

Terapia Celular y Reparación del Sistema Nervioso Central

Profesor Gustavo A Moviglia

Dr. en Medicina. Director del CIITT

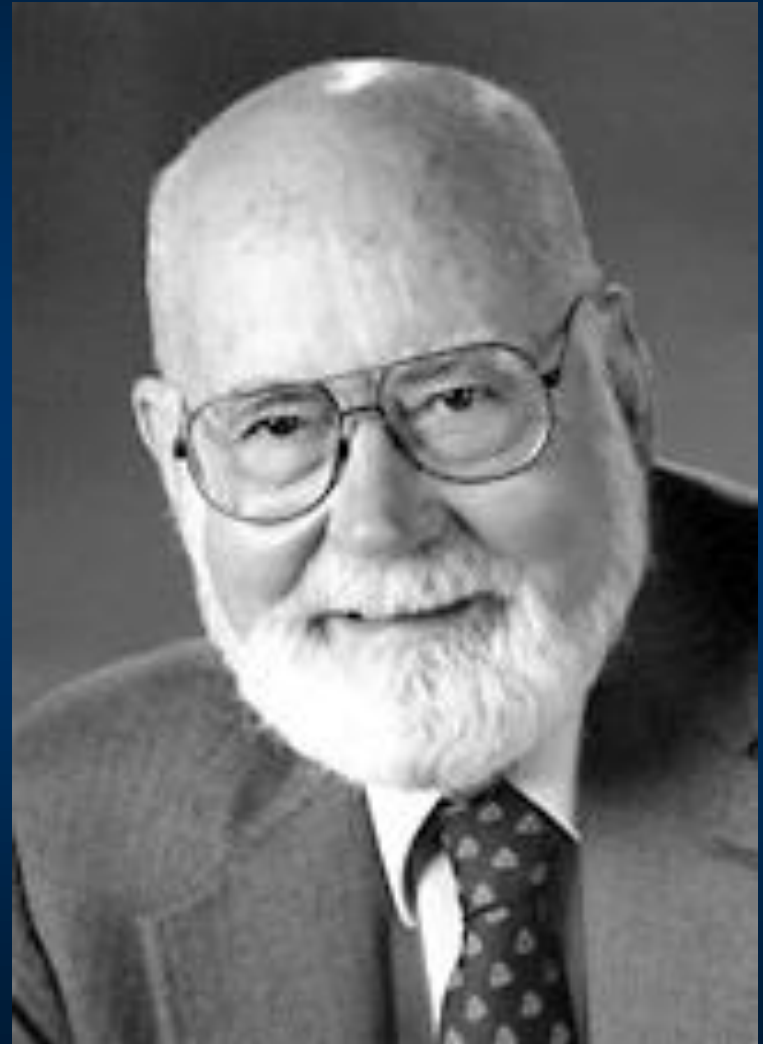
Universidad Maimónides – Buenos Aires - Argentina

Terapia con Células

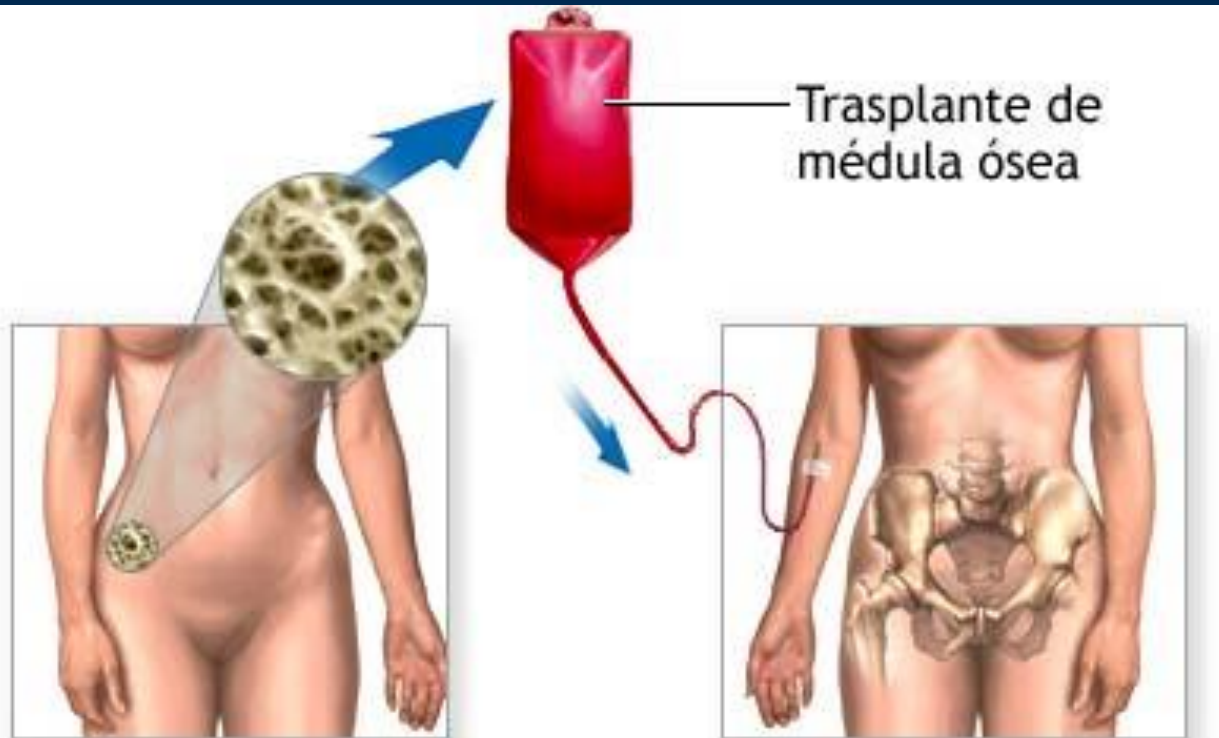
El uso de células vivas, **procesadas ex – vivo** y reintroducidas en un organismo humano con el objeto de curar, mitigar, prevenir o diagnosticar una enfermedad o condición patológica.

E. Donnall Thomas

Desarrollo desde el año 1955 en animales y humanos (1957) el trasplante de Médula Ósea. Por este motivo se le otorgó el Premio Nobel de Fisiología y Medicina en el Año 1990



Transplantes de células hematopoyéticas



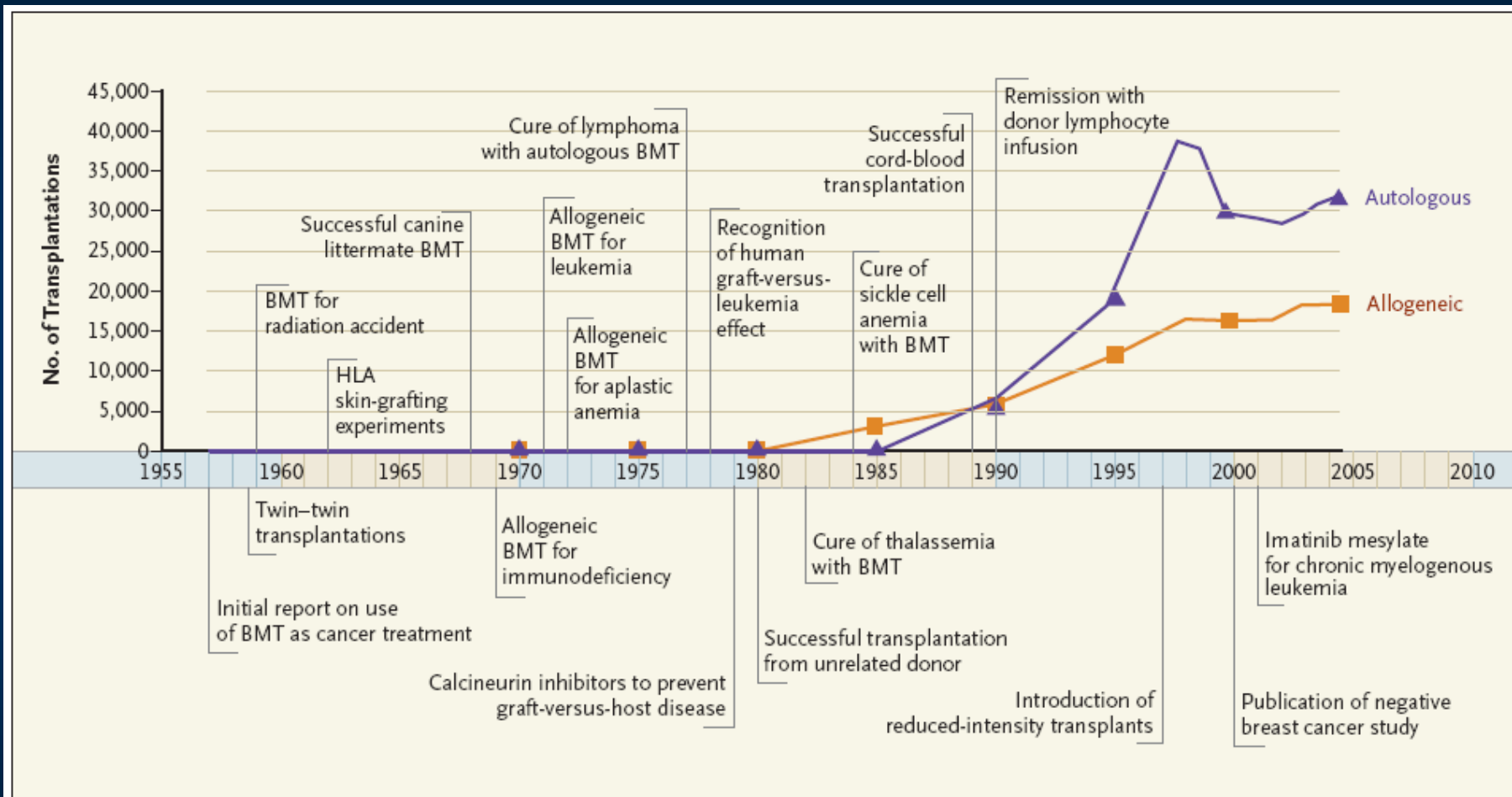
Donante

Receptor

Las células de la médula ósea del donante pueblan la médula ósea del receptor

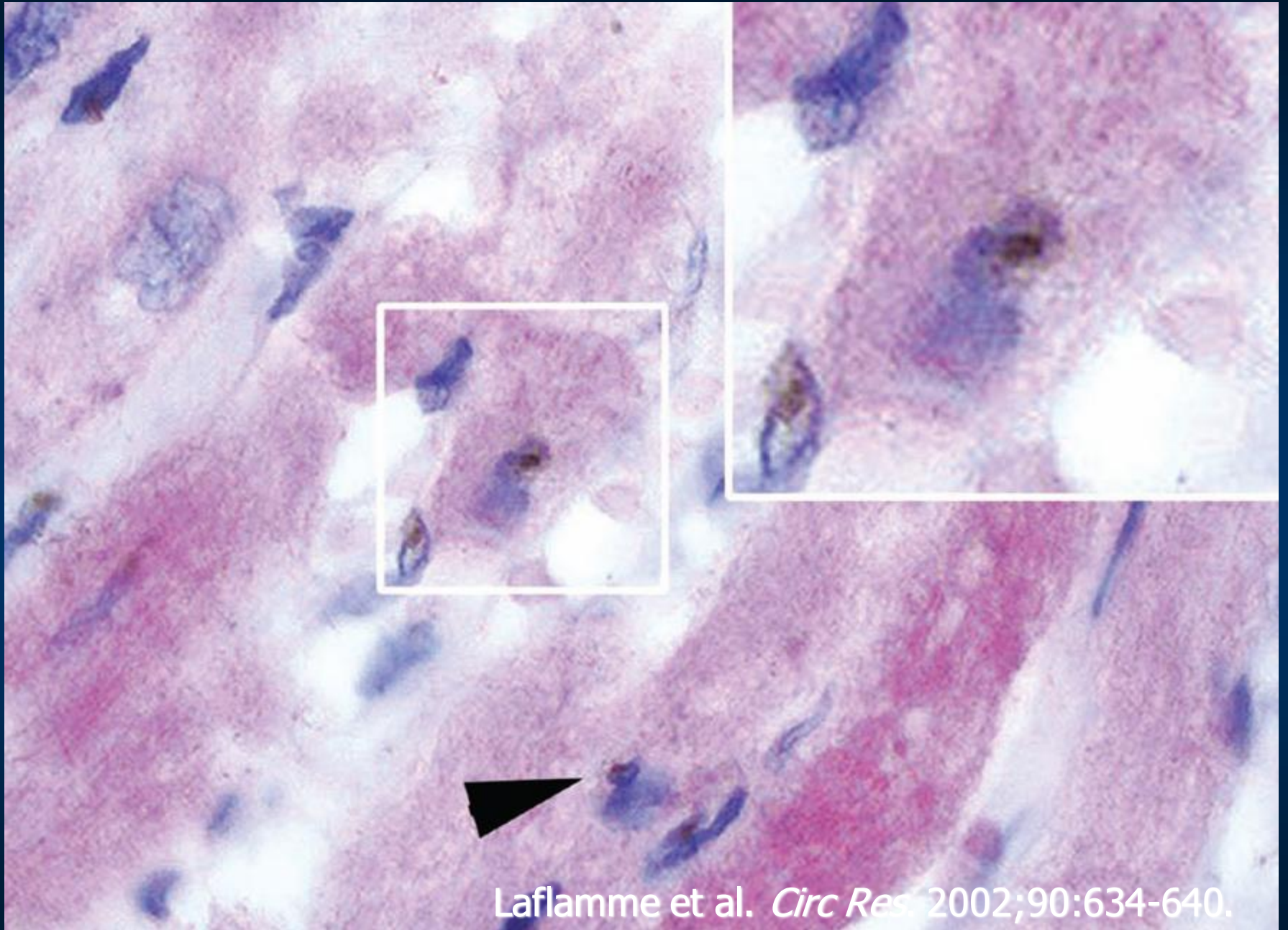
Hematopoietic-Cell Transplantation at 50

Frederick R. Appelbaum, M.D. N ENGL J MED 357;15 WWW.NEJM.ORG OCTOBER 11, 2007



Timeline Showing Numbers of Bone Marrow Transplants and Advances in the Field, 1957–2006.

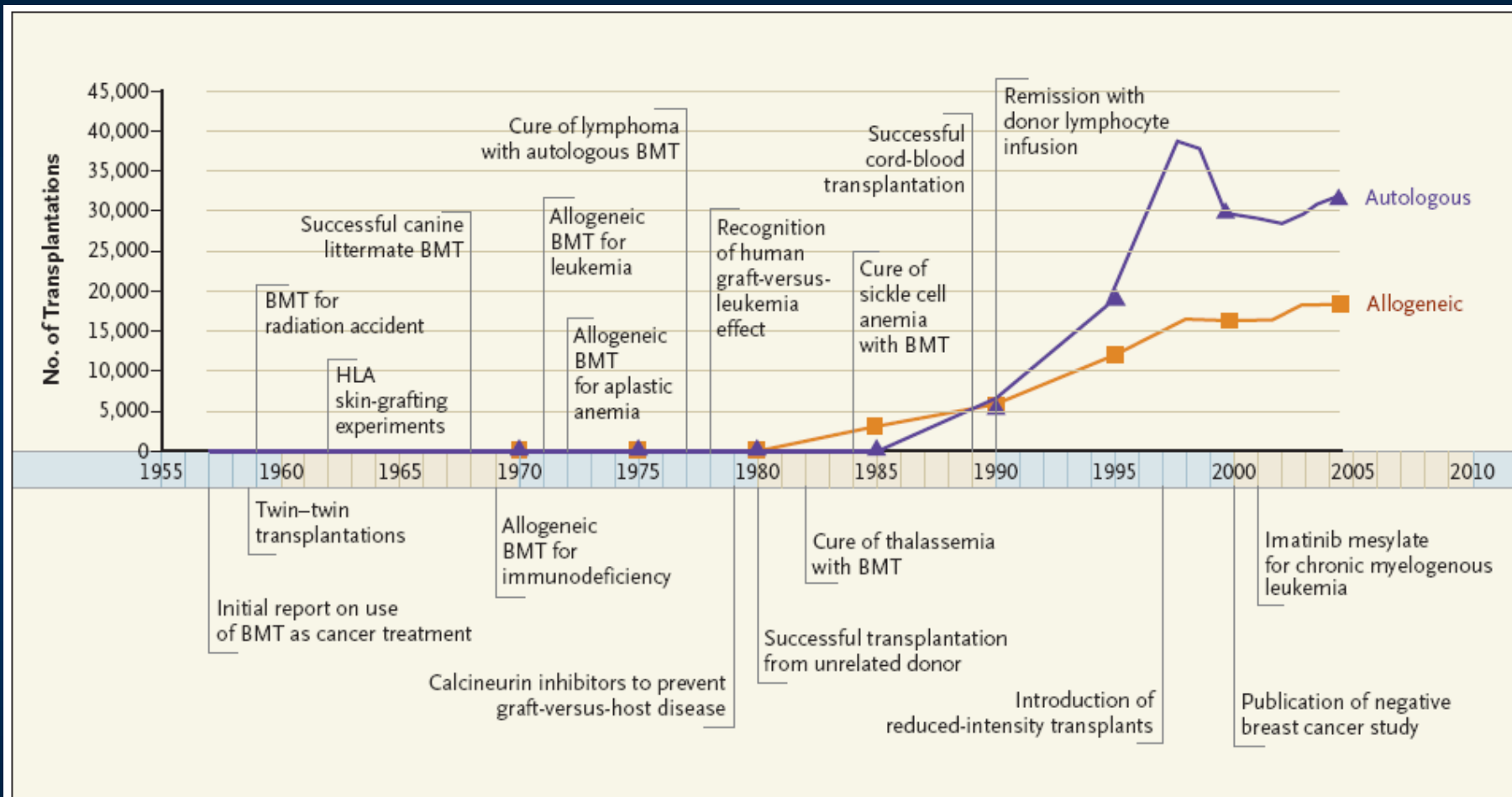
BMT denotes bone marrow transplantation, and HLA human leukocyte antigen. Data are from the Center for International Blood and Marrow Transplant Research.



Laflamme et al. *Circ Res* 2002;90:634-640.

Hematopoietic-Cell Transplantation at 50

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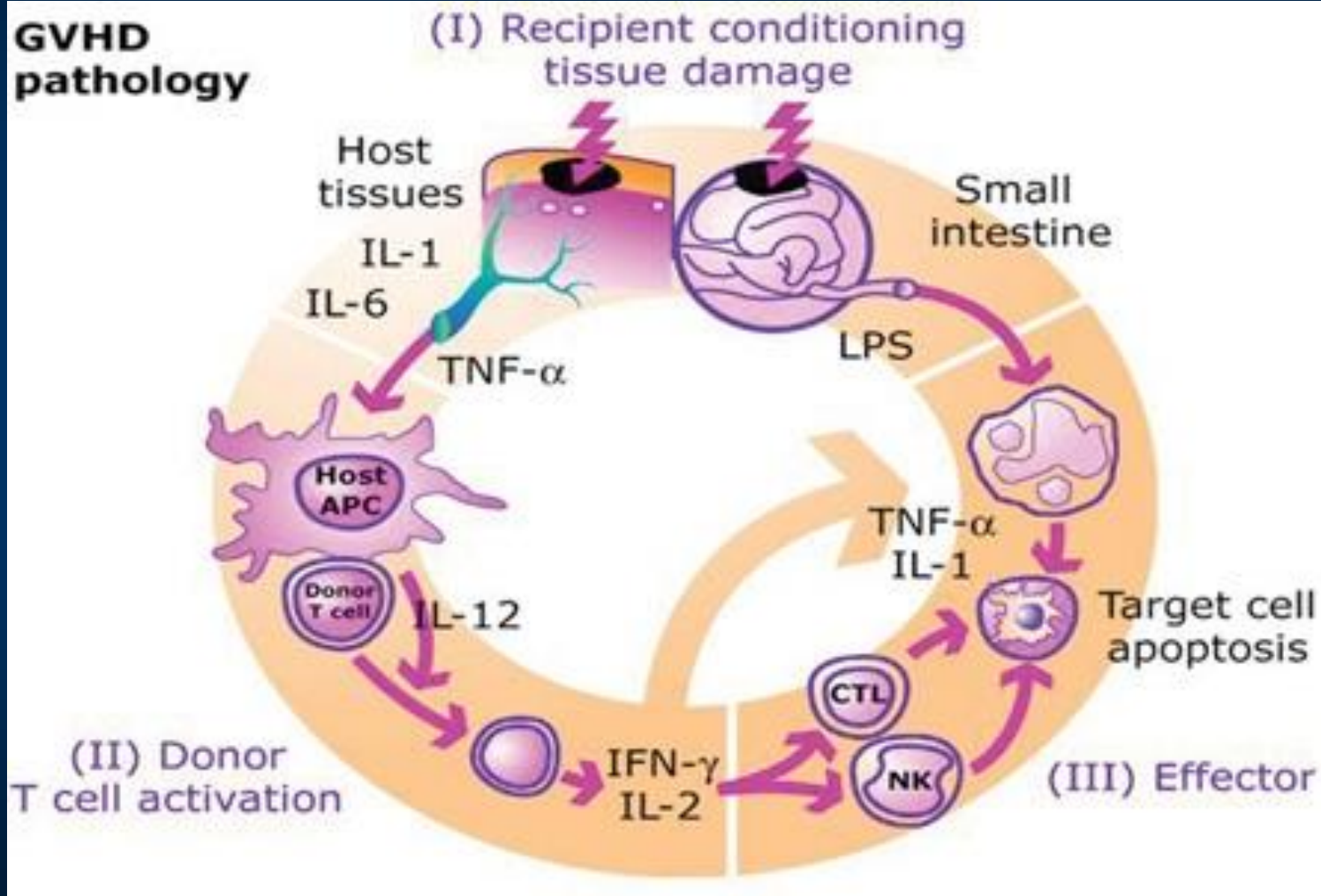
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Lecciones del Trasplante de Células Hematopoyéticas

