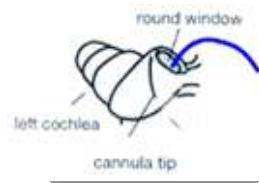
GUINEA PIGS

RILASCIO DEL FARMACO



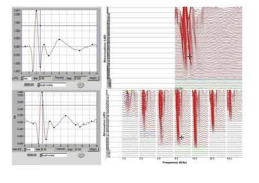
HPLC - MS

IMPIANTO BILATERALE



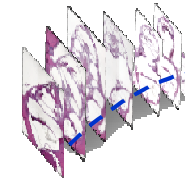
COCLEOSTOMIA

CAPACITÀ Uditiva



Compound Action Potential

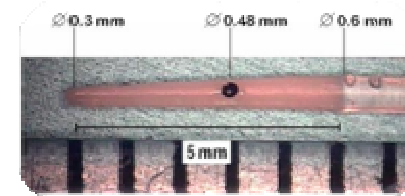
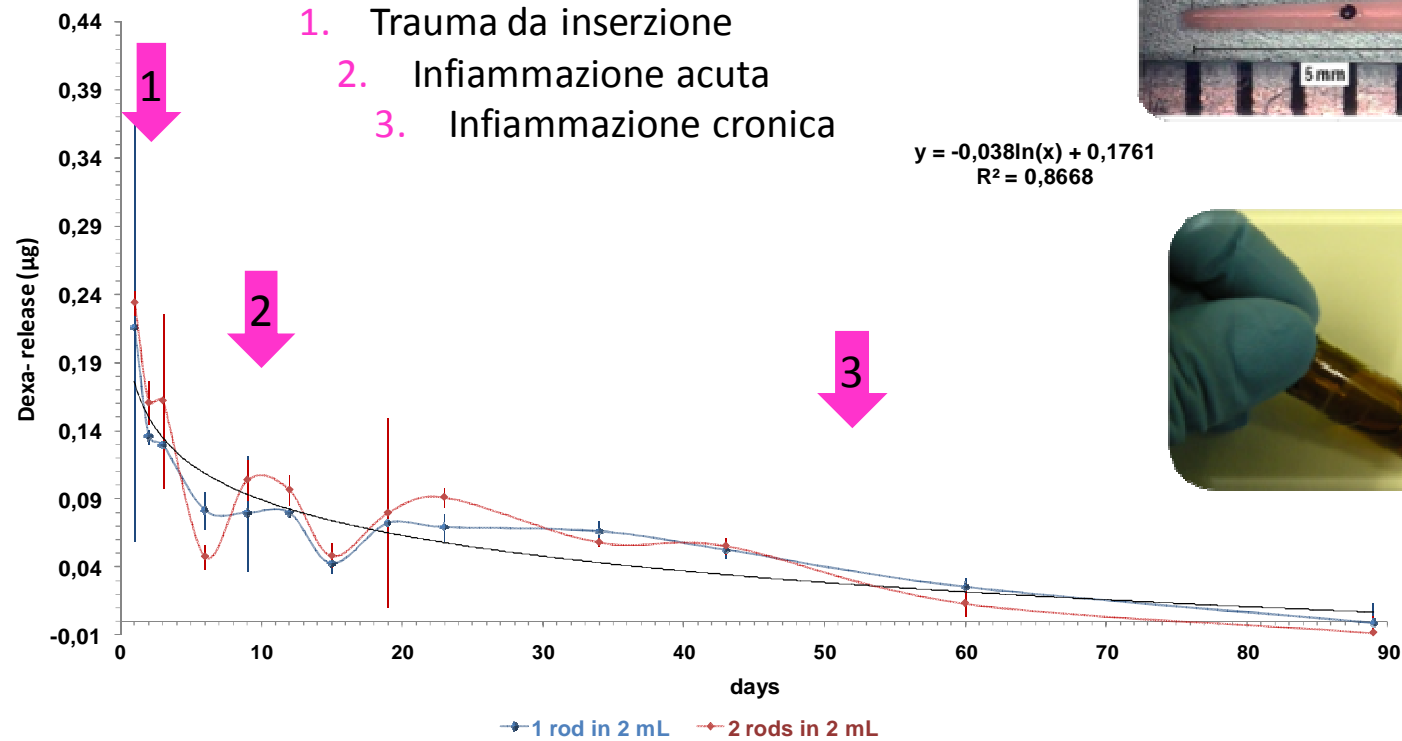
DANNI TISSUTALI



