Stem cell therapy

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The potency of cells

- Cells
- Tissues
- Organs
- Systems
- Body

300 Billion New Cells Every Day

200 Million Per Minute
How many stem cell types can be used?

- Embryonic
- **IPS**
  - *(Induced Pluripotent Stem cells):*
  - Adult cells genetically manipulated to become embryonic-like

- Adult
The importance of regenerative medicine field

- Regenerative medicine treatments were mainly proposed for rare diseases.
- Regenerative medicine allows studies on drug targets or to target personalized drugs.

Therefore, Regenerative Medicine, when carefully controlled, has an impressive potential.

Normal eye

Corneal damage due to Lost of corneal stem cells

The Eye
The pathophysiology

Renewal of human ocular surface is stem cell-mediated

Damage of corneal stem cells

Mechanism of repair of the corneal damage

Conjunctivalization (repair by conjunctival cells)

Vessel migration
Stroma opacification
The in vitro corneal reconstruction

1° step

THE LANCET
Long-term restoration of damaged corneal surfaces with autologous cultivated corneal epithelium

Graziella Pellegrinii, Carlo E Traverso, Adriano Tito Franzii, Mario Zingifian, Ranieri Canciadda, Michele De Luca

Vol 349 • April 5, 1997
The in vitro corneal reconstruction

2° step

Several Control steps on cultures

Limbal Stem-Cell Therapy and Long-Term Corneal Regeneration

Paolo Rama, M.D., Stanislav Matuska, M.D., Giorgio Paganoni, M.D., Alessandra Spinelli, M.D., Michele De Luca, M.D., and Grazziella Pellegrini, Ph.D.
Integration in patients

Conjunctivalization of ocular surface (opacity)

Surgery: Removal of conjunctiva from corneal surface

Engraftment of cultured limbus containing stem cells

Corneal restoration Stem cell "relocalization"
The clinical benefit

Before                                   After
(4 yr) now 11 y (6 yr) now 13 y (6,5 yr) now 13,5 y (1,5 years) now 10,5

Follow up at date of publication in brackets

CK12

Corneal marker restoration
**Efficacy on long term**

**Academic setting (112 patients)**

- Partial success: 16.8%
- Failure: 15.0%

**GCP setting (139 patients)**

- Partial success: 13.5%
- Failure: 10.3%

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**GMP/GCP setting (15 patients)**

- Success: 60%
- Failure: 40%
- Total: 15

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**Clinical Safety**

Retrospective evaluation of the **efficacy and safety**

Date of production: 09/08/2010

<table>
<thead>
<tr>
<th>Confirmed</th>
<th>N° eyes</th>
<th>Success</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>Final outcome</td>
<td>139</td>
<td>72.8%</td>
<td>10 years</td>
</tr>
</tbody>
</table>

**Continuous monitoring of results**

Retrospective evaluation
Confirmed safety of procedure
Why long term follow up?

• To minimize risks of harm

• To maximize contribution to general knowledge
  (results, meaning of researches, interpretability of data)

• To allow selection of the best treatments for the different types of patients
The steps to EU therapy certification and spreading

2008:
- Orphan Medicinal Product Designation by COMP
- Definition of Advanced Therapy Medicinal Product by ITF

2009:
- Inspection from AIFA
- Validation from regional authorities
  - Inspection from CNT

2010:
- Inspection from AIFA
- Scientific Advice with PEI;
  Procedure of PA #3 with CAT;
  approval PIP by PEDCO

2011:
- Acknowledgement Of status of clinically consolidated therapy:
  1° GMP-treated patient

2013:
- CTD:
  Question and answer from European medicinal agency

2014:
- Conditional Approval of the First Stem Cell Product for Commercialization in Europe

2015:
- Conditional Approval of the First Stem Cell Product for Commercialization in Europe
How to overtake HURDLES

• Public-private partnership
  - share resources and money
  - synergizes industrial and scientific know-how
  - more efficient fund raising and project planning
  - efficiently drives therapies to patients