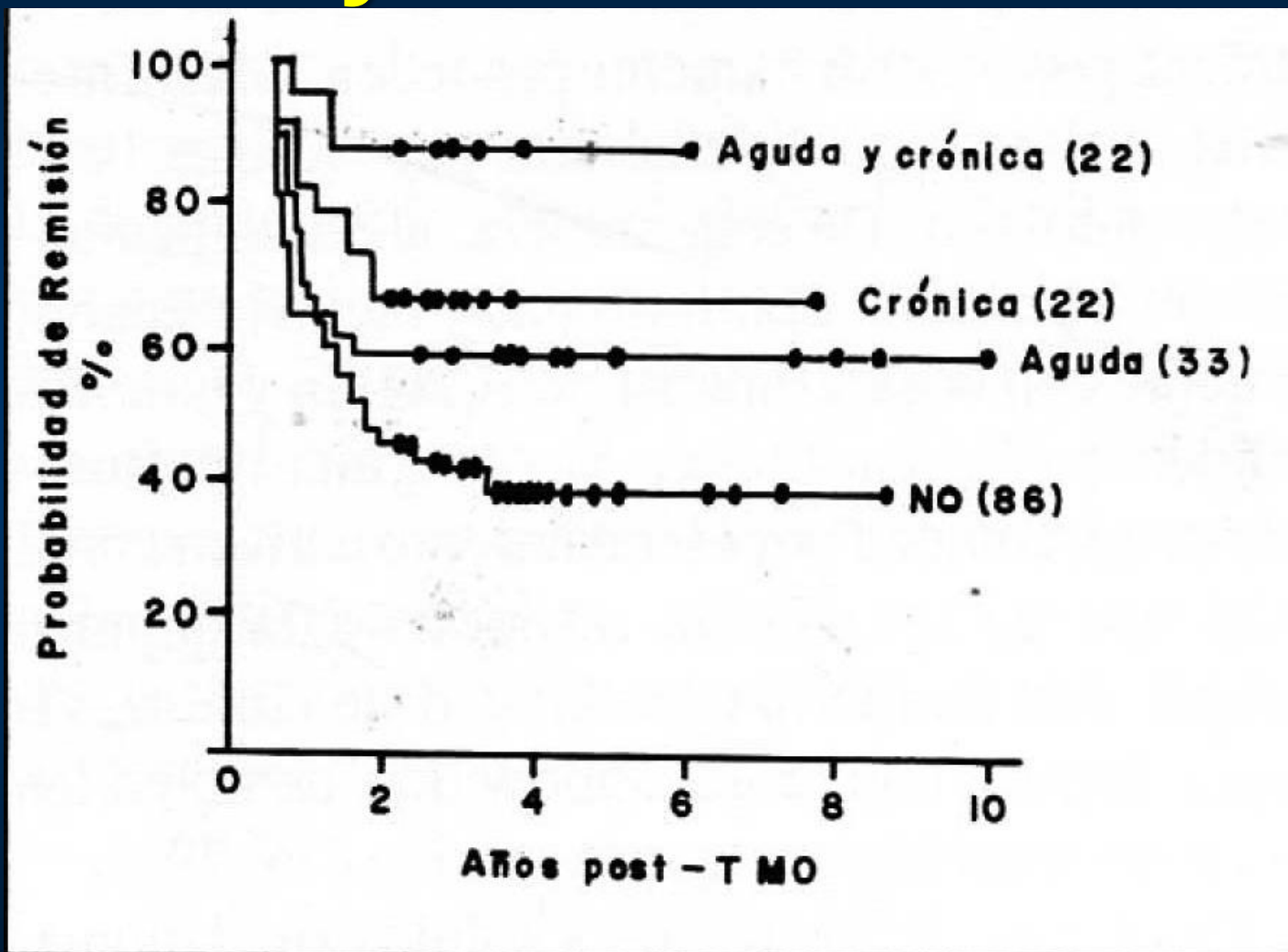
- 1.- Las células, implantadas por transfusión venosa, superan el filtro pulmonar y se dirigen a la despoblada médula ósea. **Se implantan donde el organismo las necesita y les permite.**
- 2.- **Su actuar no es instantáneo** sino que se despliega durante los días subsiguientes al implante.
- 3.- **Las células y el organismo receptor deben aceptarse mutuamente.** De su correcta recepción, por parte del paciente, depende el que estas células puedan comenzar a producir plaquetas, glóbulos rojos y glóbulos blancos.

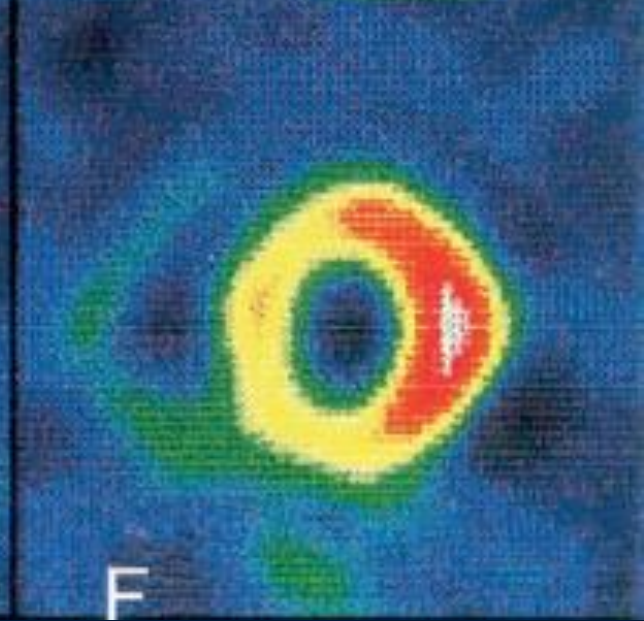
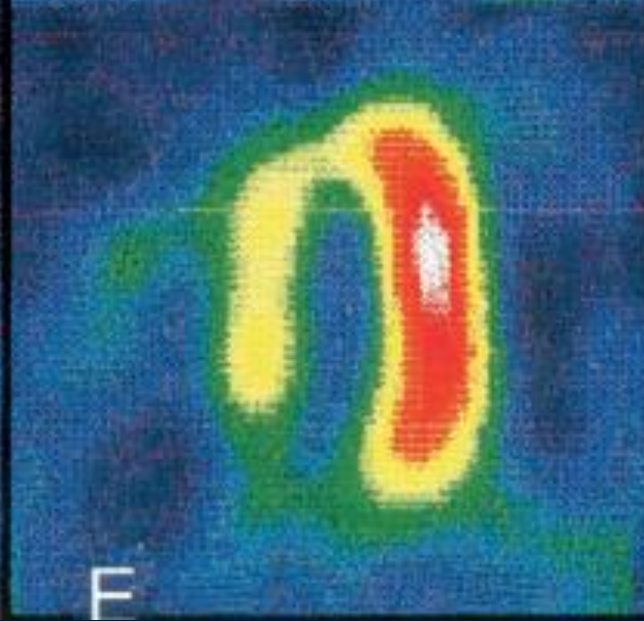
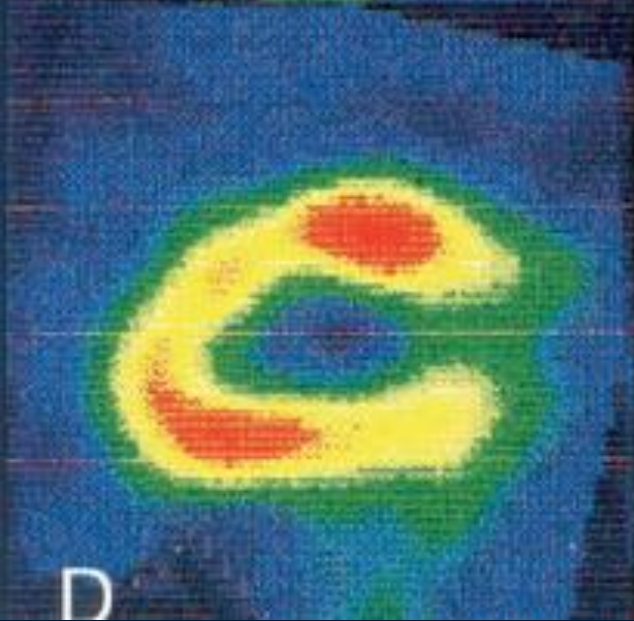
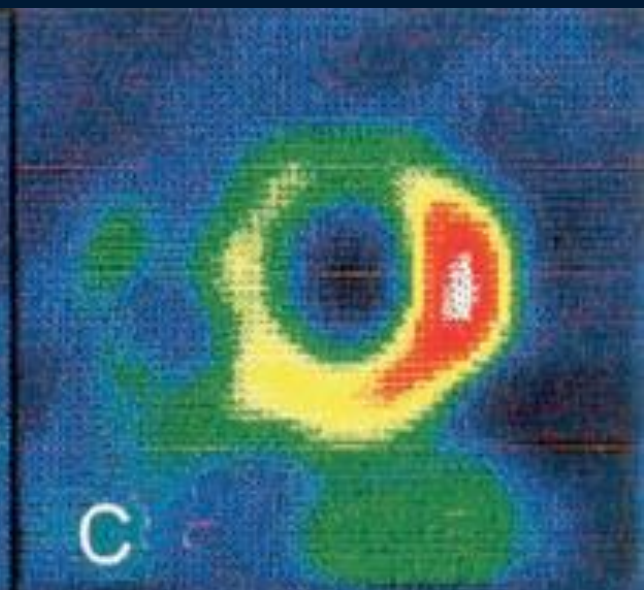
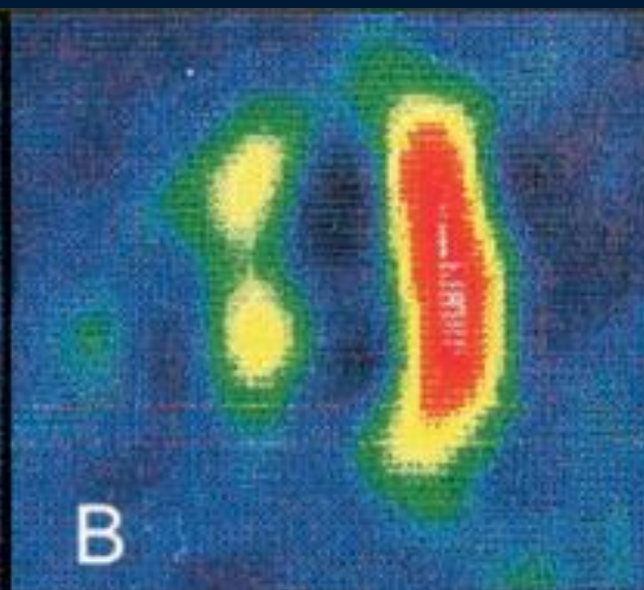
Graft Versus Host Diseases