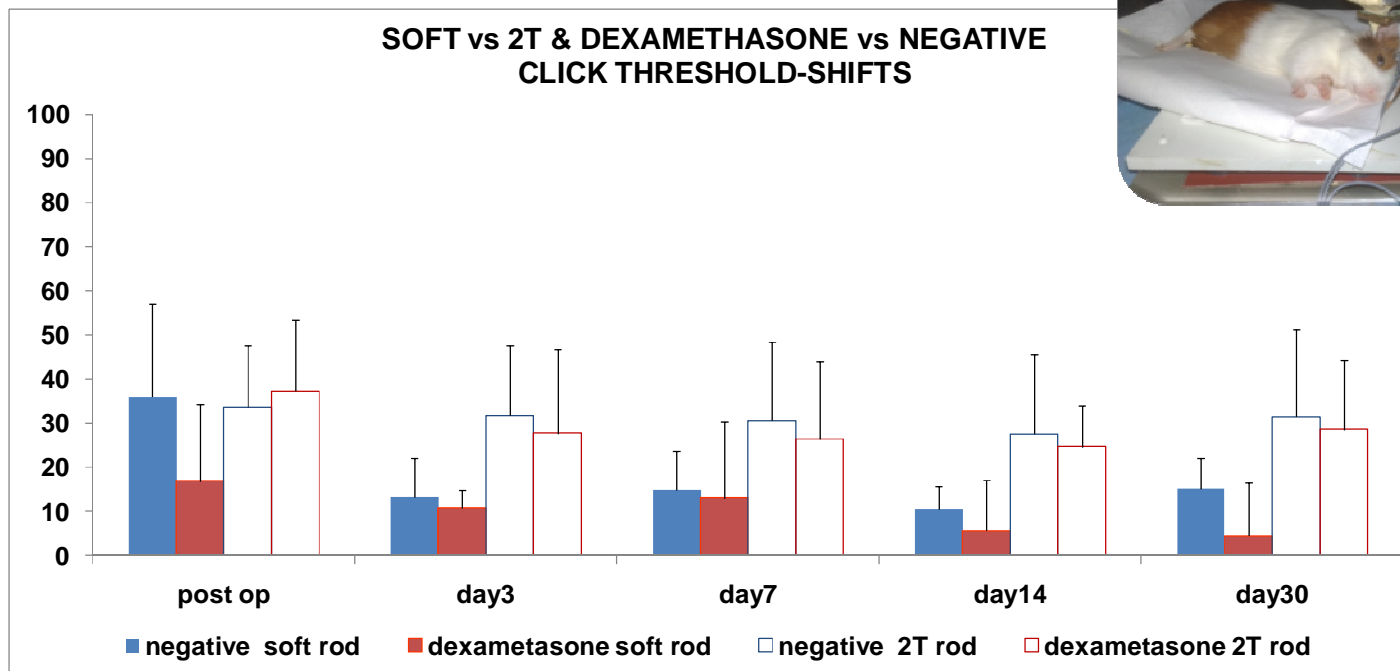
ISTOLOGIA



APPLICAZIONE DIRETTA e IMPIANTI COCLEARI



APPLICAZIONE DIRETTA e IMPIANTI COCLEARI



APPLICAZIONE DIRETTA e IMPIANTI COCLEARI

CRESCITA DI TESSUTO FIBROSO

SCALA TIMPANICA

COCLEOSTOMIA

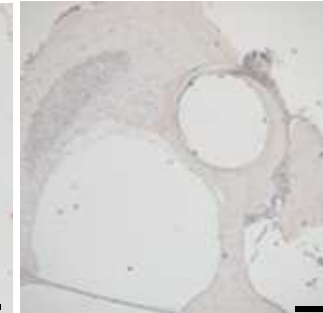
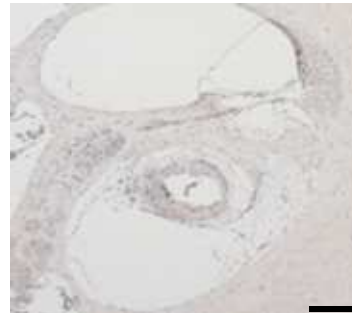