• Public-private partnership requires well defined agreements and objectives
How to overtake HURDLES

• The commitment to these complex therapies requires well educated and responsible people

• Training of operators is patient-oriented

• Continuous training and re-training in the organization

• Matrix hierarchy to improve responsibility, interconnection between operators and best perception of the whole process
How to overtake HURDLES

• Treatments require different scientists, surgeons, regulators, and patients

Therefore

• Networking and planning together all activities

we connect patient’s association (i.e.: Debra Sud Tirol for gene therapy) with research activities

As well as a network of surgeons contributing to diagnosis and knowledge (i.e.: diagnosis was quickened)

with common aims and credit
What is requested from patient's association

- Spread knowledge of pathologies, symptoms, quality of life, problems
  (continuous updating on points to consider and long term results/risks)

- Life long cost of pathologies with no or poor therapeutic alternatives should be known
What is requested from patient’s association

- **Actively** join the research projects

- Help scientist to have patient’s samples as well as *normal control samples* (often much more difficult to find)

- **Harmonization** of criteria/priority within the patient’s association
personalized medicine

Real, efficaceous and safe treatments

It’s all about your genome, and we have something JUST for you.
The gene therapy approach

Genetically Defective cells

Transgene

Genetically Corrected autologous epithelium

Transplant
THANK YOU FOR YOUR ATTENTION!
Normal homeostasis: Segregation of corneal regenerative properties in the human limbal area
The in vitro corneal reconstruction

1 mm biopsy

Stimulation of proliferation & differentiation

CONTROLS on Several markers Clonogenicity, microbiology

CULTURED CORNEAL EPITHELIUM ON SUBSTRATE

THE LANCET

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Resting stem cell Activated stem cells and early TA

The NEW ENGLAND JOURNAL OF MEDICINE

Limbal Stem-Cell Therapy and Long-Term Corneal Regeneration

Paolo Rama, M.D., Stanislav Matuska, M.D., Giorgio Paganoni, M.D., Alessandra Spinelli, M.D., Michele De Luca, M.D., and Graziella Pellegrini, Ph.D.
Corneal regeneration by cultures of limbal stem cells
(up to 10 years follow-up in a mono-centric study)

Long term clinical results in 112 patients with chemical-burn (86.6% unilateral and 13.4% bilateral)
all patients had severe symptoms, loss of vision and no alternative therapy

<table>
<thead>
<tr>
<th>SUCCESS (% of total)</th>
<th>PARTIAL SUCCESS (% of total)</th>
<th>FAILURE (% of total)</th>
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<tbody>
<tr>
<td>76.6%</td>
<td>13.1%</td>
<td>10.3%</td>
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KEY FIRST RESULTS
Retrospective evaluation of the efficacy and safety of autologous cultivated limbal stem cells transplantation for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns

PROTOCOL NUMBER: HLSTM01
Date of production: 09/08/2010
AND
Retrospective evaluation of the safety of autologous cultivated limbal stem cell transplantation for restoration of corneal epithelium in patients with limbal stem cell deficiency

PROTOCOL NUMBER: HLSTM02
Date of production: 29/09/2010

GCP STUDY DOUBLE BLIND EVALUATION confirmed efficacy (72.8%) and safety of procedure
Limbal-corneal lesion
- advice on how to accelerate drug development, based on your experience

- What should be changed in the classical regulatory and scientific environment?

- What are the hurdles you are currently facing? How are you planning to overcome them?

Vd PDA presentation

- Graziella, I may ask you how you would compare cell (Holoclar) and gene therapy in this respect.

- Solutions to speed-up drug approval

- What patients can do, besides lobbying?
Corneal regeneration by cultures of limbal stem cells (up to 14.5 years follow-up in a multi-centric study)

Long term clinical results in 154 patients (up to 14.5 years follow up, median of 8 years)

All patients had severe symptoms, loss of vision and poor or no alternative therapy.