GVHD pathology

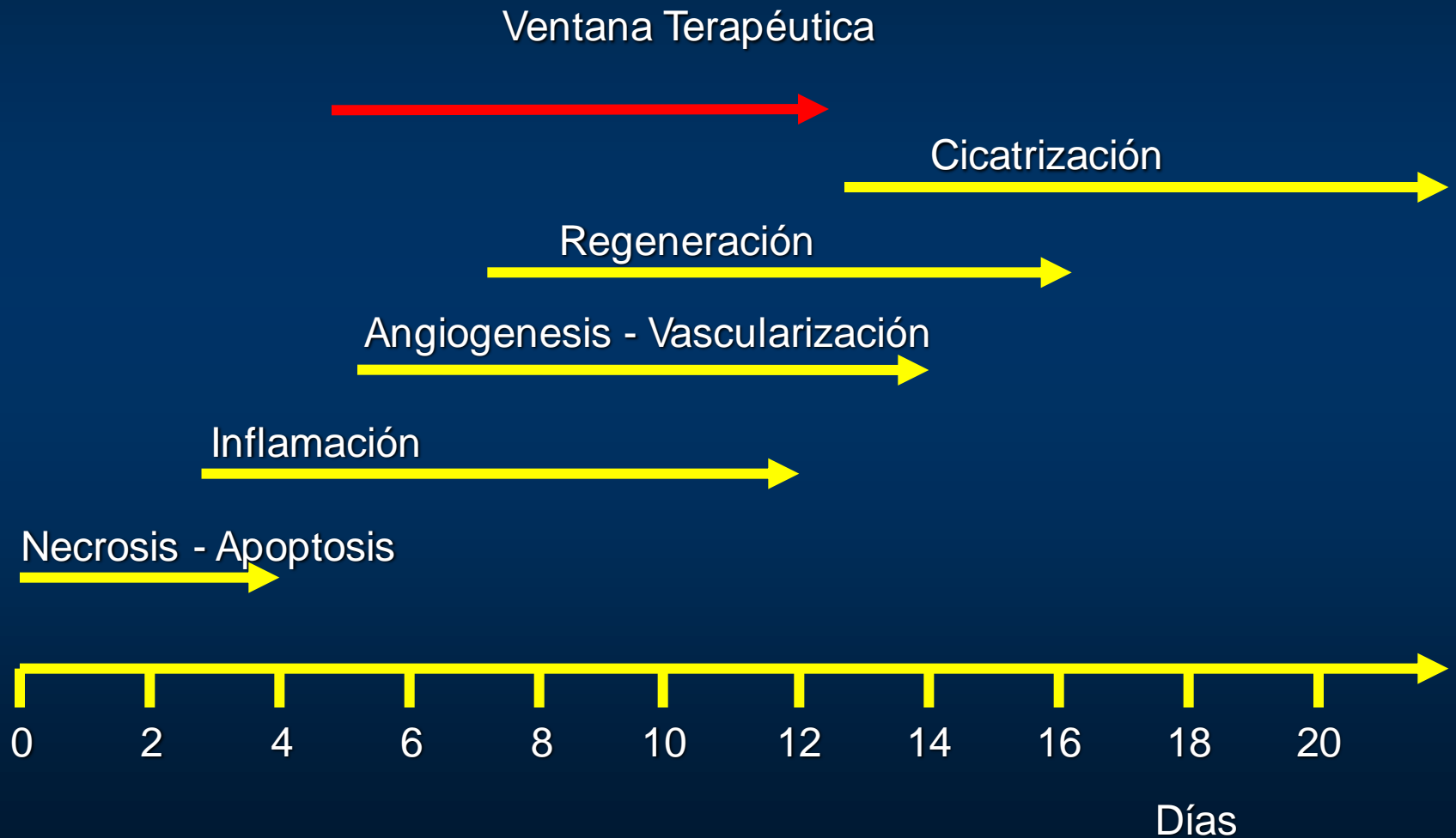


Efecto Injerto Contra Leucemia

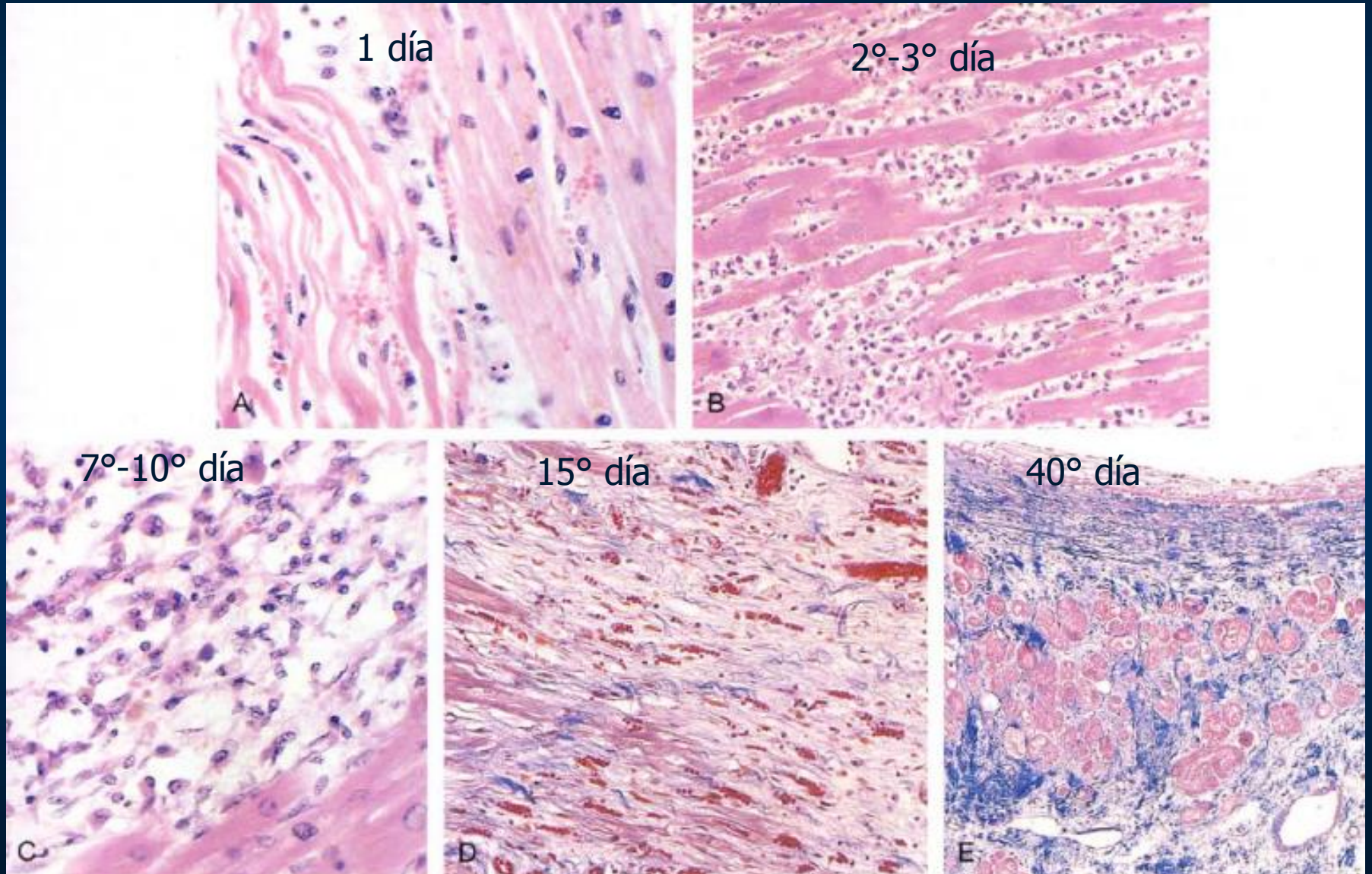


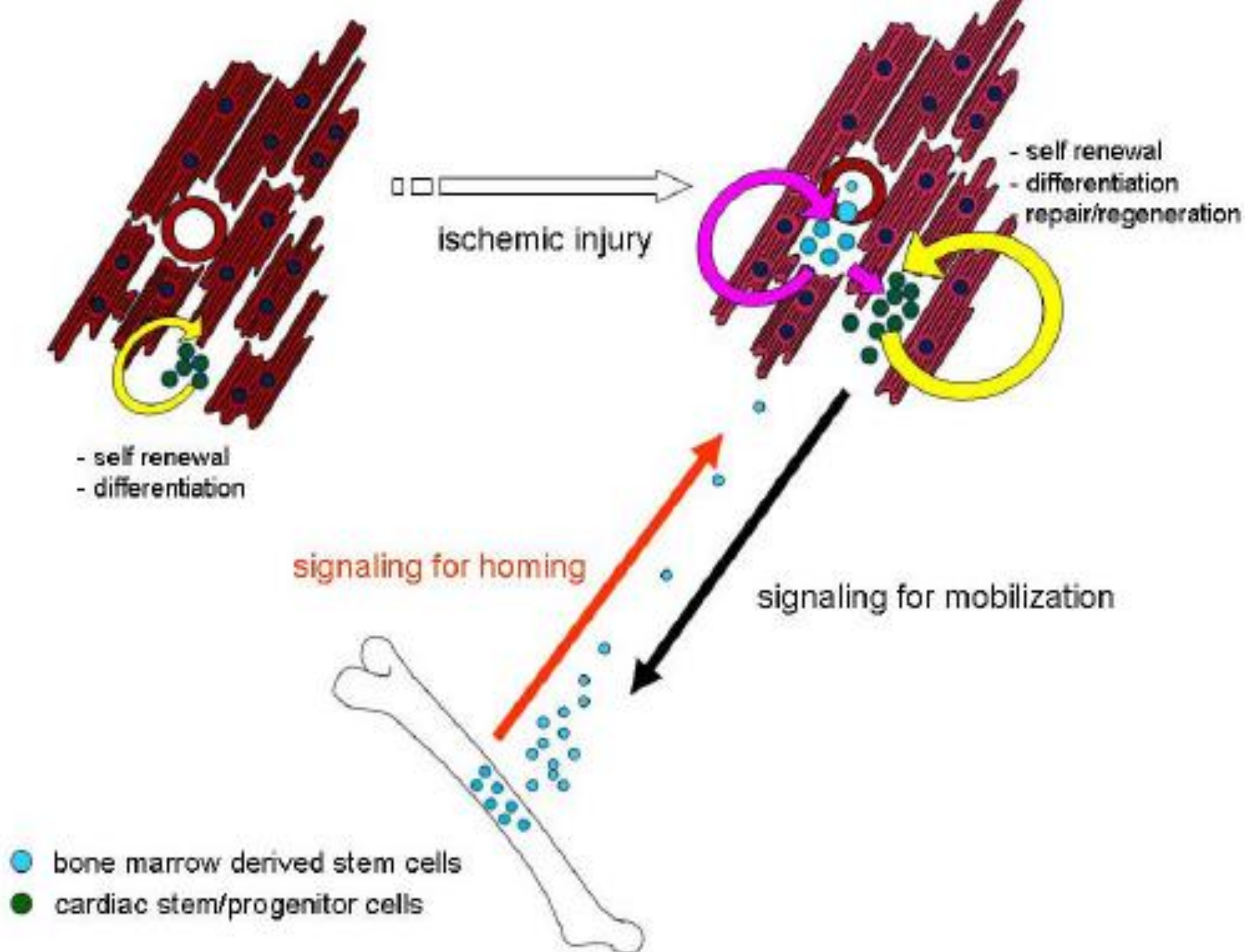


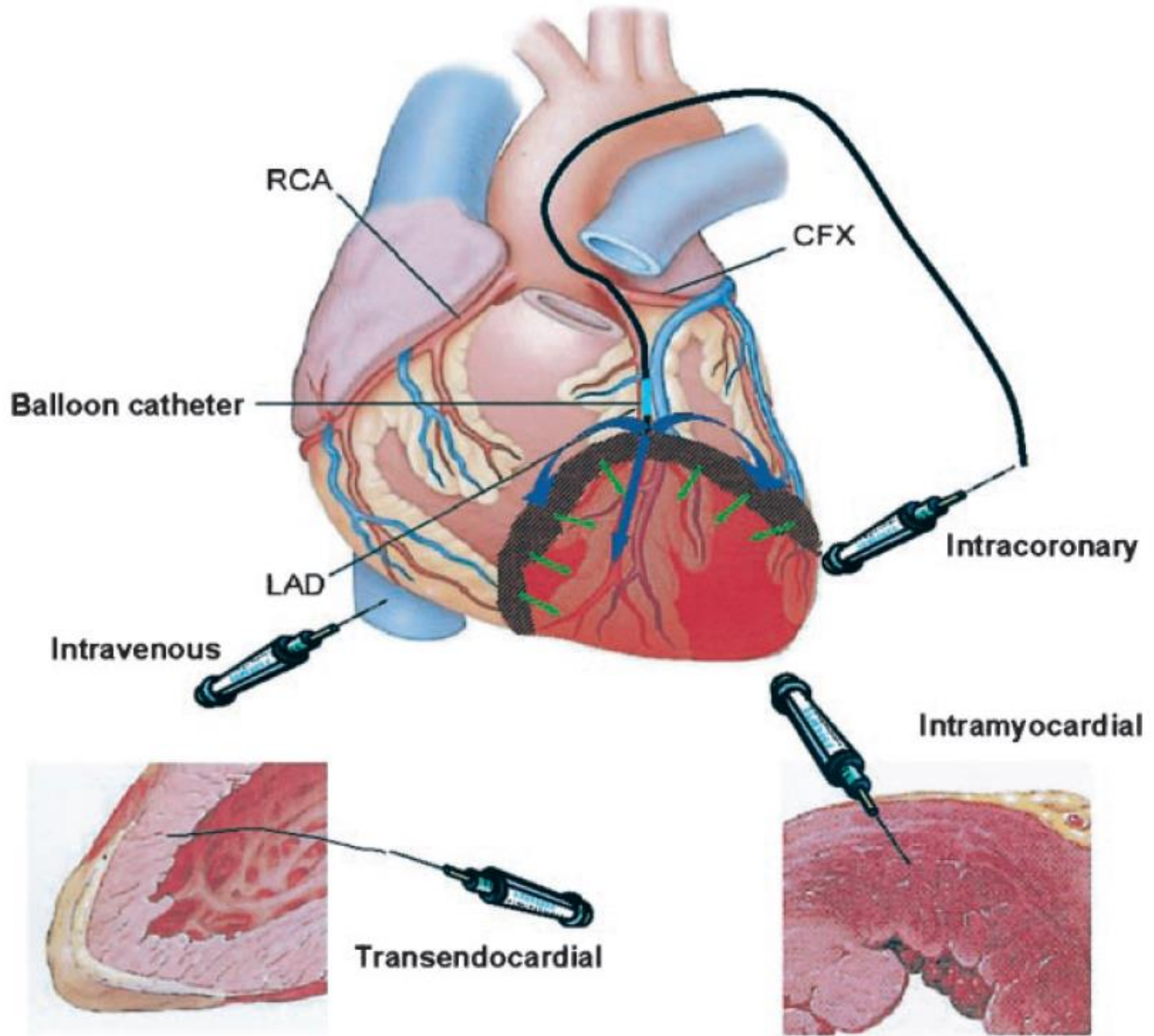
Evolución de la Lesión del IAM



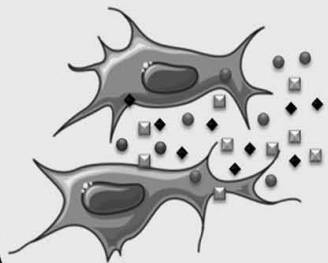
Evolución del IAM





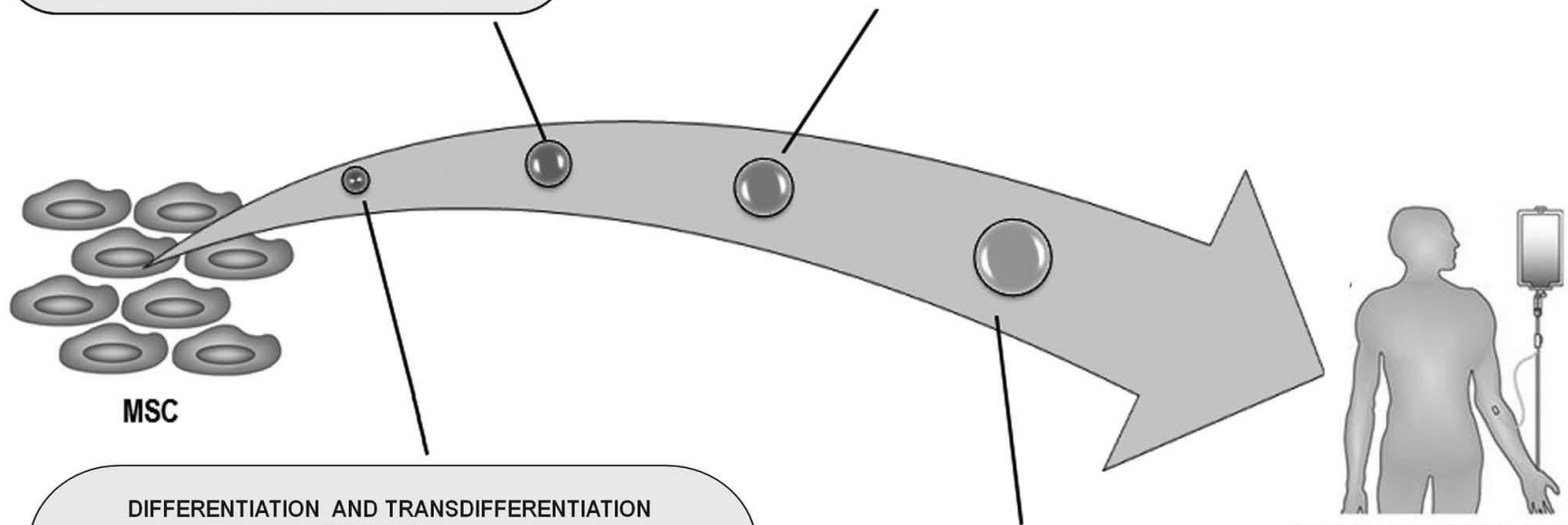
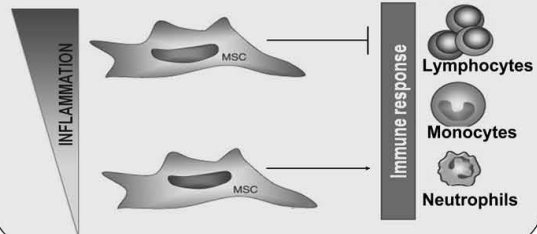


PARACRINE EFFECT



- Cytokine
- Chemokine
- ◆ Growth Factors

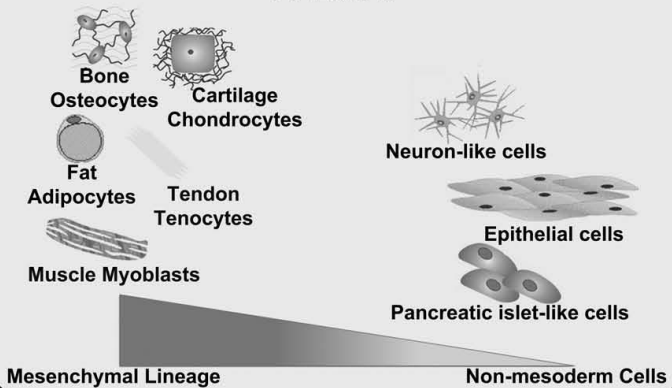
IMMUNOMODULATION



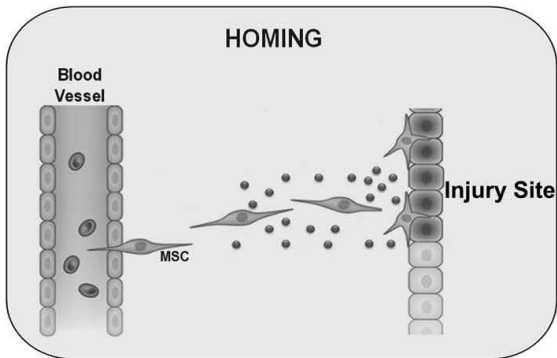
MSC

MSC-BASED THERAPY

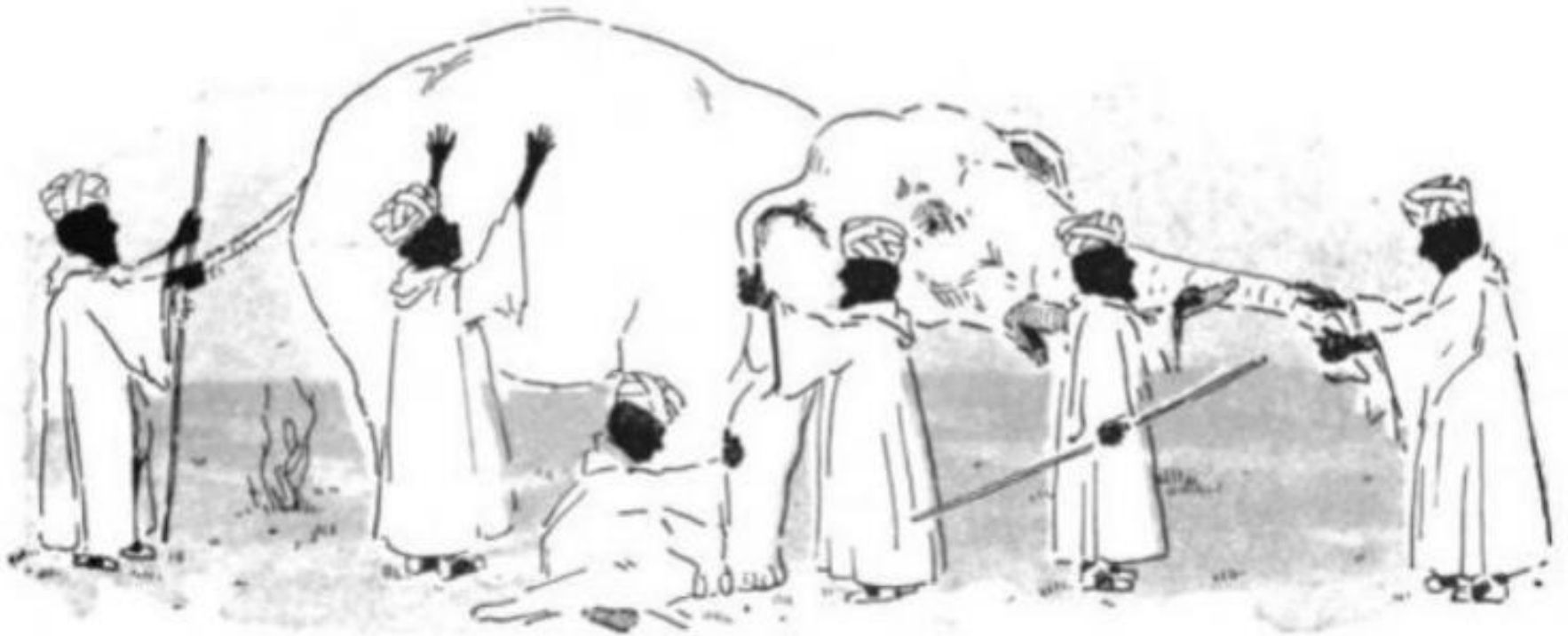
DIFFERENTIATION AND TRANSDIFFERENTIATION POTENTIAL

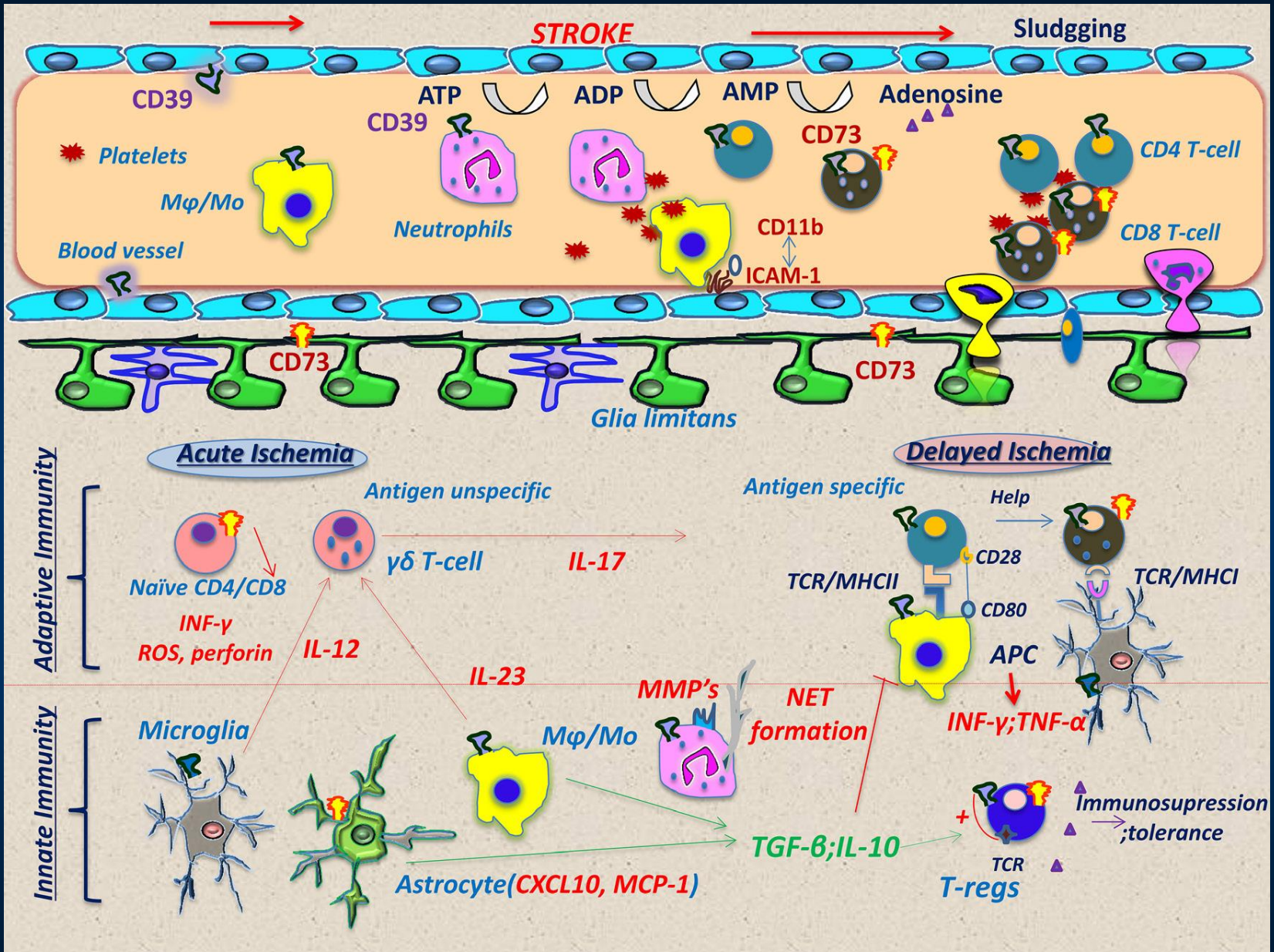


HOMING

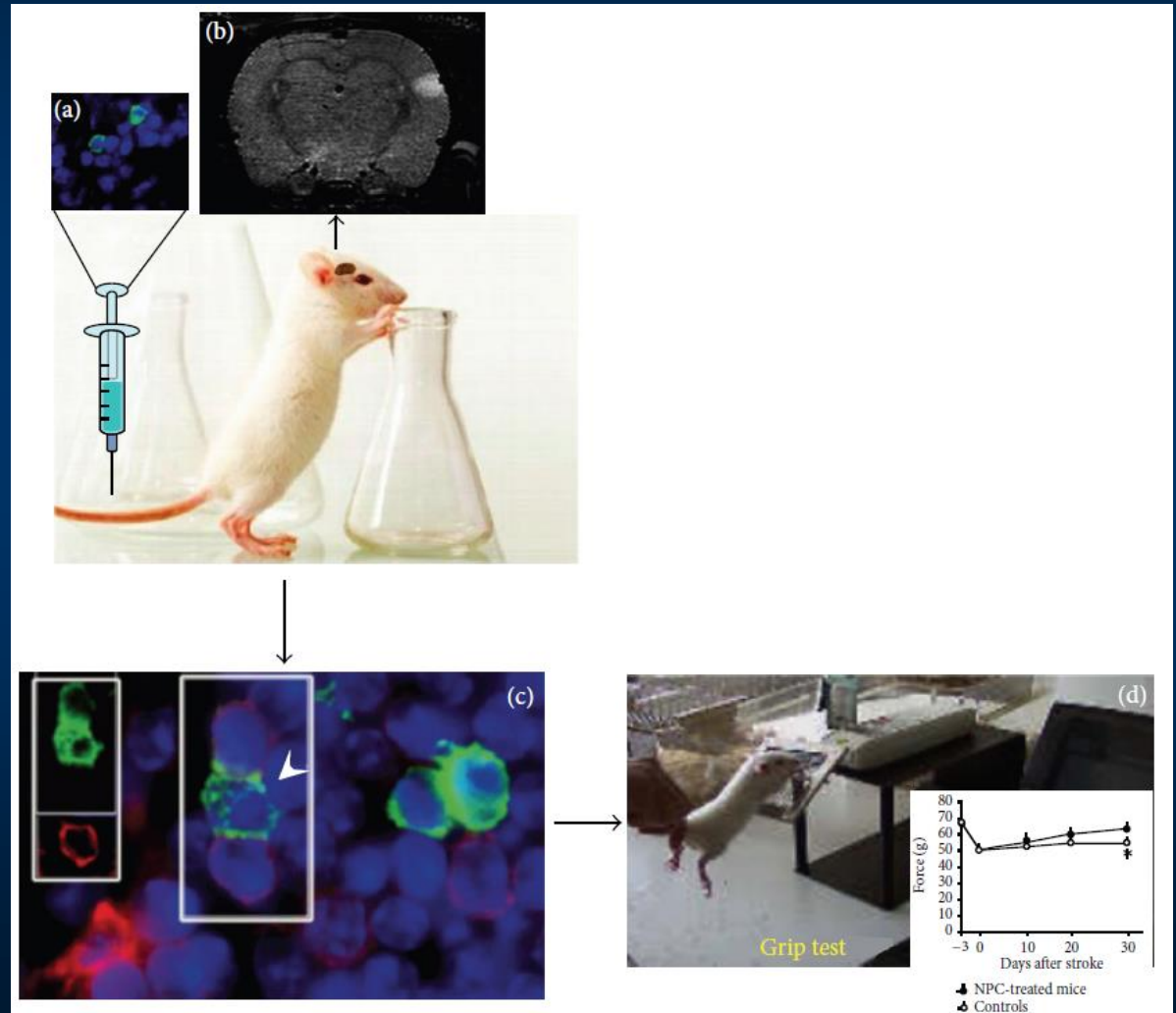


Puntos de Vista Parciales



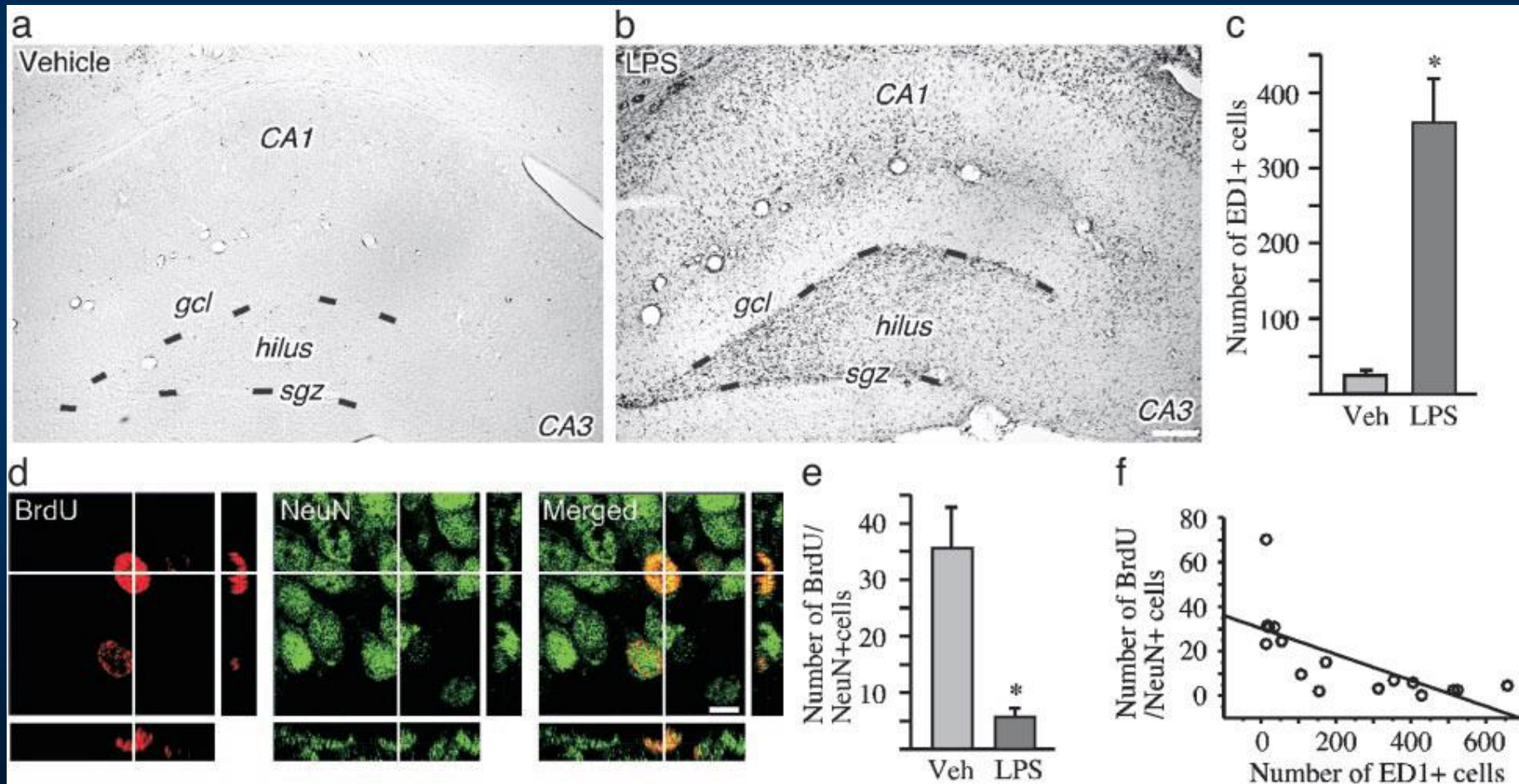


Th1 Inflammation Acts Synergistic with Cellular Therapy



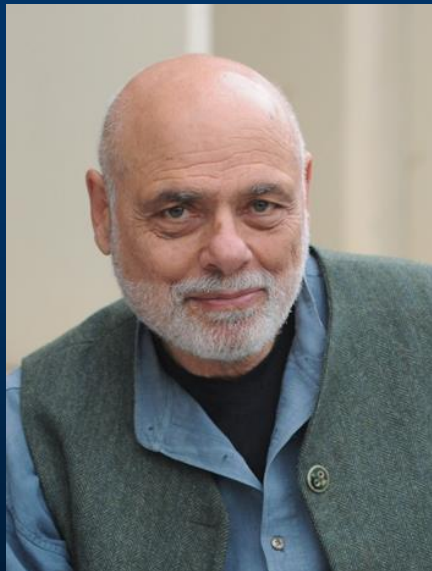
Popa-Wagner et al. Neural Plasticity Volume 2015, Article ID 839638, 7 pages