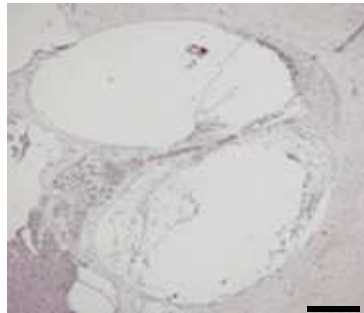
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SOFT 60 days

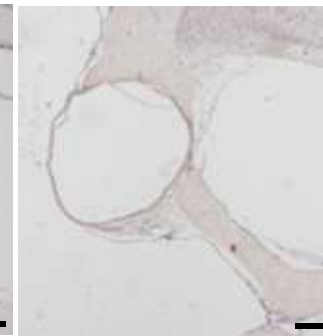
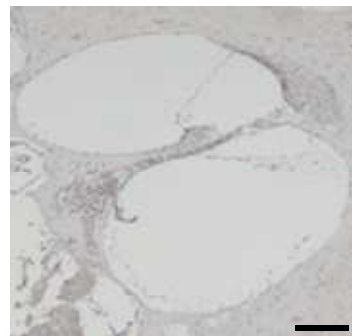
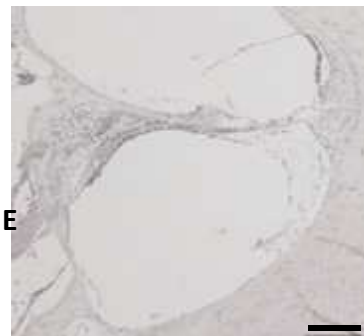
SOFT 30 days

SOFT 60 days

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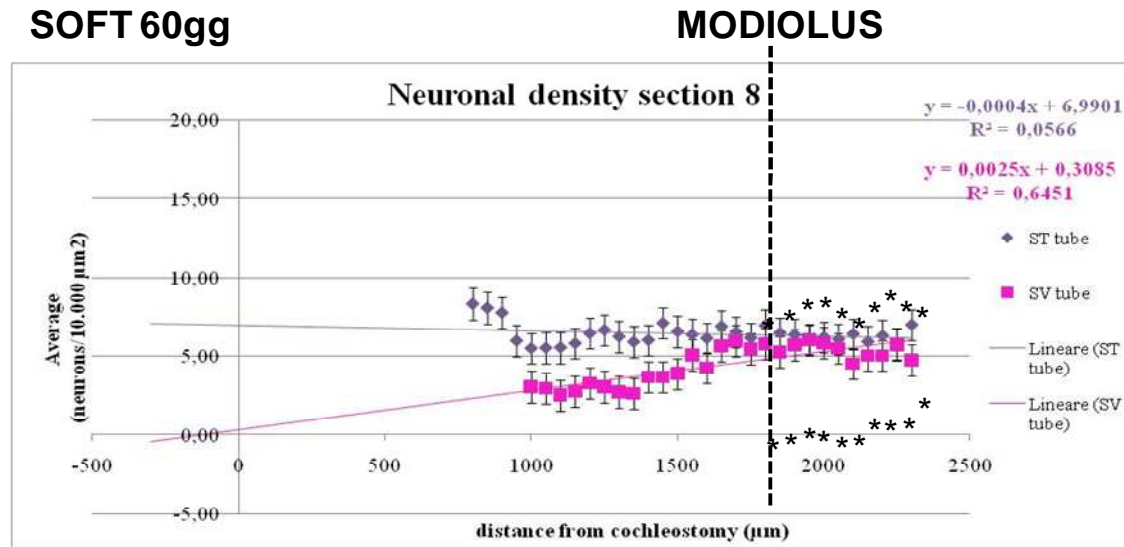


ELUTING
DEXAMETHASONE
RODS

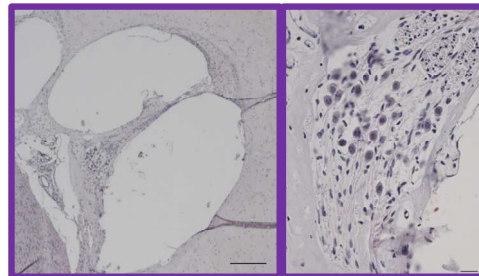


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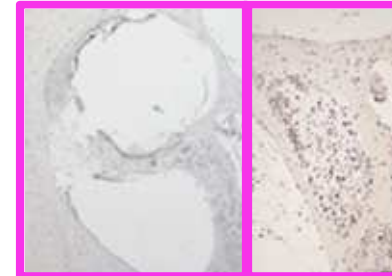
APPLICAZIONE DIRETTA e IMPIANTI COCLEARI



C.I. corretto



C.I. mal posizionato



"STATO DELLA RICERCA SULLA SORDITÀ"

FARMACI CONIUGATI A NANOPARTICELLE

A questo proposito siamo coinvolti in un

progetto europeo, NanoEar,

il quale prevede di testare più tipi di nanoparticelle

incluse in dendrimeri, micelle o lipidi o complessi

polimerici, per costruire un tipo di

NAOPARTICELLA MULTIFUNZIONALE

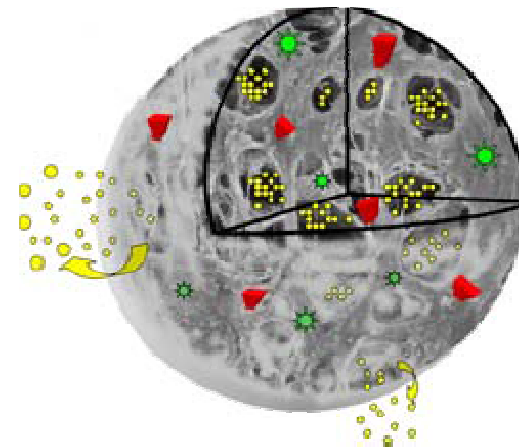
in grado di rilasciare molecole

in tessuti specifici dell'orecchio interno

EU Research proposal: **NMP-2004-3.4.1.5-1**

**Nanotechnology-vectors for targeted
drug and gene delivery**

NANOEAR



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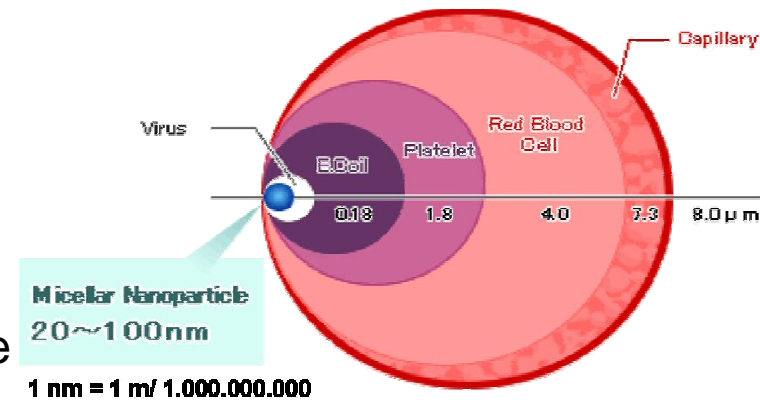


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FARMACI CONIUGATI A NANOPARTICELLE

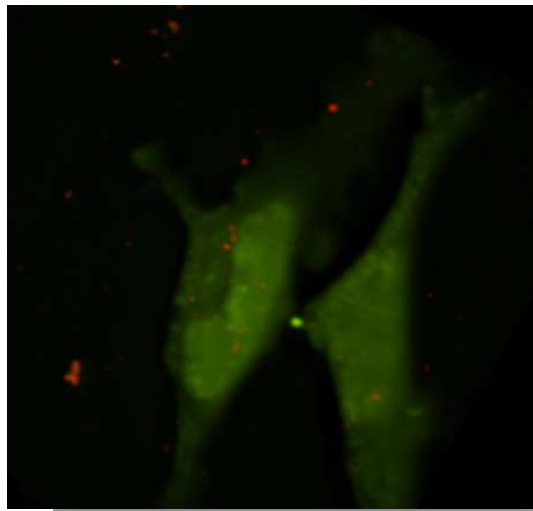
L'utilizzo delle NPs per la diffusione dei farmaci permette di avere