Th2 Inflammation as Detrimental for Neurogenesis



Factores que Promueven La Reparación Tisular

- Células Pro-reparadoras (Inductoras y Estructurales)
- Apoyadas sobre una matriz extracelular apropiada
- Embebidas en un medio humoral adecuado
- Exigido funcionalmente en la justa medida

The cover of the journal 'Nature Medicine' features a dark background with a complex network of glowing green and yellow neurons. The text is white and yellow. The title 'nature medicine' is at the top left. The volume and issue information 'VOLUME 5 NUMBER 1 JANUARY 1999' is at the top right. The website 'http://medicine.nature.com' is below the title. The main article title 'Protective autoimmunity' is in the center. Below it are five sub-articles listed in white text.

nature
medicine

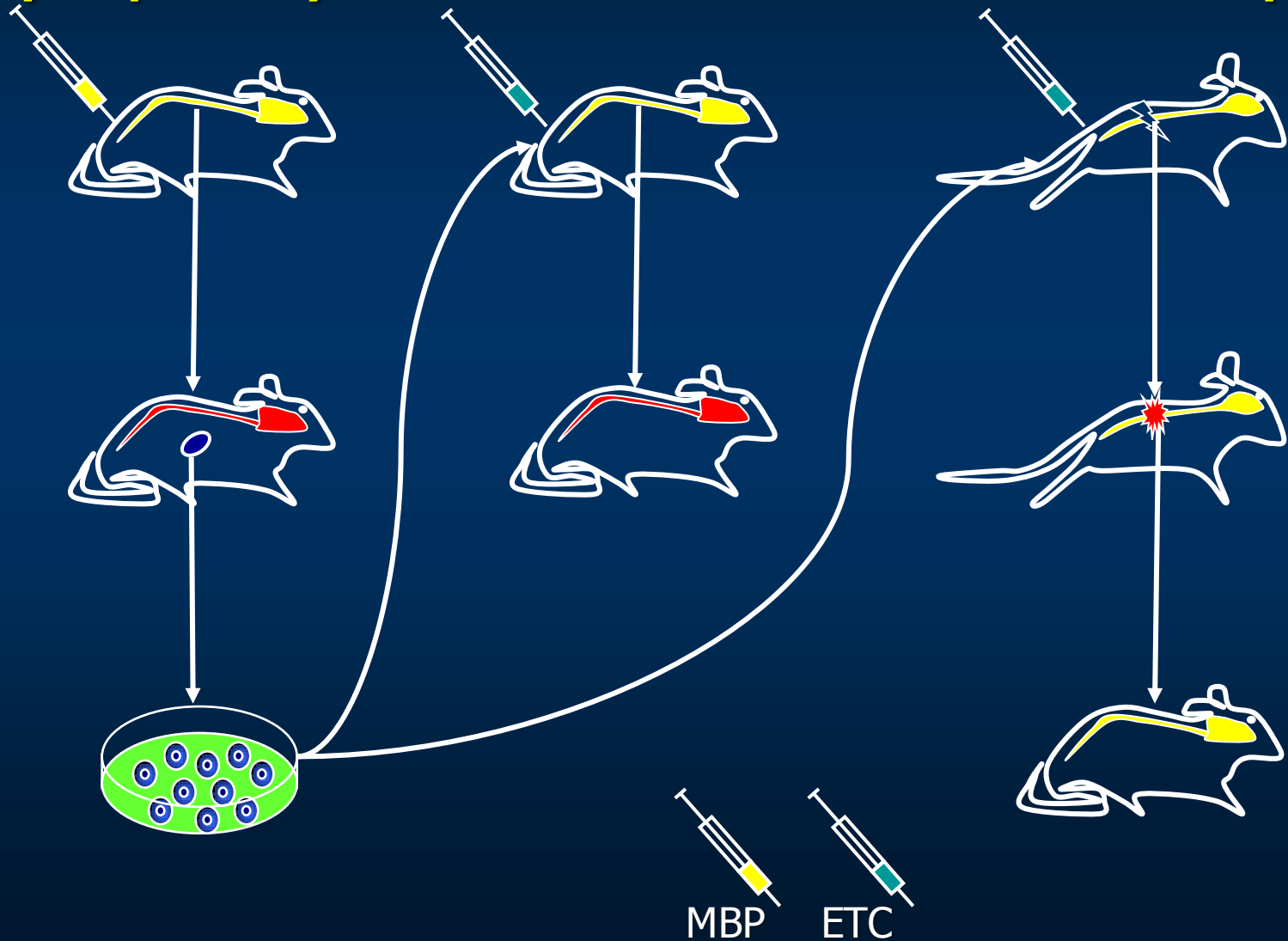
VOLUME 5 NUMBER 1
JANUARY 1999

<http://medicine.nature.com>

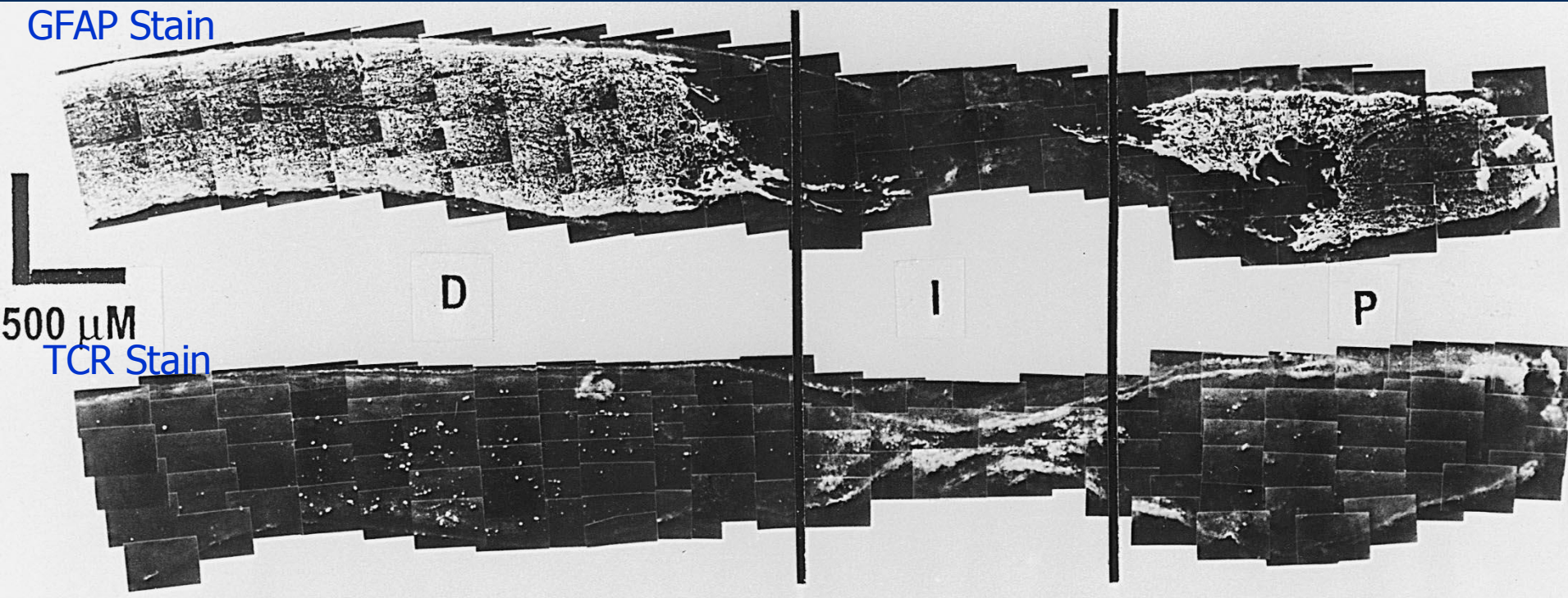
Protective autoimmunity

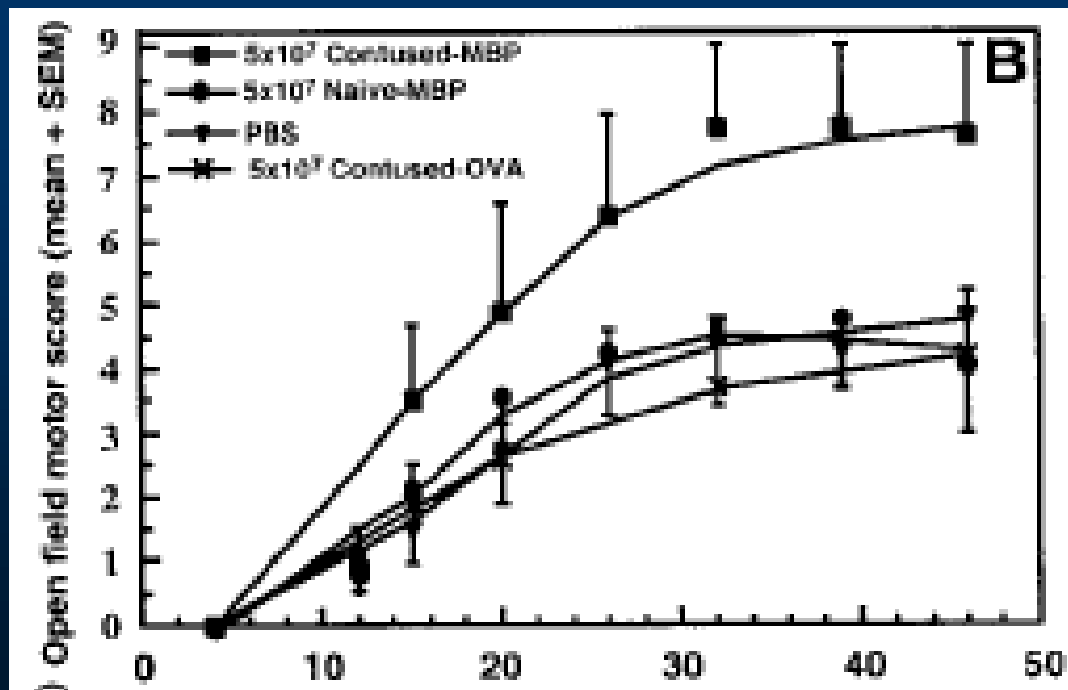
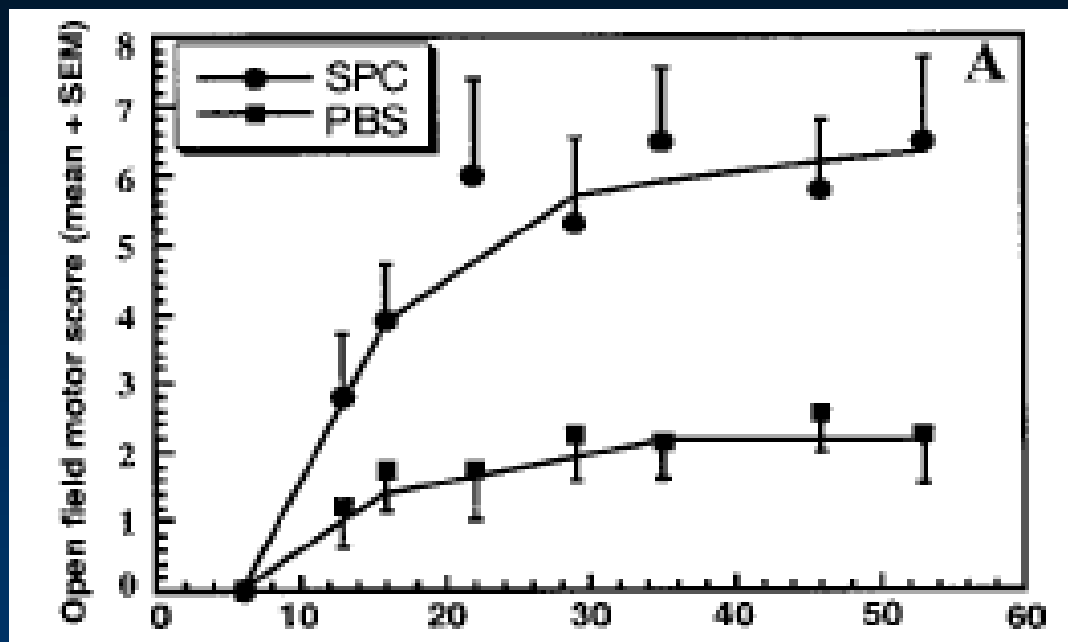
- New co-receptors clarify AAV transduction patterns
- Fibrinogen-coated microcapsules block bleeding
- Excitotoxic neurodegeneration in Alzheimer
- Eradicating HIV—many ways to skin a cat
- Reducing apoptosis in nigral transplants

Protective Autoimmunity Induced by Lymphocytes Procures SCI Recovery.

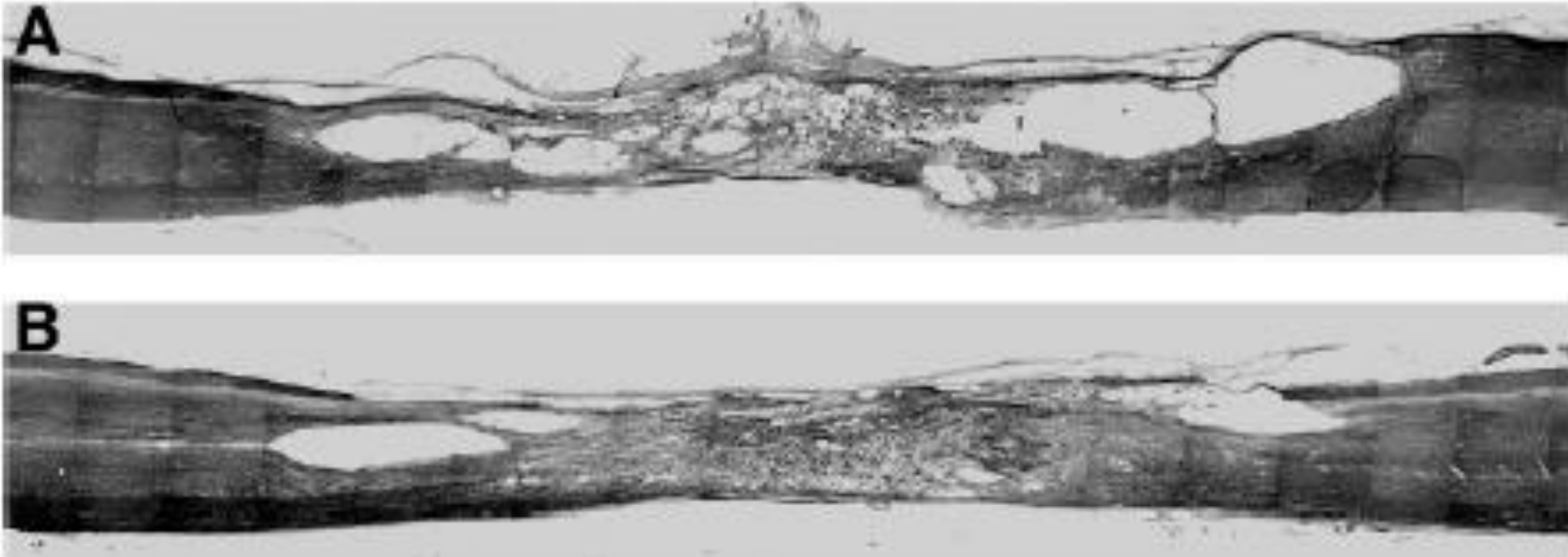


Injured Site Attracts Activated T Cells



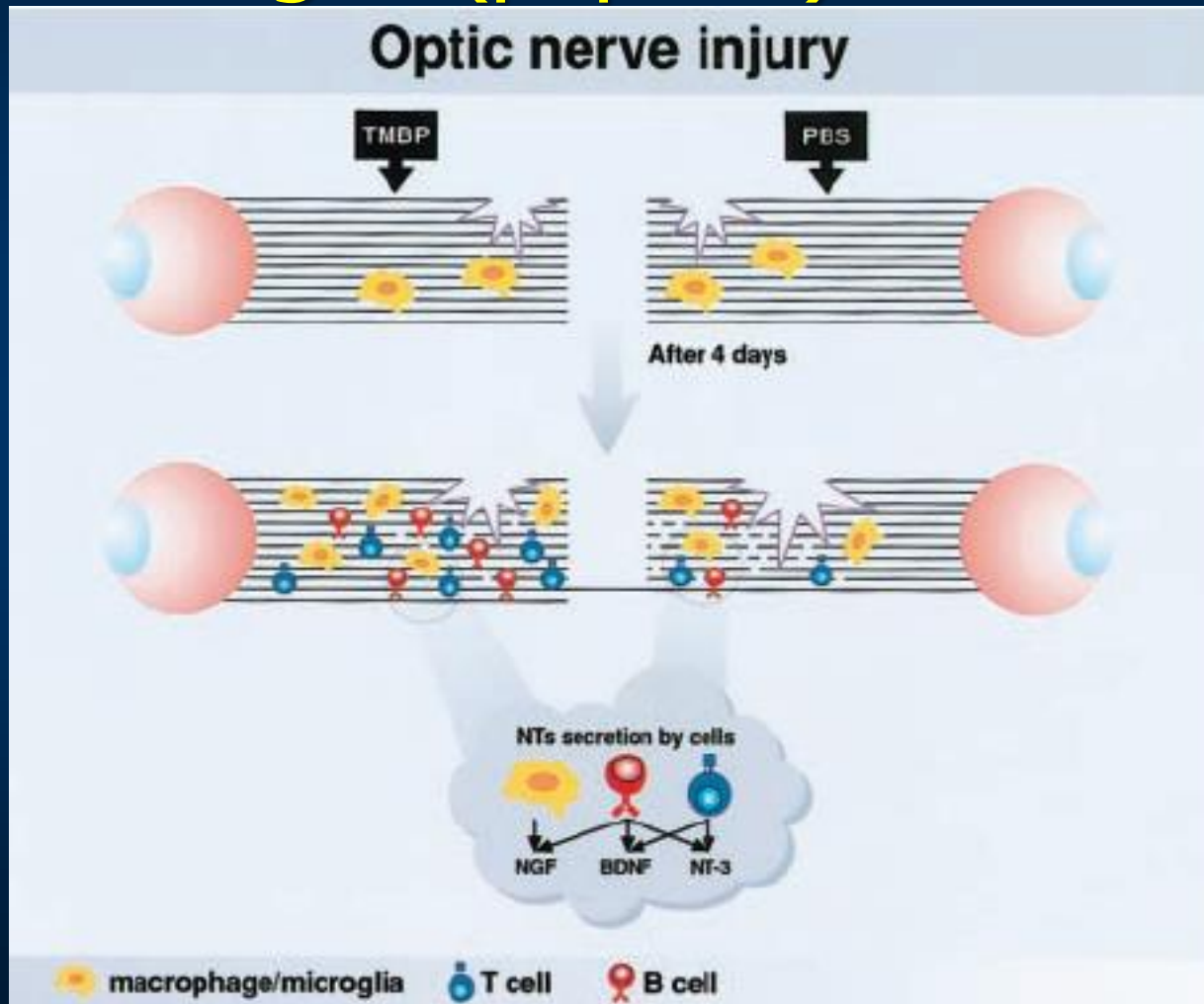


Activated T Cell Mediated Repair

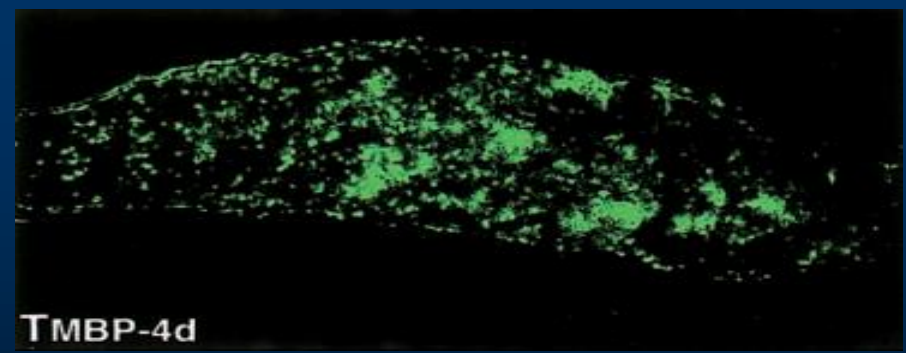
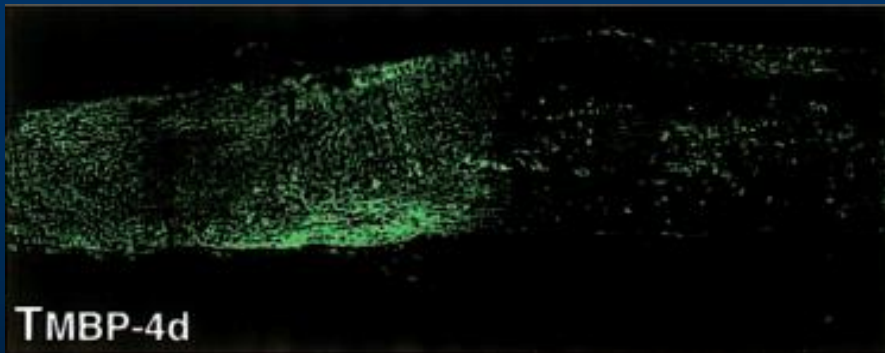