- Aumento della solubilità
- Aumento della biodisponibilità
- risposta terapeutica più veloce
- diminuire le dosi da somministrare

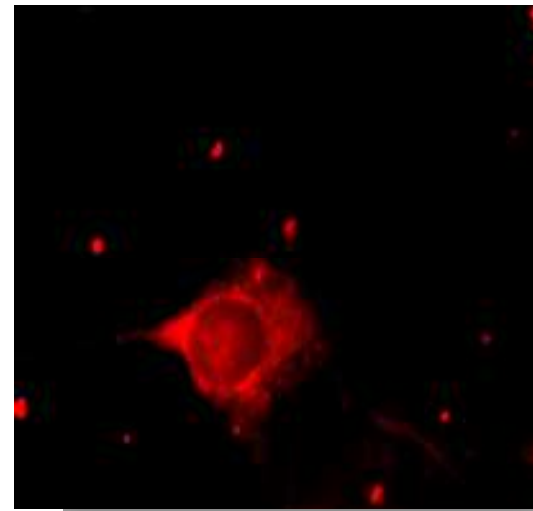


FARMACI CONIUGATI A NANOPARTICELLE

USO DI NPs COME DELIVERY SYSTEM



HeLa
EGFP/HBPL-Texas Red



OC-k3
Qdot

Elisa Corbacella, Alessandro Martini e Ilmari Pyykko (2011).

Il rilascio di farmaci nell'orecchio interno basato sulle Nanotecnologie

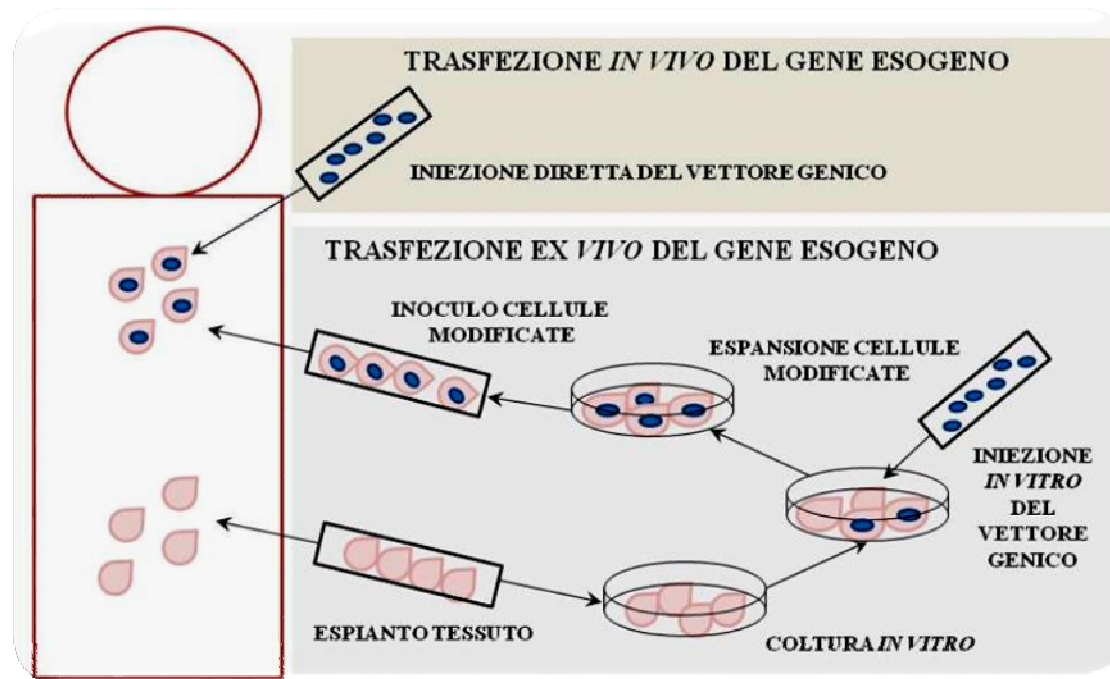
In: Nano & Biotech in Audiologia e Otologia, a cura di A. Martini e G. Paludetti. ISBN 978 88 7241



TERAPIA GENICA

Vettori di trasporto

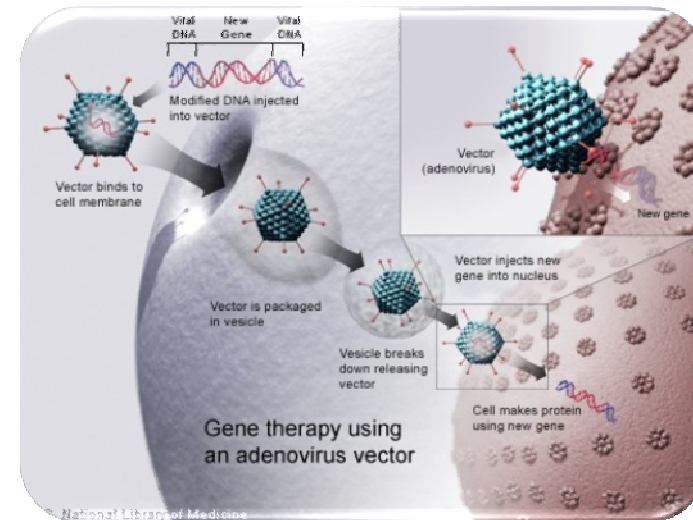
- Virus (es. retrovirus, adenovirus)
- Liposomes
- siRNA
- Sistemi trasponibili



TERAPIA GENICA

VETTORI VIRALI

- Retrovirus
- Adenovirus
- Adeno-associated virus
- Herpesvirus
- Poxvirus



Vantaggi:

- Integrazione stabile del gene

Svantaggi:

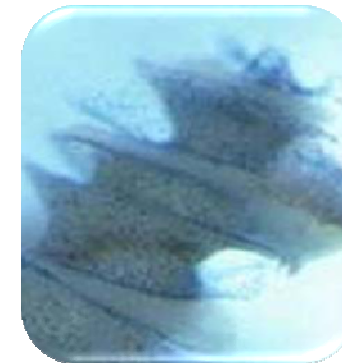
- Piccole dimensioni dei geni da trasferire
- Sicurezza
- mutagenesi
- Immunogenicità/potenziale infiammatorio

TERAPIA GENICA

APPLICATA all'orecchio interno



Neuroscience Letters 207 (1996) 137-141



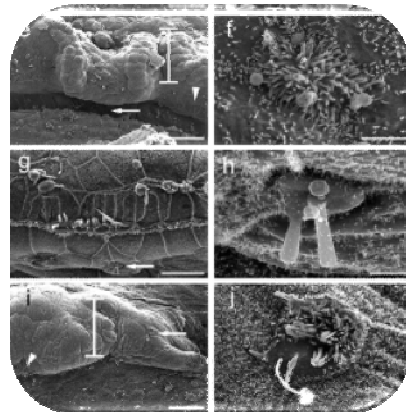
The Journal of Neuroscience, June 1, 2003 • 23(11):4395-4400 • 4395

Adenoviral-mediated gene transfer into guinea pig cochlear cells in vivo

Yehoash Raphael^{1,*}, Juan C. Frisanch², Blake J. Roessler²

¹Kresge Hearing Research Institute, Department of Otolaryngology, 1150 W. Medical Center Drive, Ann Arbor, MI 48109-0648, USA

²Department of Internal Medicine, University of Michigan Medical School, MSRB MI Room 9303, 1150 W. Medical Center Drive, Ann Arbor, MI 48109-0648, USA



Brief Communication

Math1 Gene Transfer Generates New Cochlear Hair Cells in Mature Guinea Pigs *In Vivo*