Hauben E et al. J Neurosci 2003; 25: 8808-19

Protective Autoimmunity induced by self antigen (peptide) vaccination



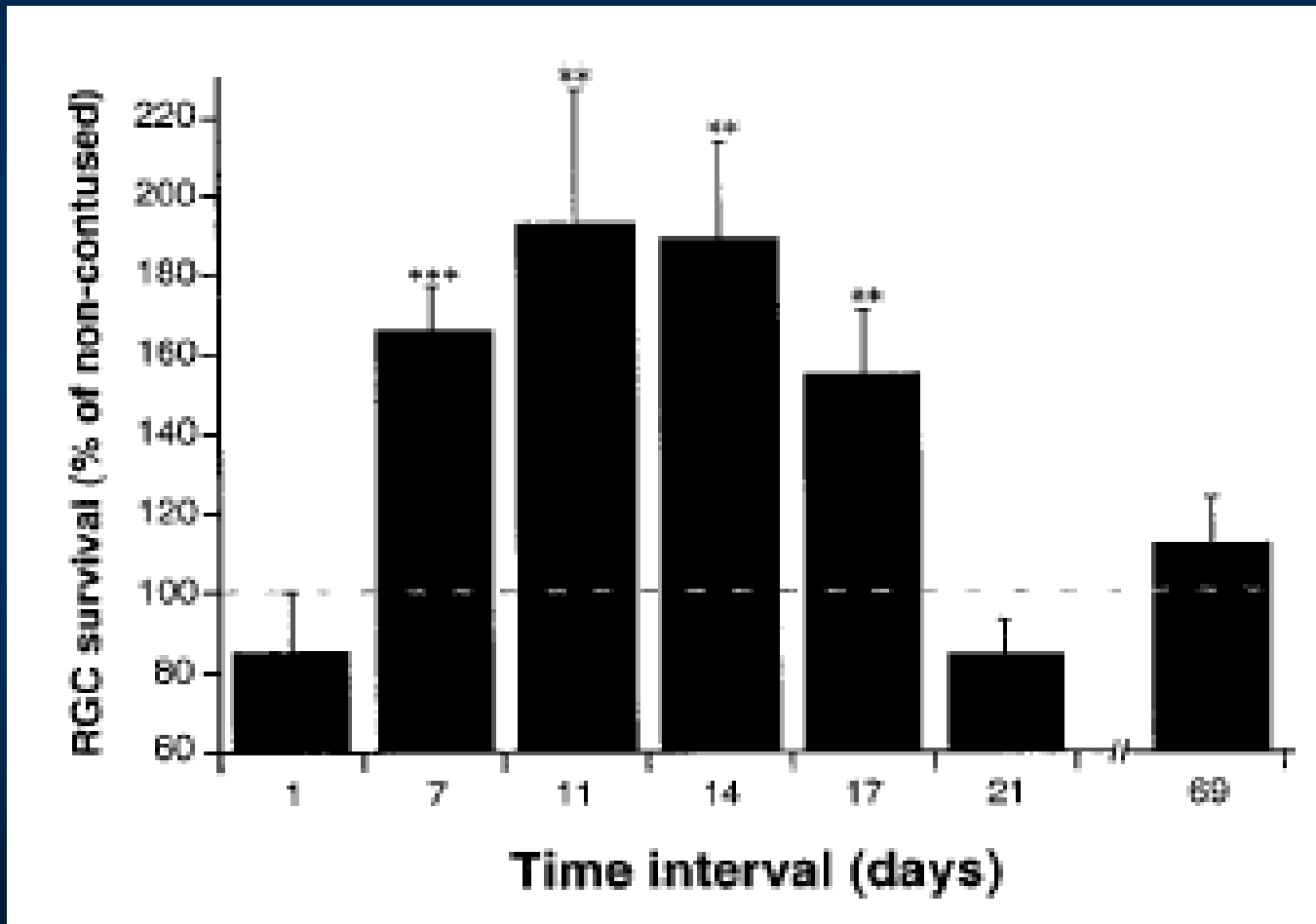
Secretion of Neurotrophins by T Cells after MBP Vaccination

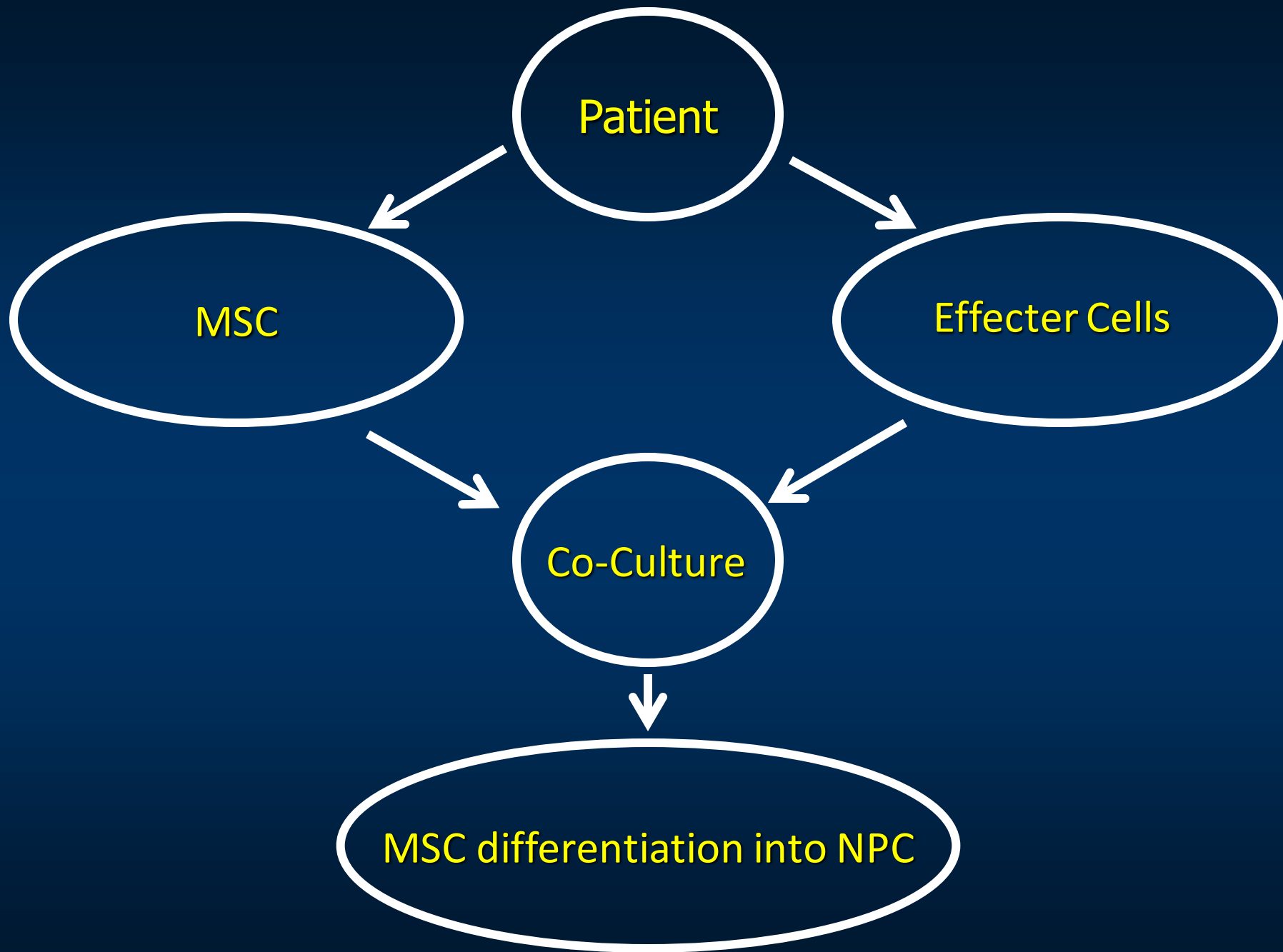


BDNF

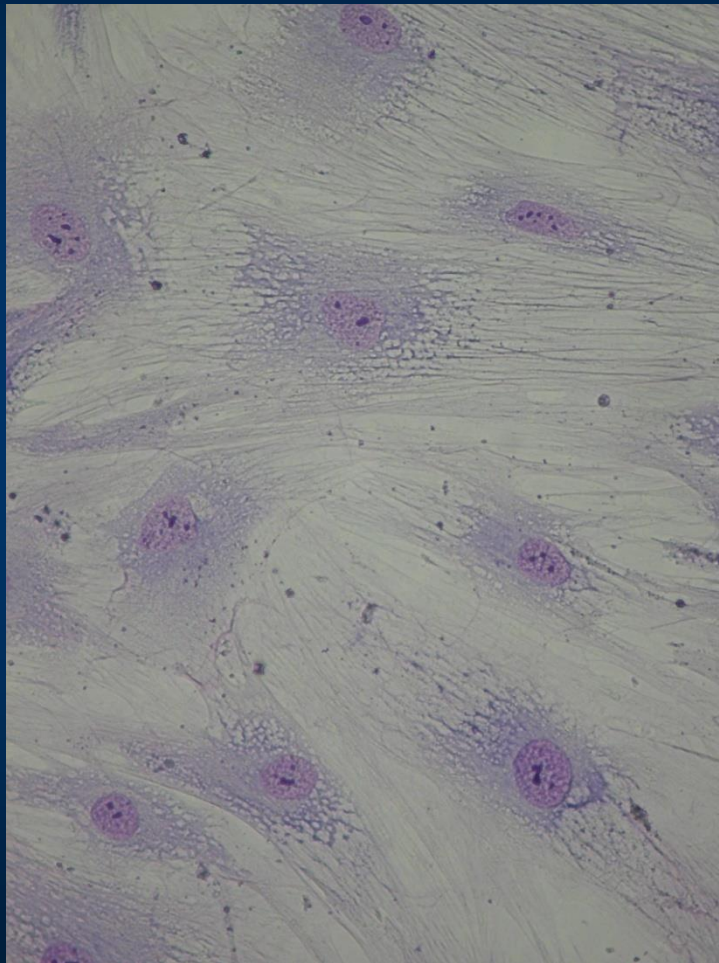
NT-3

Therapeutic Window for Activated T Cell Mediated Repair

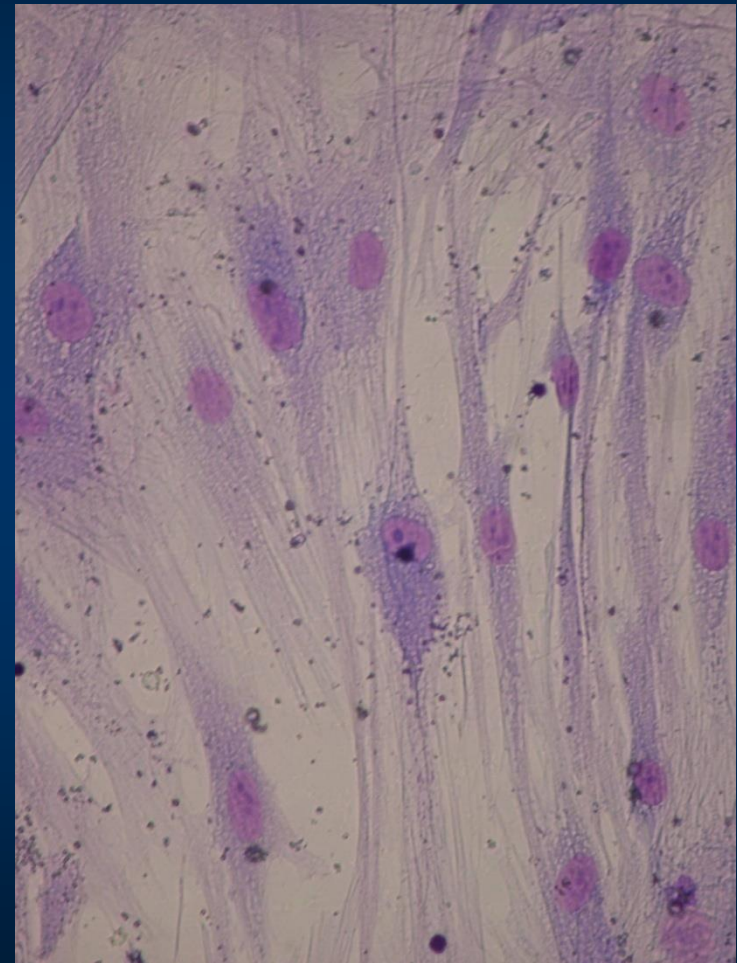




MSC After 48 hr of Co Incubation with EC against Polipeptides from Hydrolyzed Cow Brain

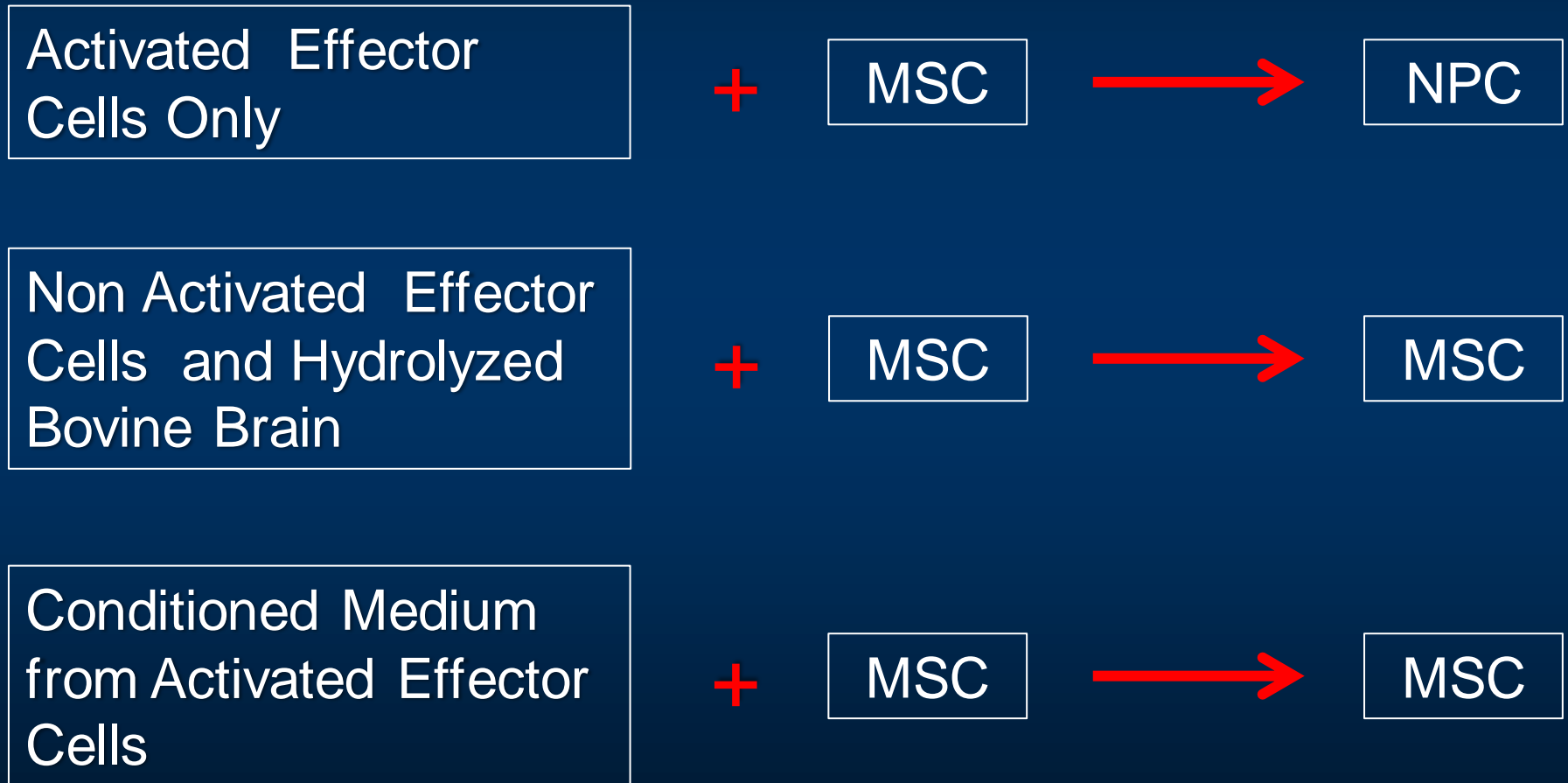


Control MSC Culture

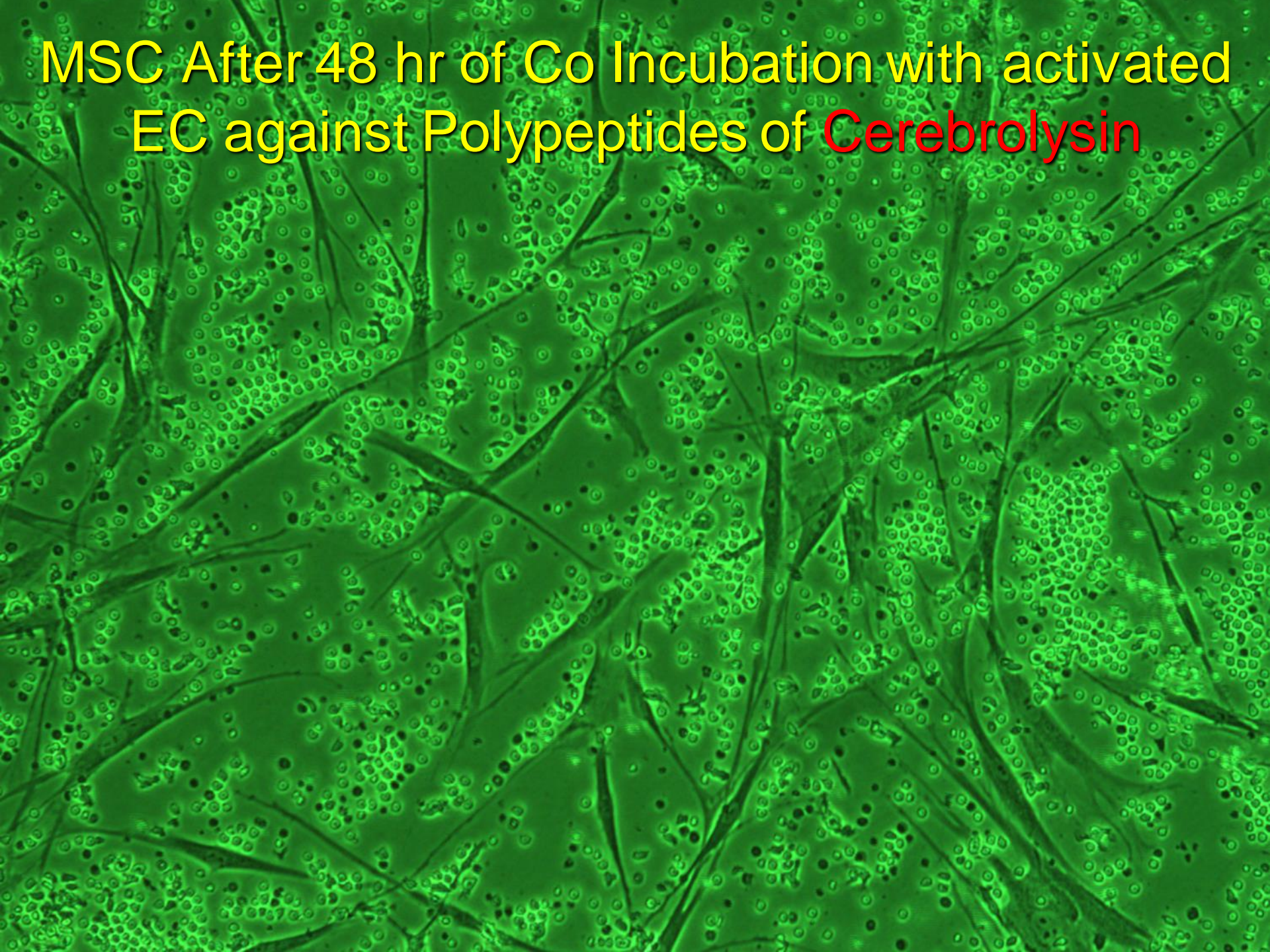


MSC + ETC 48 hr Culture

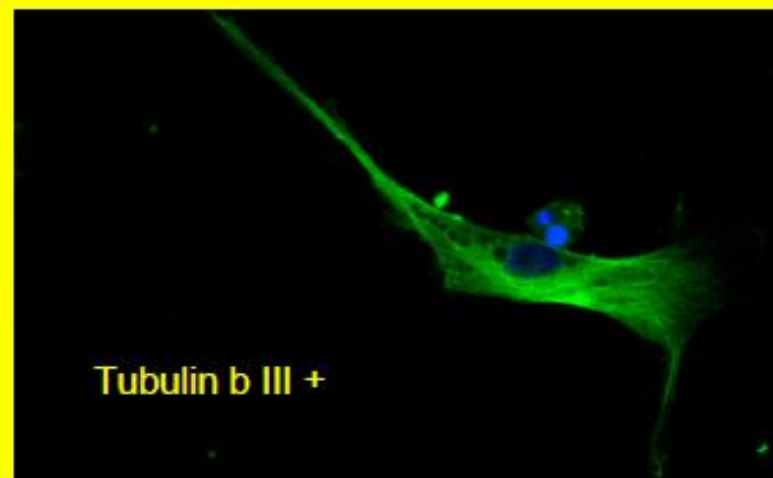
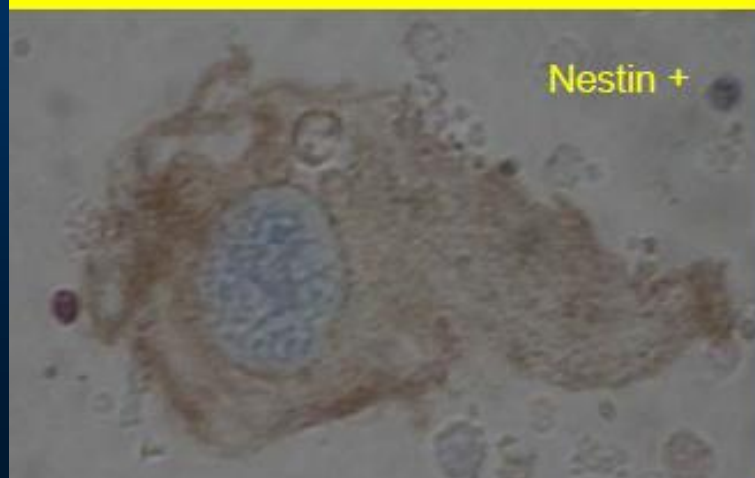
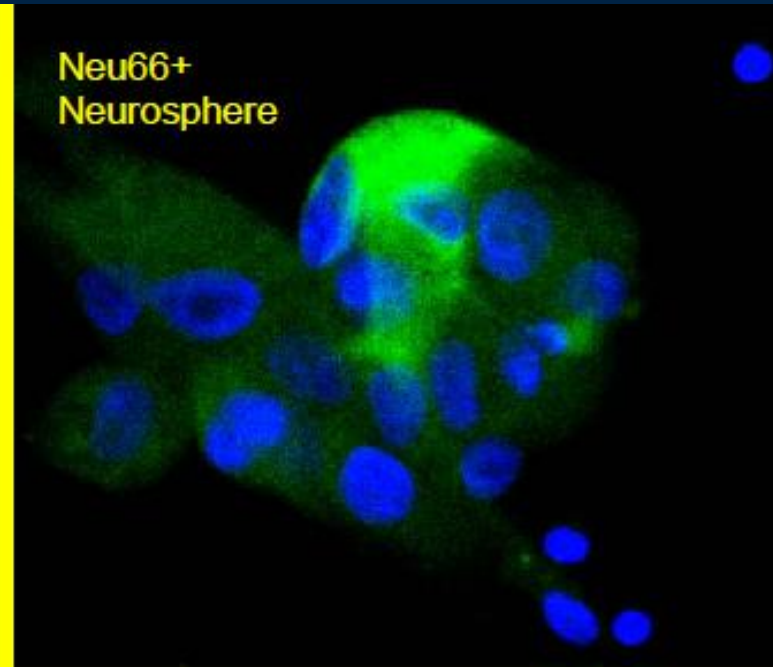
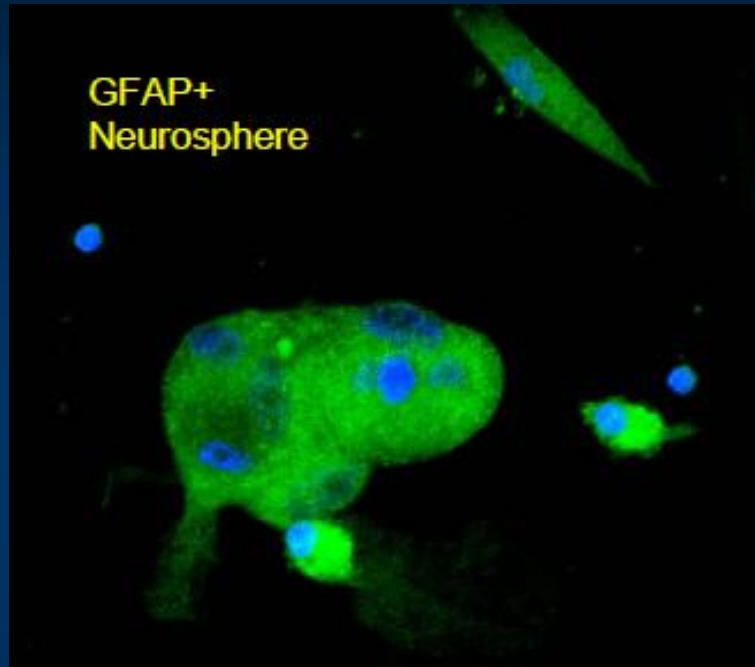
Lymphocytes against hydrolyzed bovine brain induce the differentiation of BM-MSc to NPC