Kohei Kawamoto,^{1,2} Shin-Ichi Ishimoto,^{1,3} Ryosei Minoda,^{1,4} Douglas E. Brough,⁵ and Yehoash Raphael¹

¹Kresge Hearing Research Institute, Department of Otolaryngology, The University of Michigan, Ann Arbor, Michigan 48109-0648, ²Department of Otolaryngology, Kansai Medical University, Moriguchi, Osaka, 570-8506, Japan, ³Department of Otolaryngology, Tokyo University, Bunkyo-ku, Tokyo, 113-8655, Japan, ⁴Department of Otolaryngology-Head and Neck Surgery, Kumamoto University School of Medicine, Kumamoto, 860-8556, Japan, and ⁵GenVec Inc., Gaithersburg, Maryland 20878



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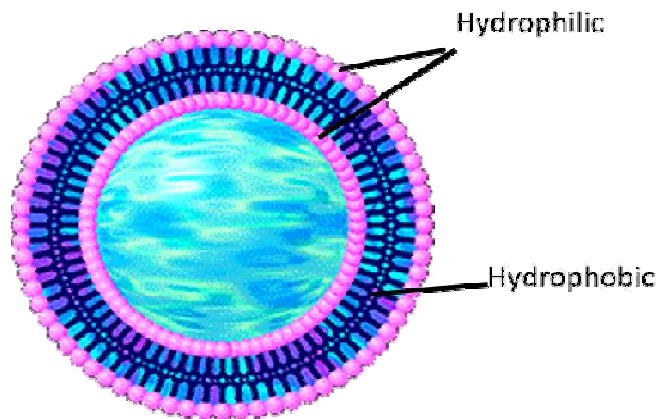
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TERAPIA GENICA

VETTORI NON VIRALI

- Liposomes=lipoplexes
- Polycations=polyplexes
- siRNA

Liposomes=lipoplexes



VANTAGGI

- Disegno versatile
- Non-immunogenic e non-tossici
- Prodotti farmaceutici ben caratterizzati e riproducibili

SVANTAGGI

- No integrazione nel genoma ospite
- Possibili ripetizioni di somministrazione

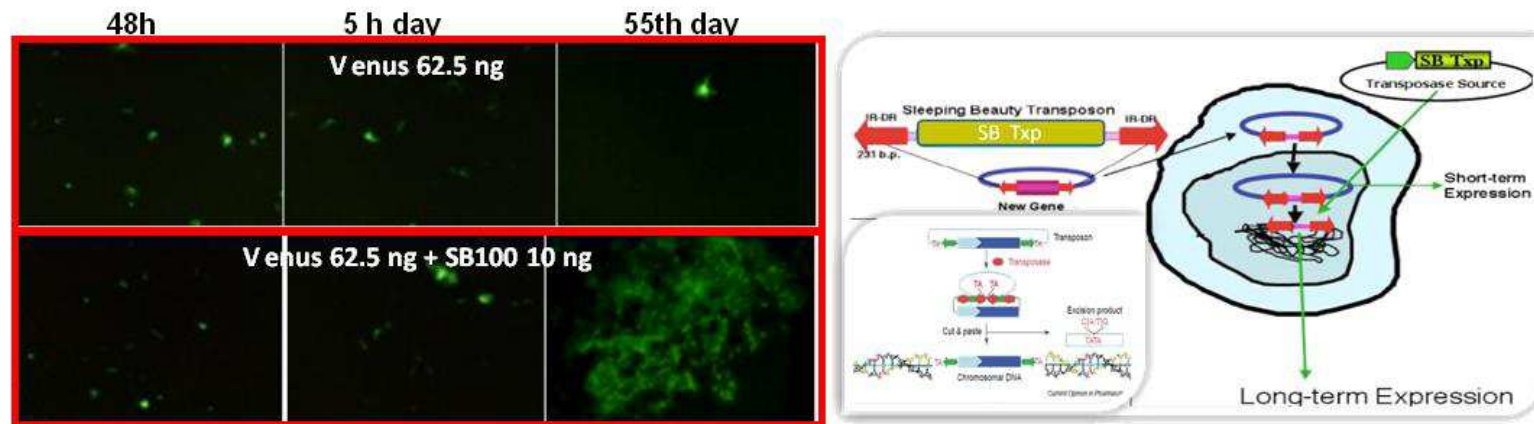
TERAPIA GENICA

IN VITRO efficienza di trasfezione

Modello *in vitro* hFASC stem cells

con **Sleeping Beauty transposable system**

Efficienza di co - Transfection in hearing fetal stem cells



Laura Astolfi, Valeria Guaran, Alessandro Martini (2011)