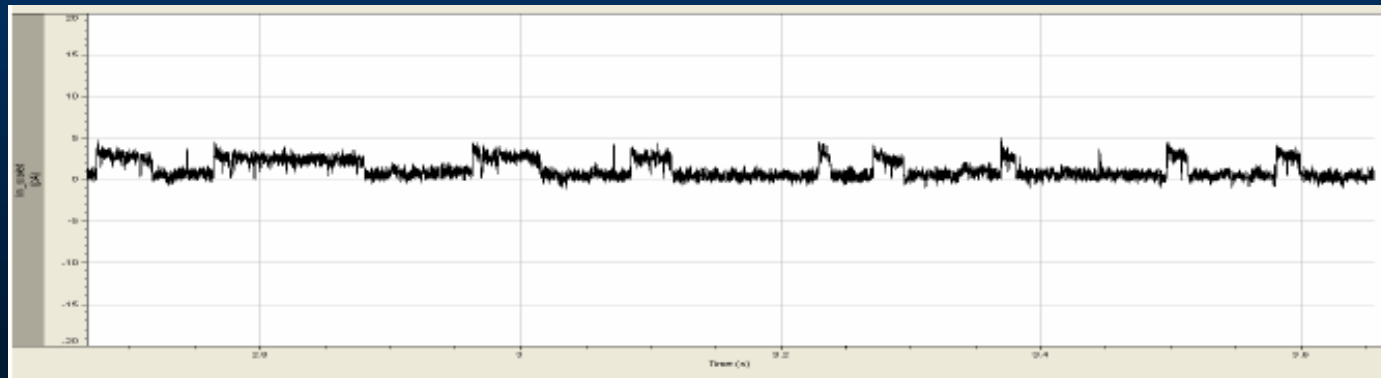
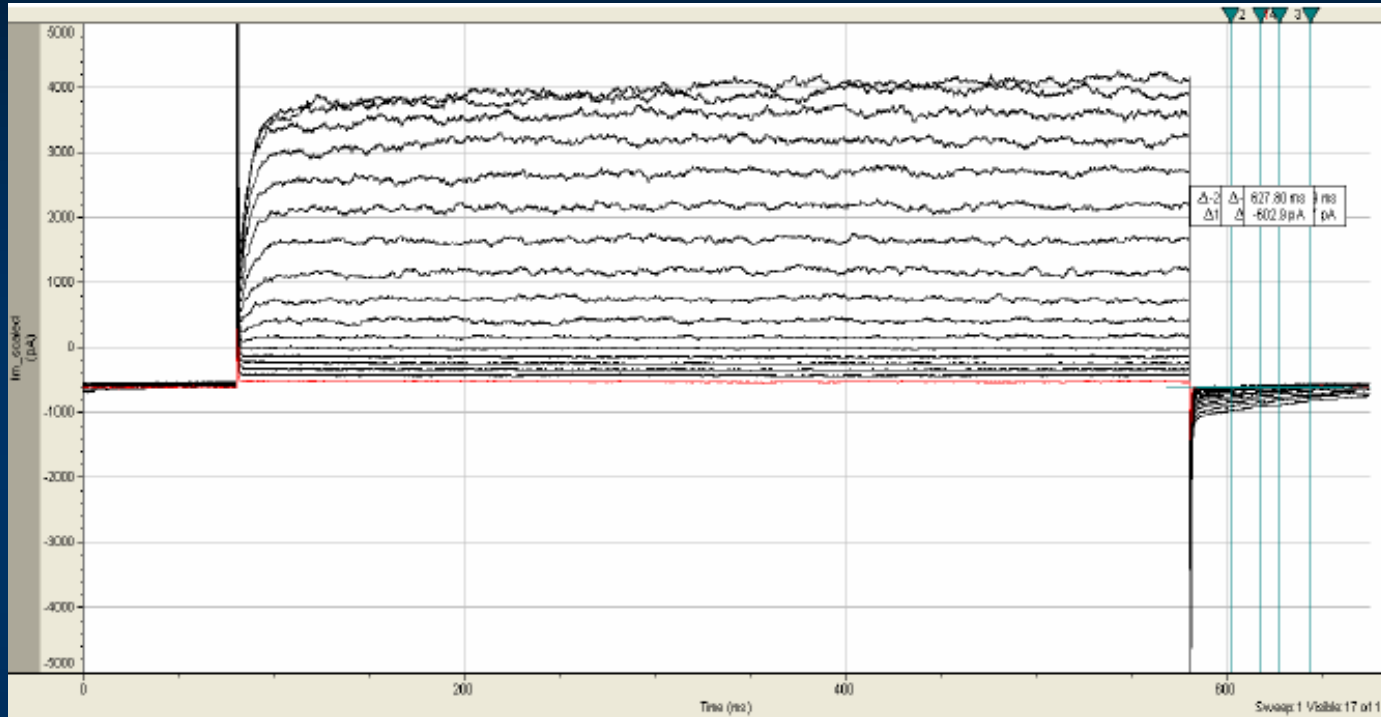
MSC After 48 hr of Co Incubation with activated
EC against Polypeptides of **Cerebrolysin**



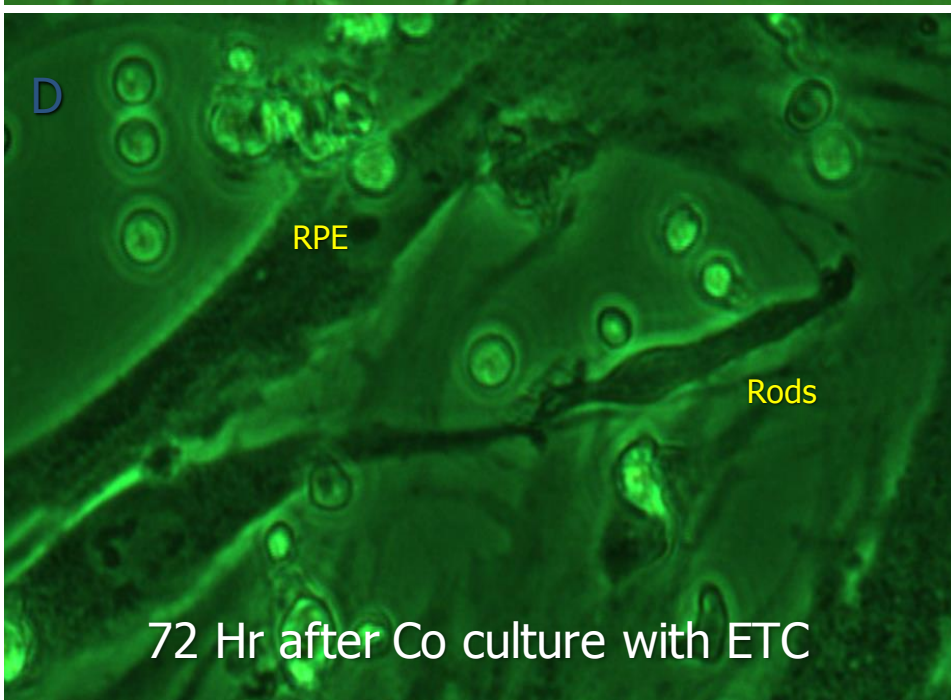
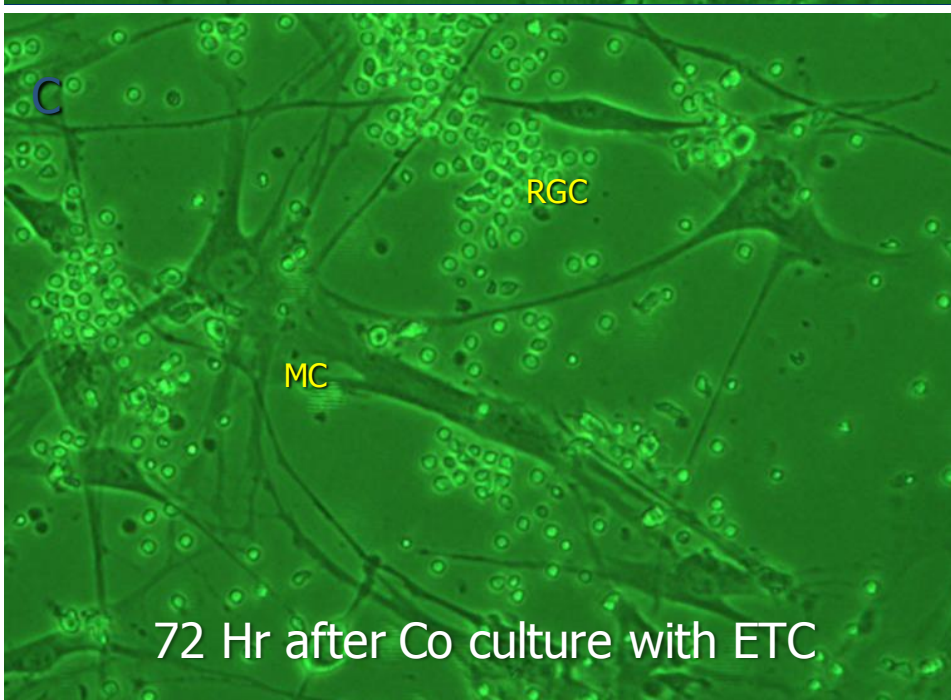
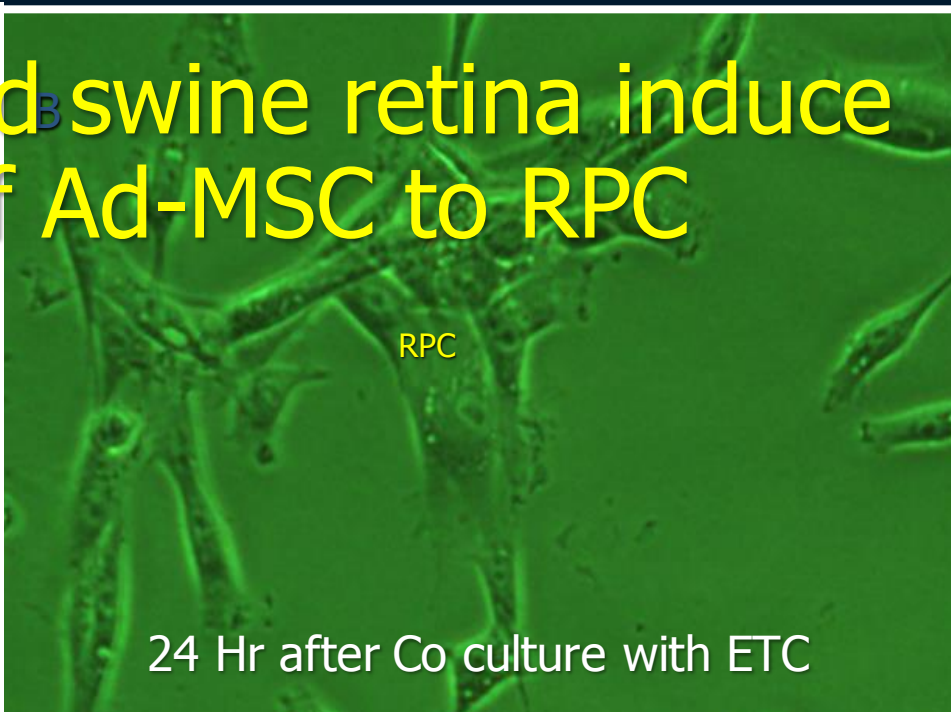
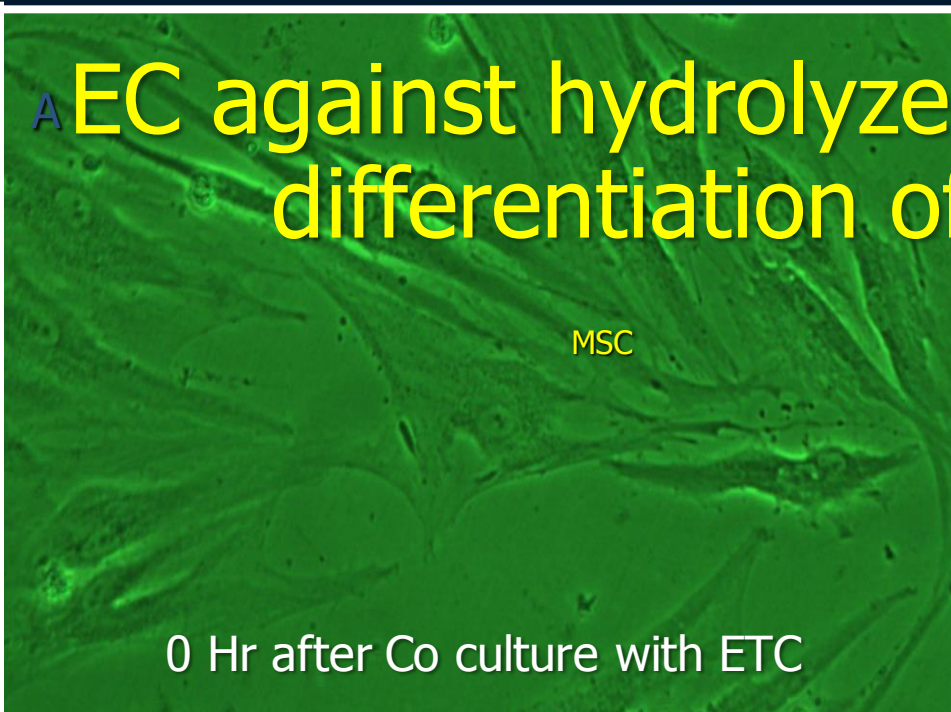
Lymphocytes against **Cerebrolysin** induce the differentiation of Ad-MS-C to NPC

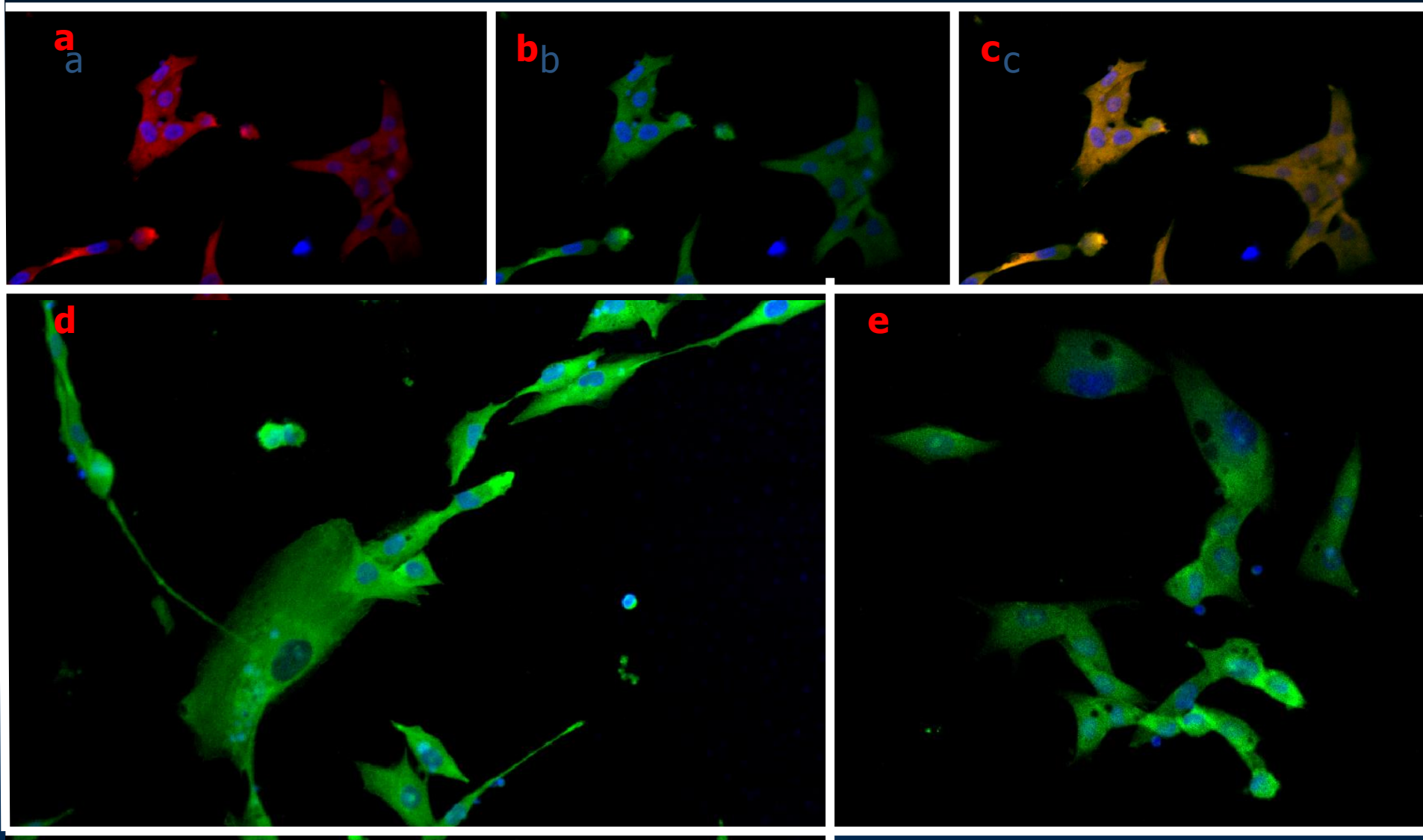


Electric Activity of Differentiated MSC



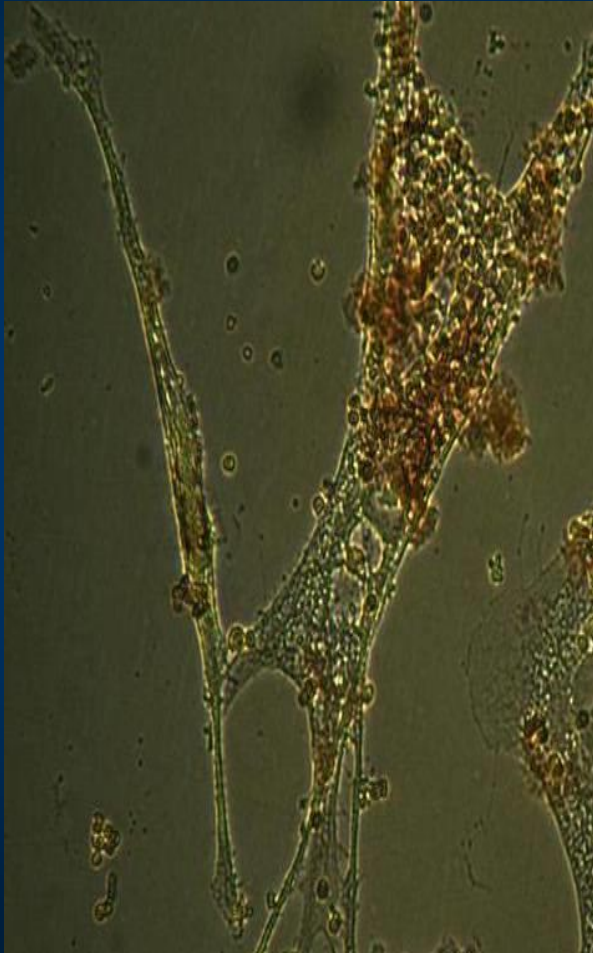
A EC against hydrolyzed swine retina induce differentiation of Ad-MSC to RPC



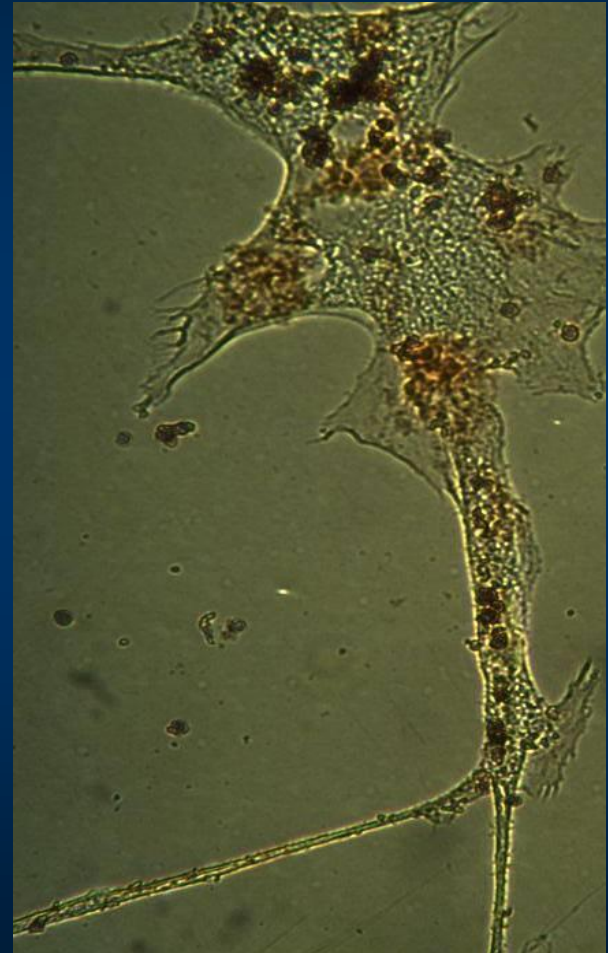


Confocal microscopy analysis of the cultured cells.
a GFAP-positive cells. **b** Bestrophin 2-positive cells.
c Merge a and b image. **d** Tubulin beta III-positive cells.
e OPN1 SW-positive cells

Lymphocytes against hydrolyzed swine pancreatic islets induce differentiation of Ad-MSC to insulin and glucagon producer cells

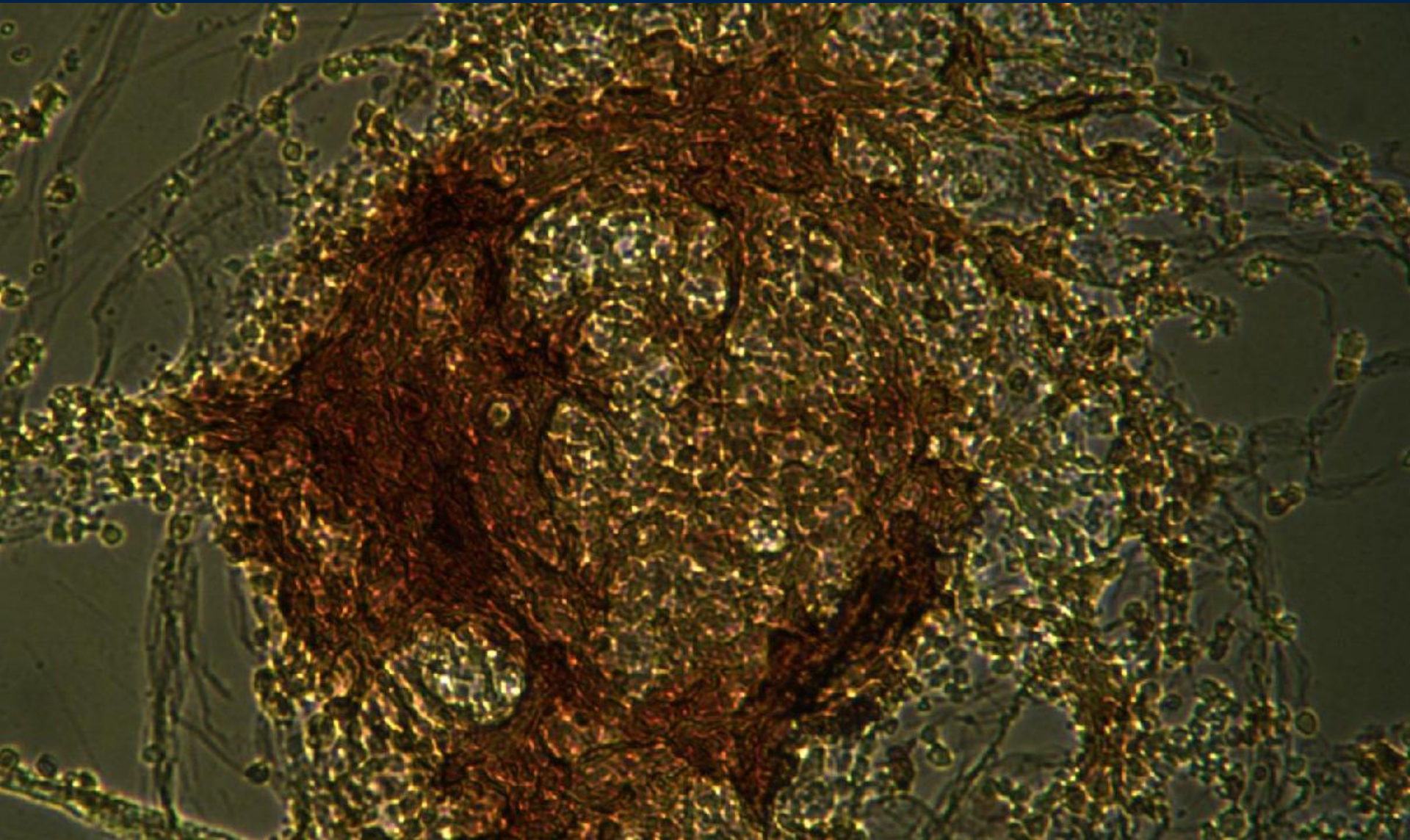


MSC 48 Hr MSC+ETC+PIM Culture
Immunoperoxidase Insulin Staining

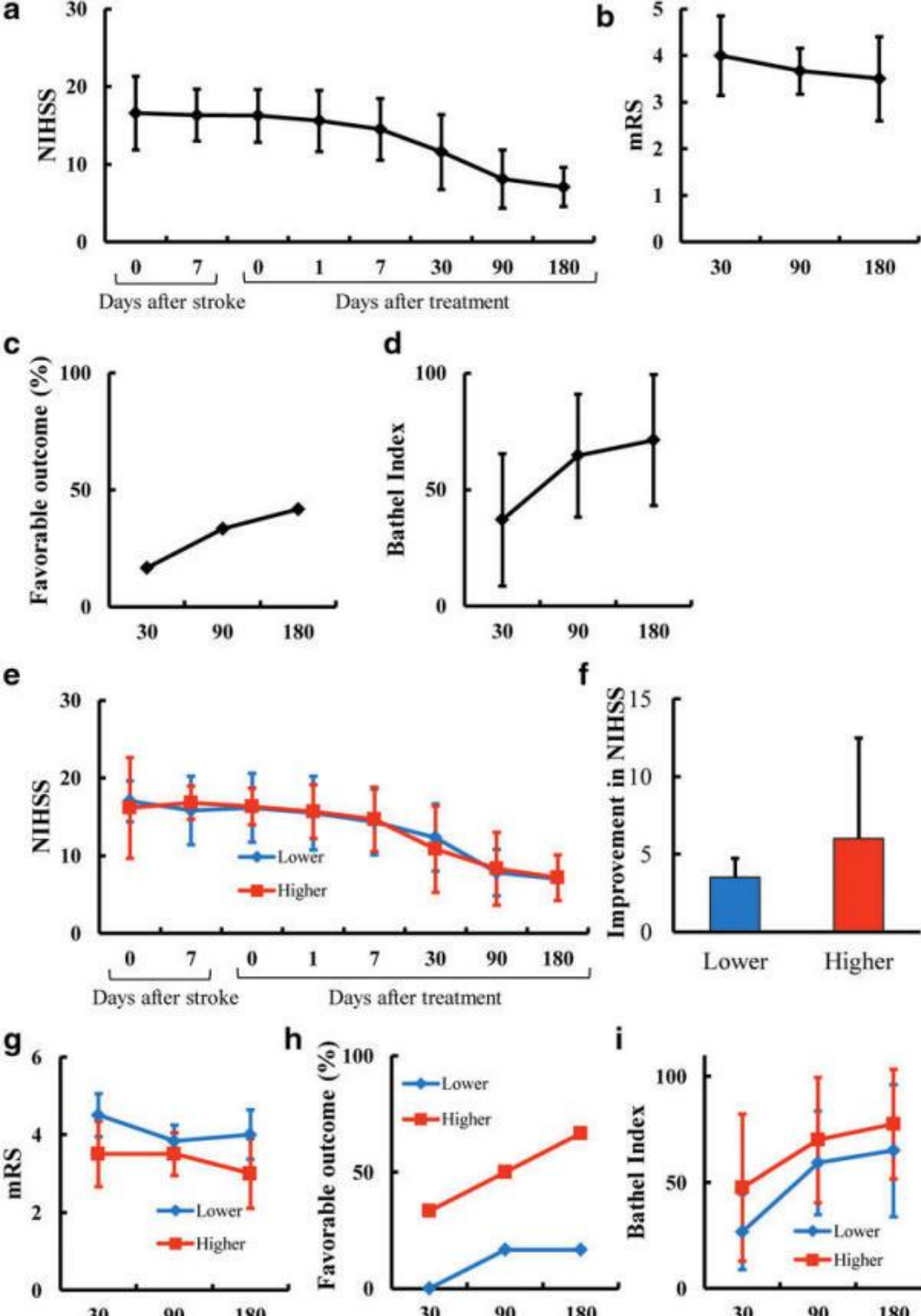


MSC 48 Hr MSC+ETC+PIM Culture
Immunoperoxidase Glucagon

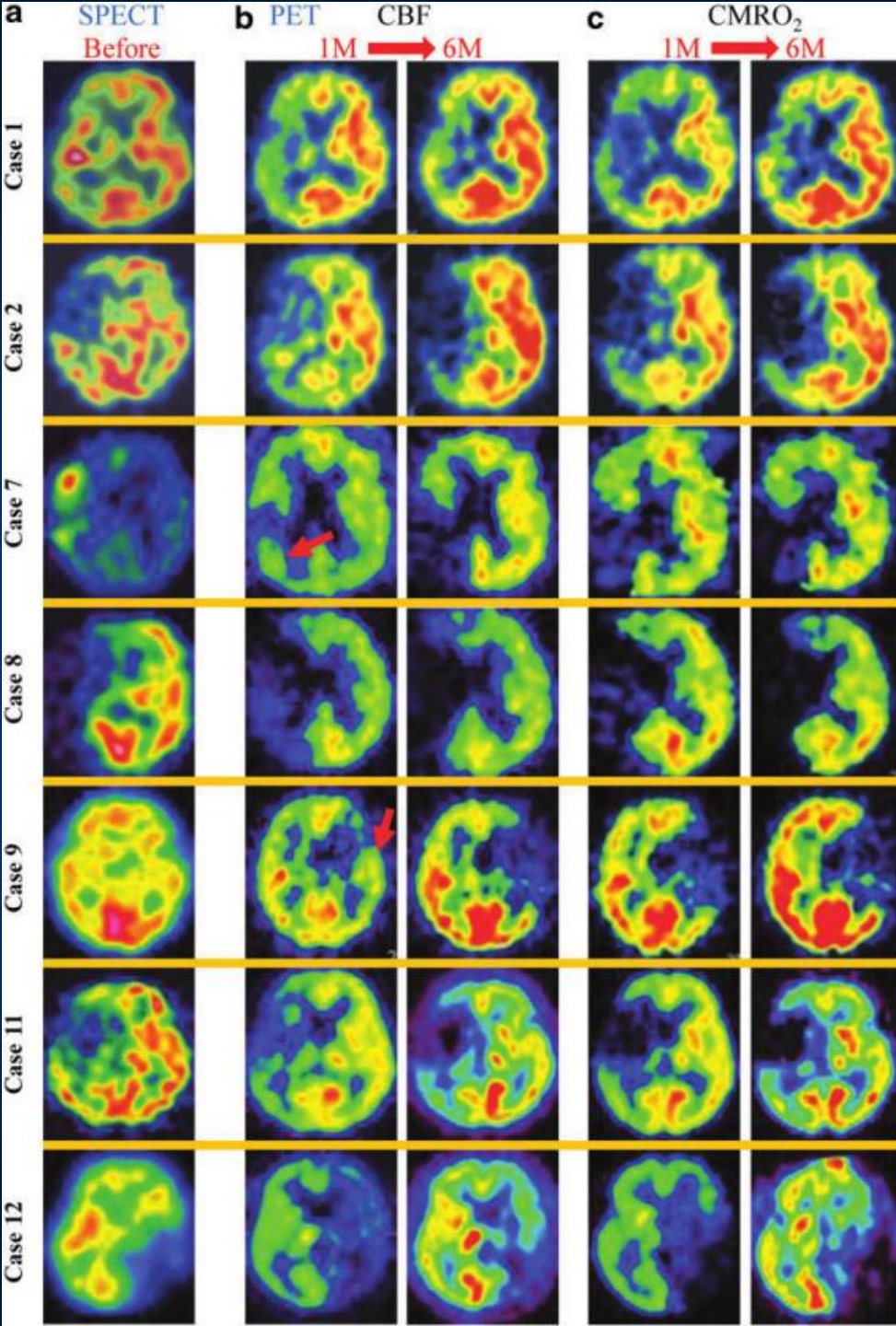
Insulin and Glucagon Secreting Islet elaborated from Patient adMSC



BMMNC at 7 days post Stroke - Clinical Trial Phase 1-2



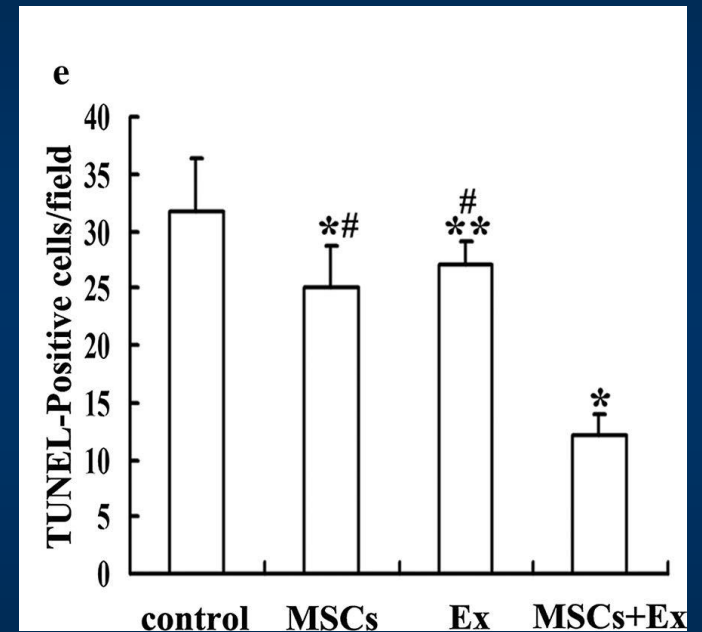
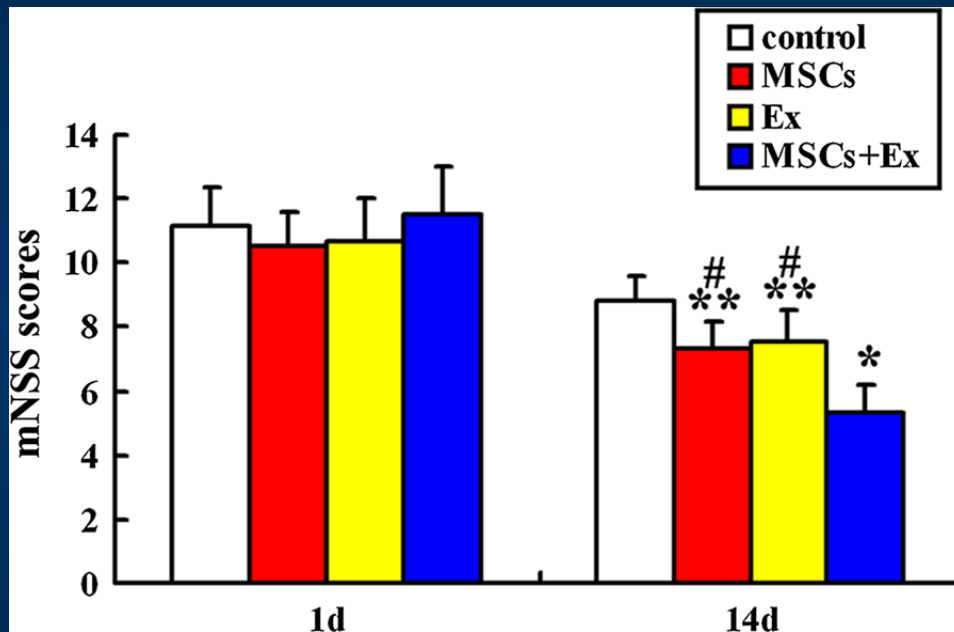
Taguchi A et al. Stem Cells Dev. 2015 ; 24(19):2207-18



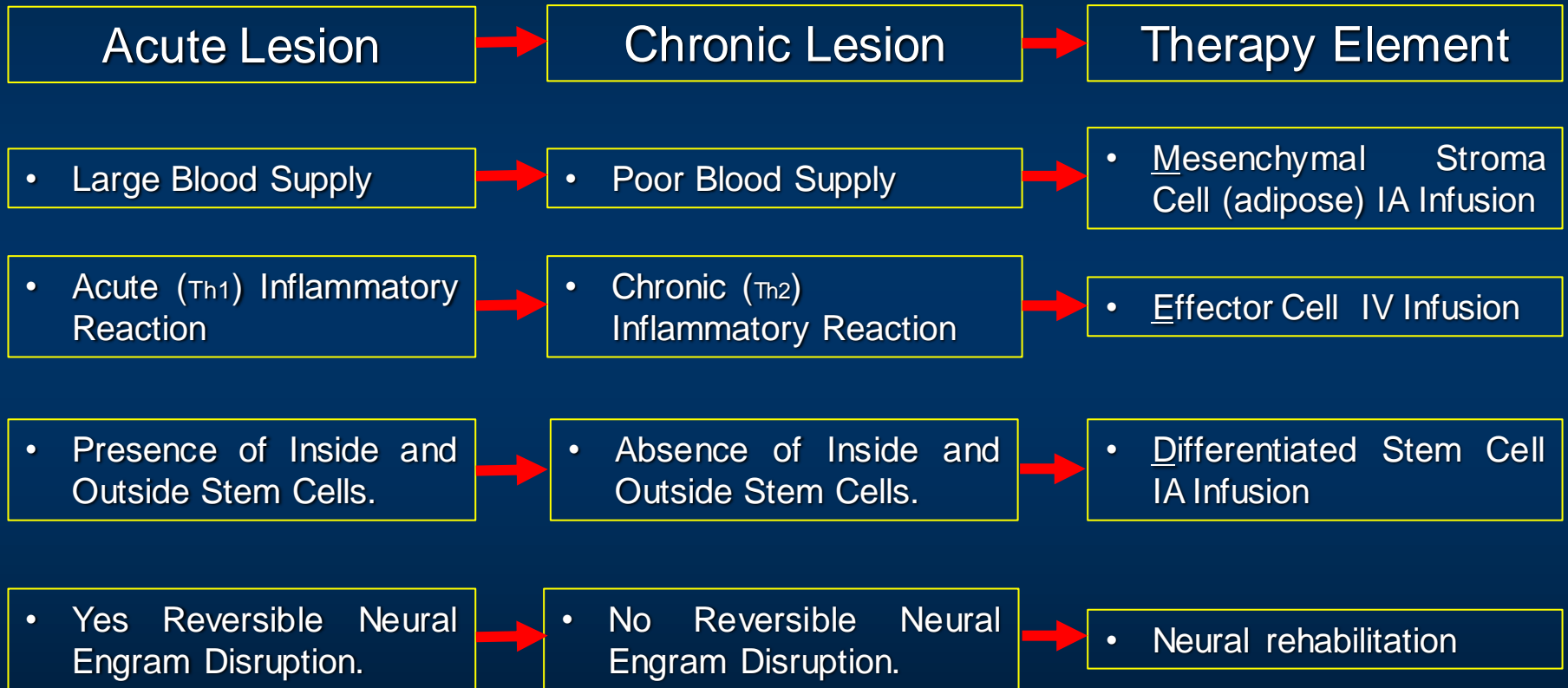
BMMNC at 7 days post Stroke - Clinical Trial Phase 1-2

Taguchi A et al. Stem Cells Dev. 2015 ; 24(19):2207-18

Cellular Therapy and Rehabilitation



Clinical Differences between Acute and Chronic Spinal Cord Injured Patients Associated to Therapeutic Strategy



T12 ASIA A/Frankel A, Flaccid paraplegic, 10 Years Evolution, RESULTS AFTER 30 MONTHS OF TREATMENT

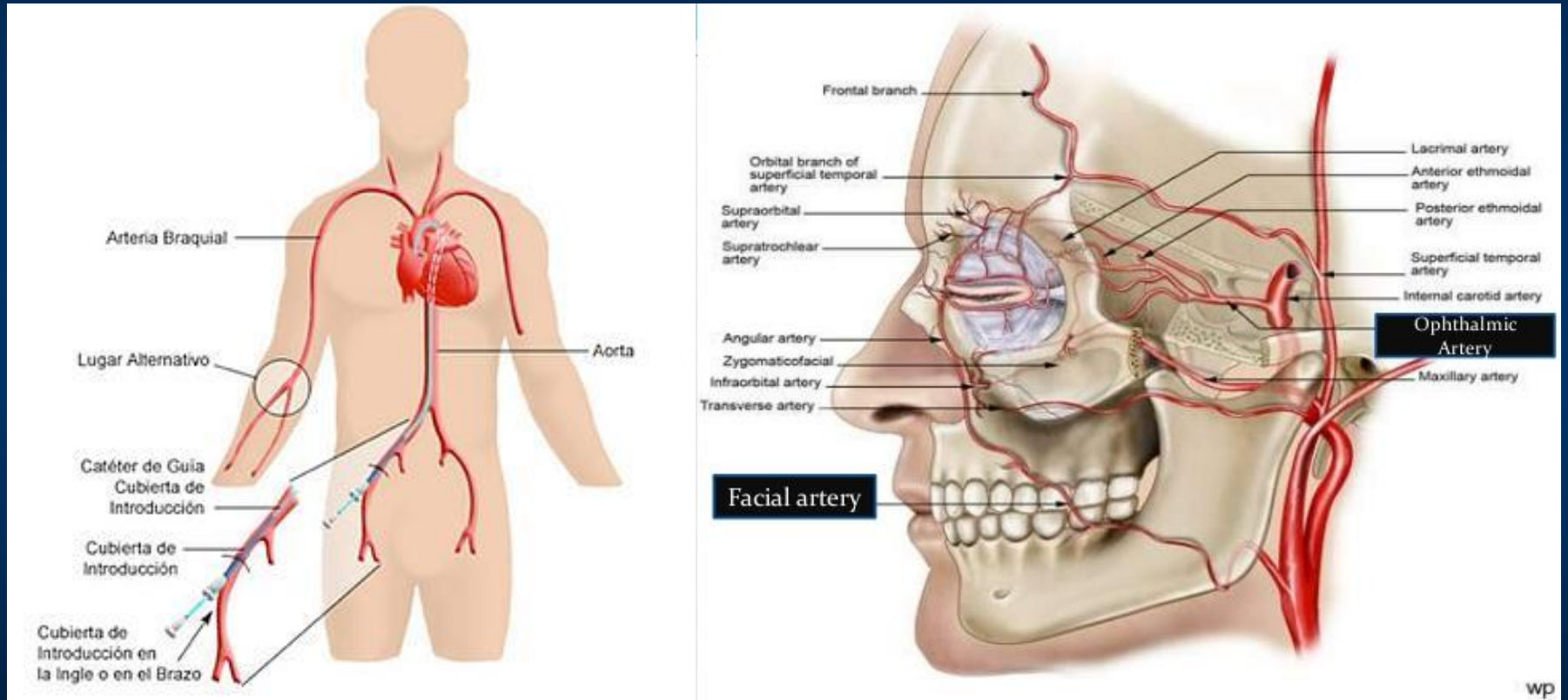


Spontaneous Recovery of Muscle innervation of a Frankel A SCI Patient only will be achieved until 2.5 years after the accident and results no will go further than 3 segments below of the last preserved spinal cord segment.