Terapia genica per l'orecchio interno: presente e futuro

In: Nano & Biotech in Audiologia e Otologia, a cura di A. Martini e G. Paludetti. ISBN 978 88 7241

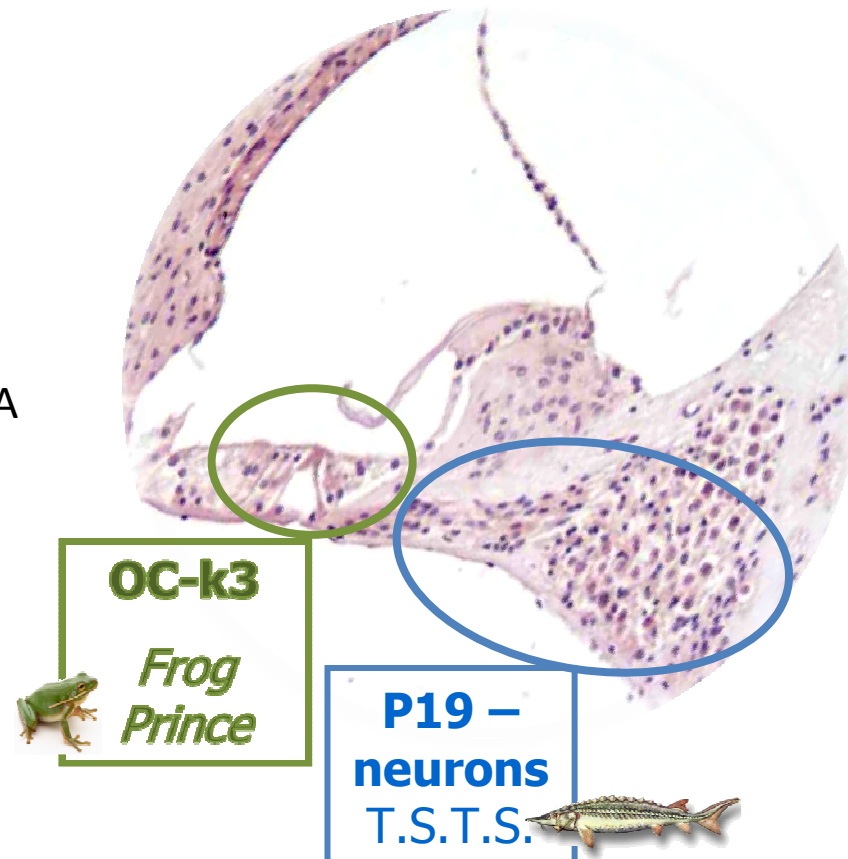
TERAPIA GENICA

-con STEM CELL
in protocolli ex-vivo
verifica dell'integrazione
verifica di dove e come agiscono

- Nuovi SISTEMI DI TERAPIA GENICA

no virus
Integrazioni stabili
differenti target cells

FUTURE APPLICAZIONI



"STATO DELLA RICERCA SULLA SORDITÀ"

PROSPETTIVE FUTURE

The image shows three overlapping screenshots of PubMed search results. The top-left screenshot is for the search term "inner ear and stem cells", showing 1523 results. The top-right screenshot is for "inner ear and gene therapy", showing 380 results. The bottom-right screenshot is for "inner ear nanoparticles", showing 59 results. Each screenshot includes the search bar, filters, and a list of search results with titles and abstracts.

CELLULE STAMINALI

GENE THERAPY

NANOTECNOLOGIE



Laboratorio di Bioacustica



Università di Padova



Campus Biomedico Pietro d'Abano

"STATO DELLA RICERCA SULLA SORDITÀ"



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GRAZIE PER L'ATTENZIONE