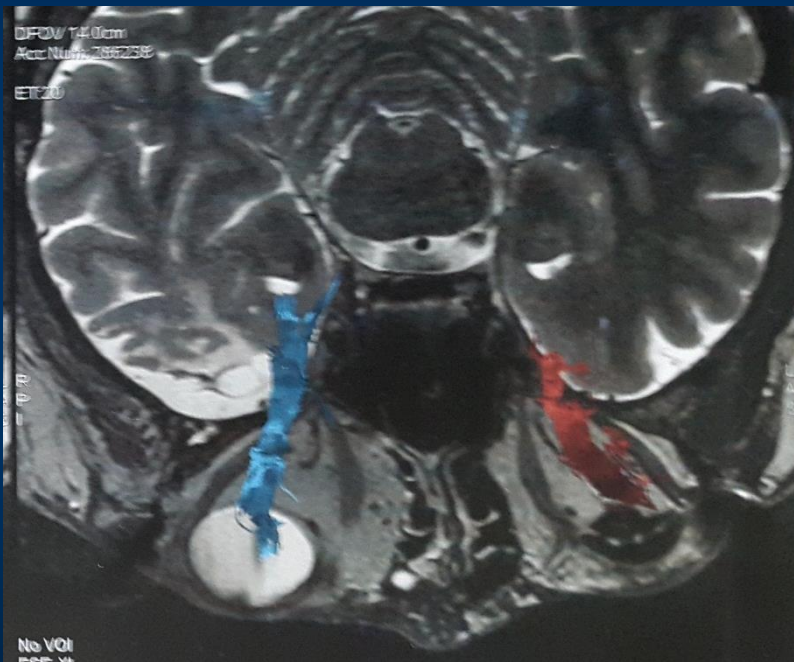
Rational of the MED Therapeutic Approach for Optic Nerve and Retina Damage

- Restoring the disrupted (choroidal) blood vessels through Intra Ophthalmic Artery Infusion of cultured autologous **a-MSC**
- Modulating the Inflammatory Reaction through Intra Venous Auto Aggressive Effector T Cell Infusion. **(ETC)**
- Restoring the Supply of Specific Stem Cells through Intra Artery Infusion of Differentiated MSC into Retina Progenitor Cell. **(DSC)**

Intra Artery Infusion



Treatment Results of Optic Nerve Lesion

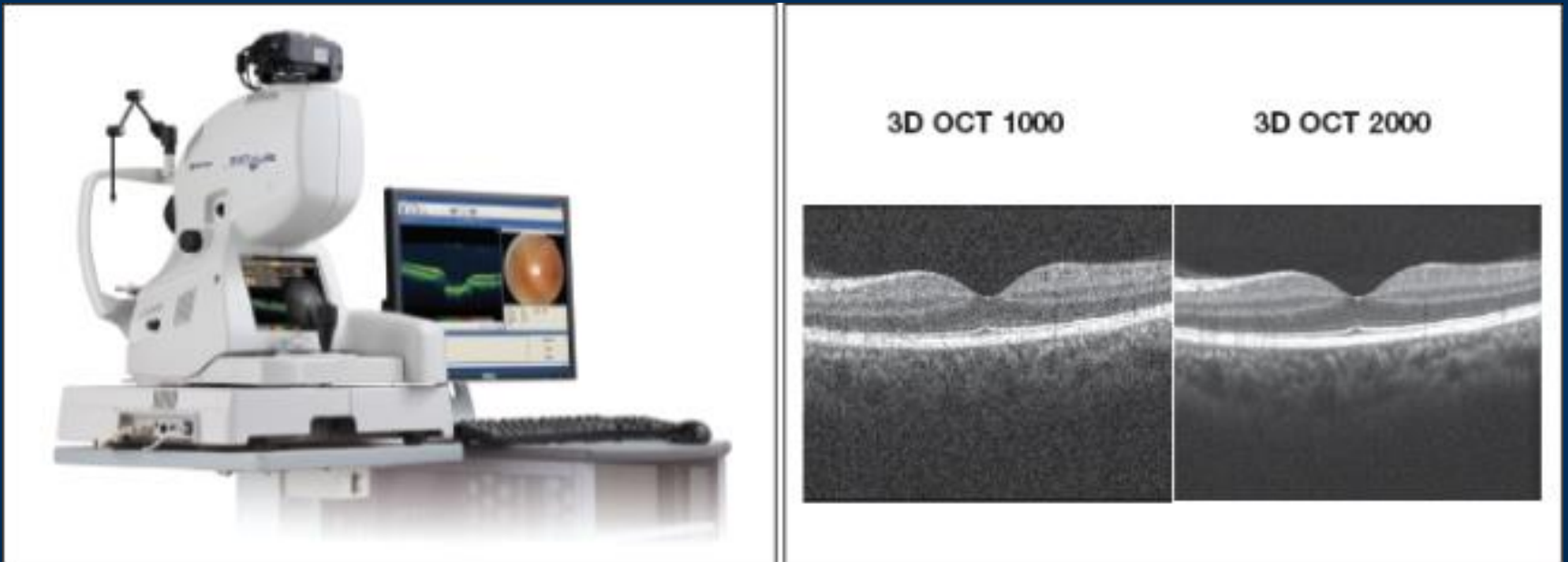


Pretreatment Optic Nerve Tractography

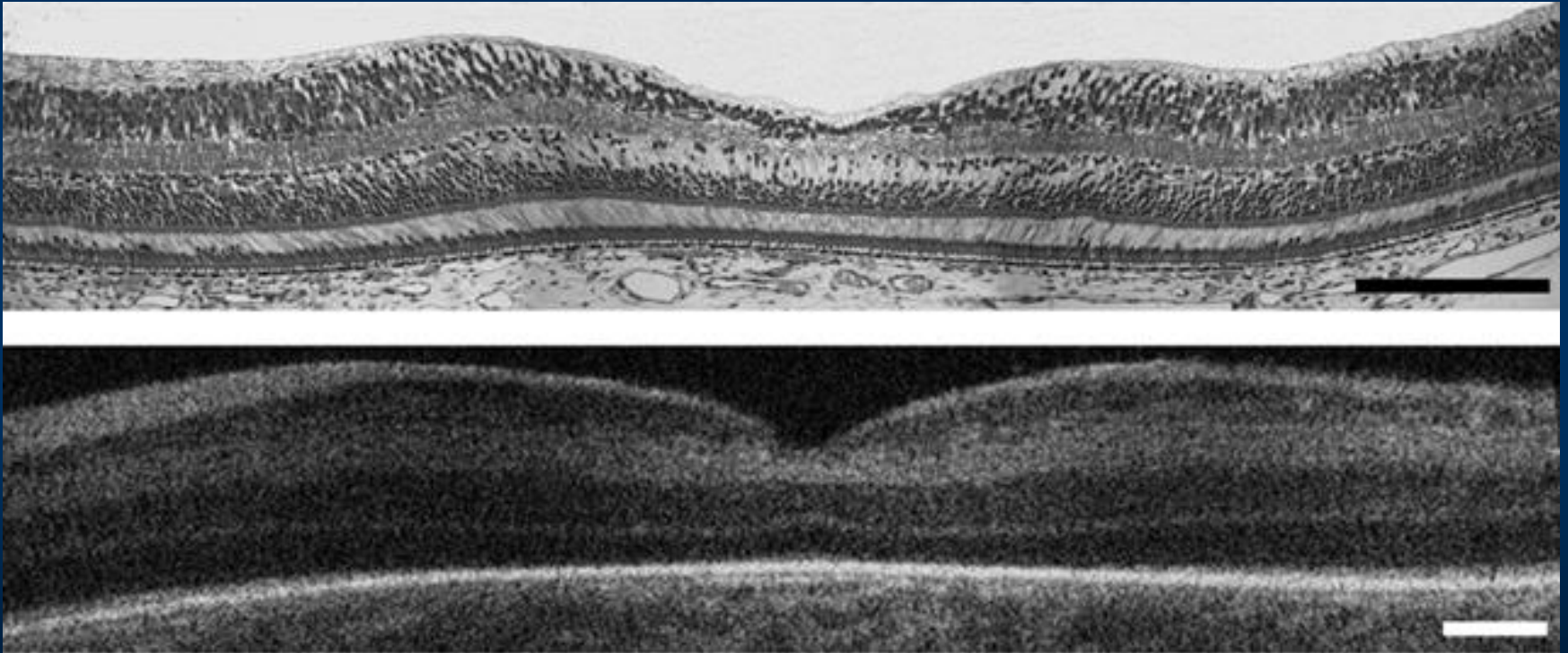
Optic Evoked Potentials of the Right Optic Nerve		
Wave	Pre Treatment	Post Treatment
N1	171	60
P1	200	119
N2	224	167

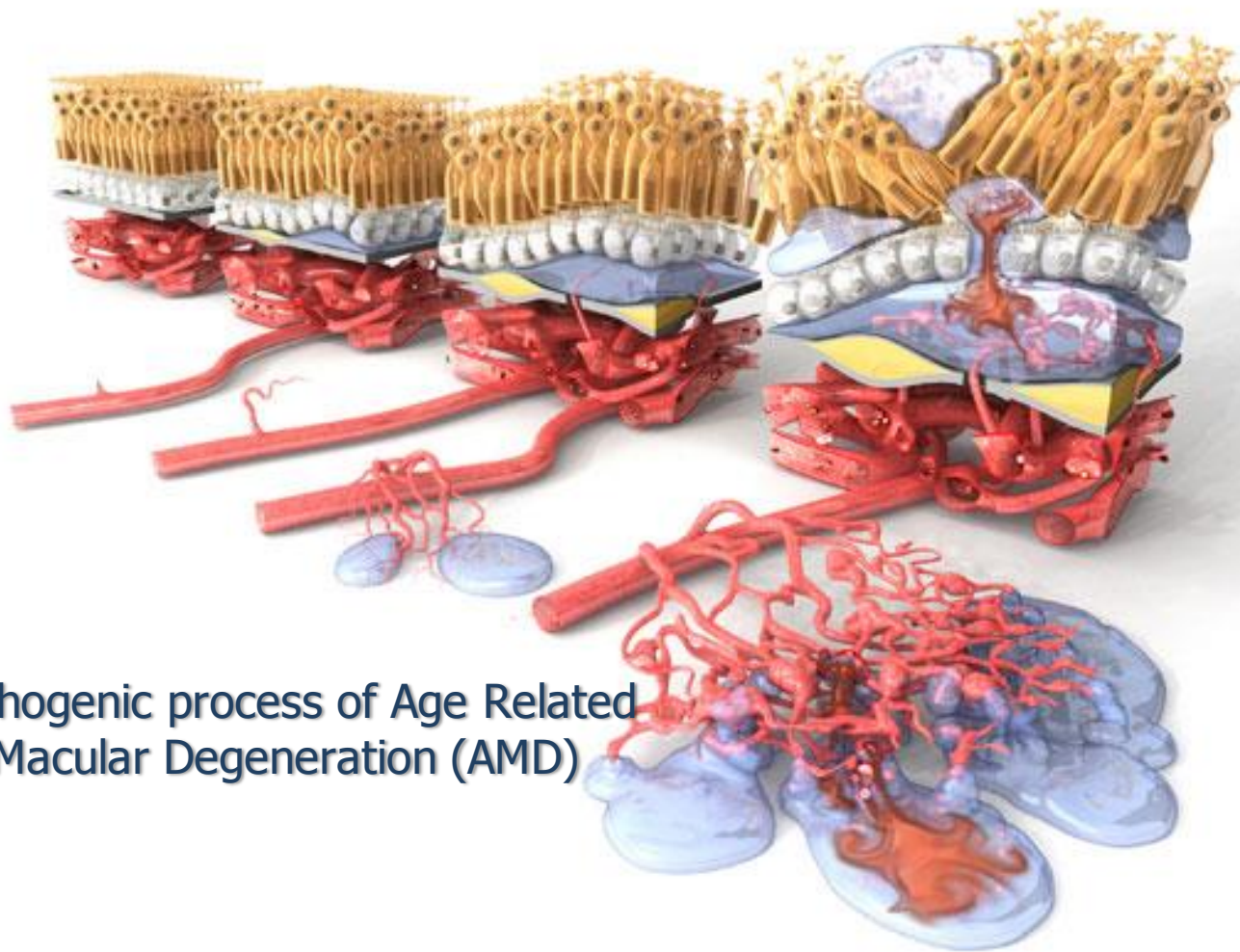
Electroretinogram of the Right Retina		
Wave	Pre Treatment	Post Treatment
a	12,9	11,7
b	49,2	49,2

Optic Coercive Tomography (OCT)



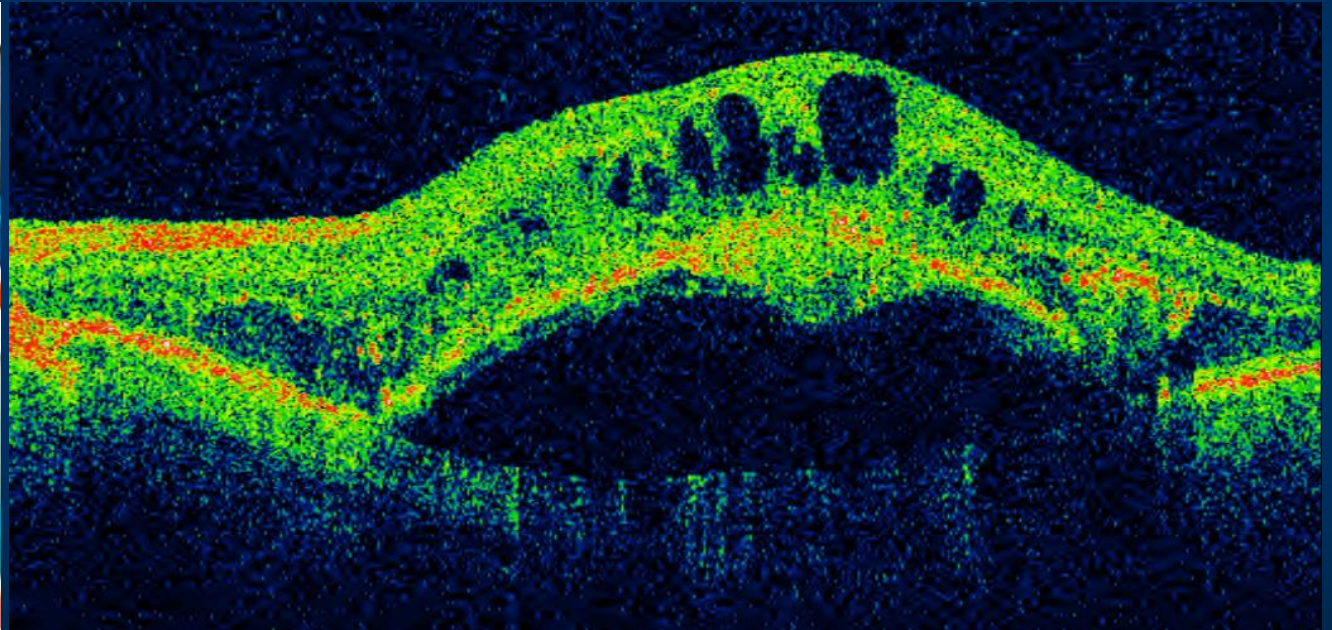
Comparación Imágenes de OCT e Histología de la Retina





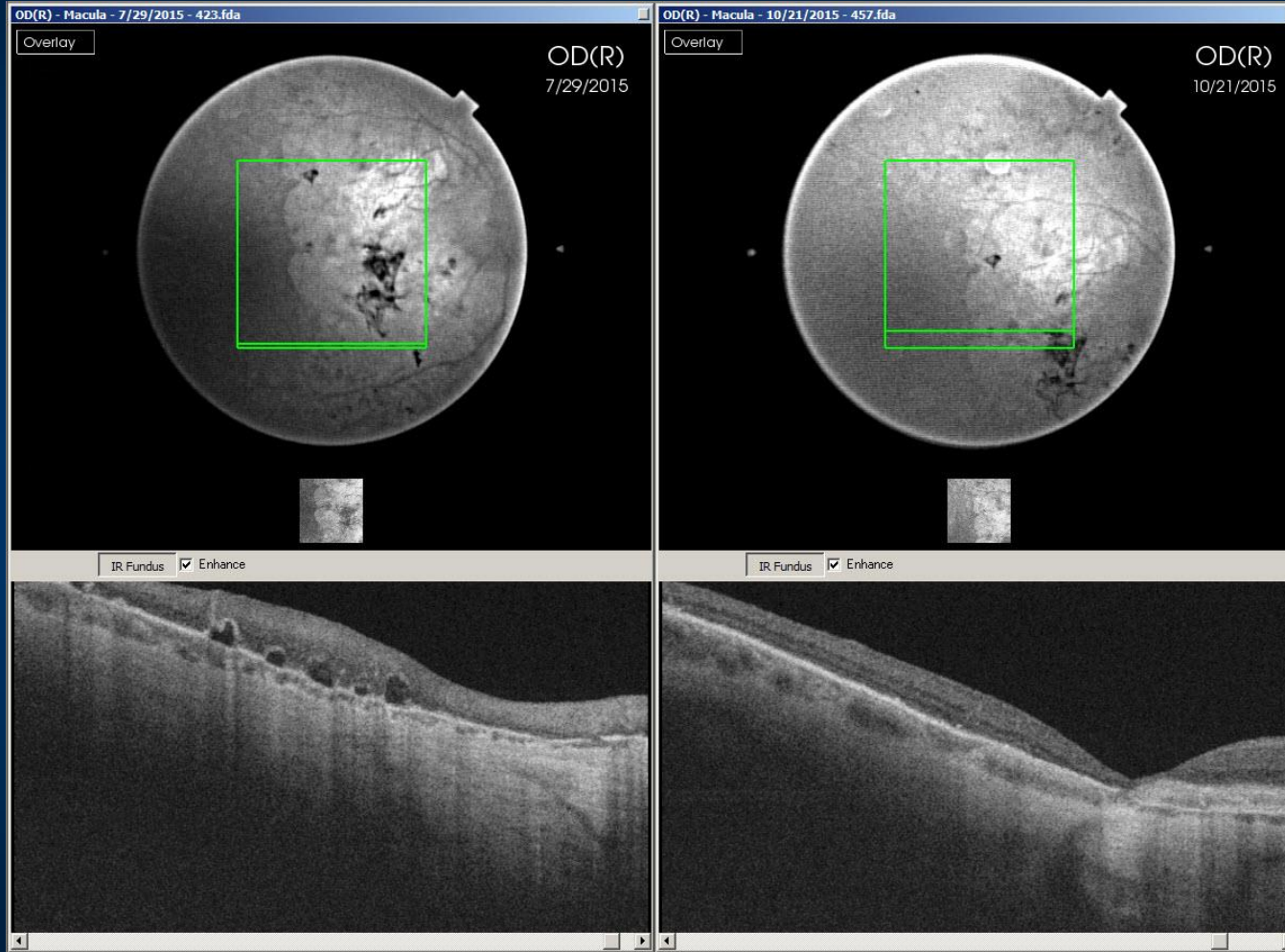
Pathogenic process of Age Related Macular Degeneration (AMD)

Age Related Macula Degeneration (AMD)



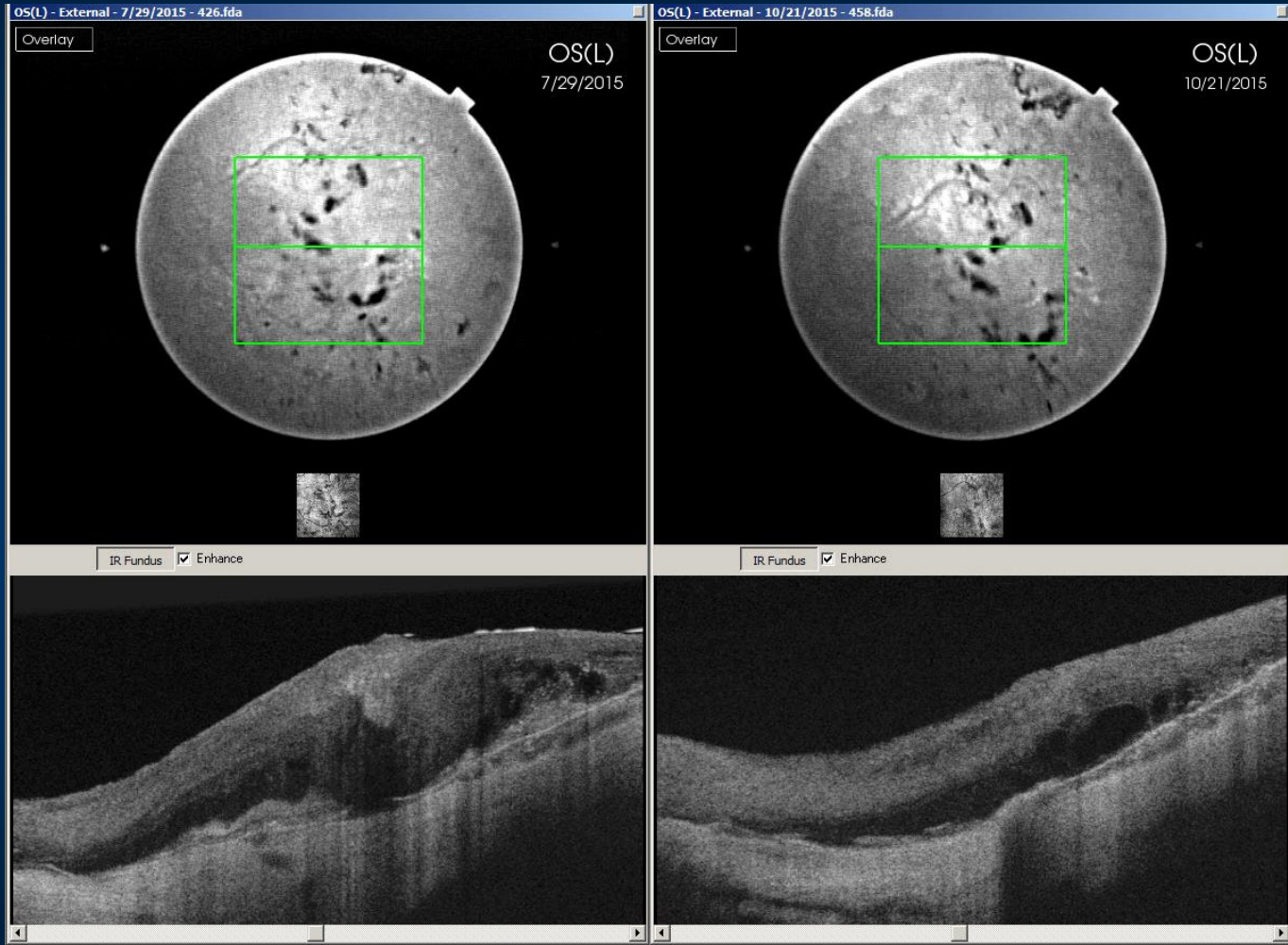
Pre Treatment

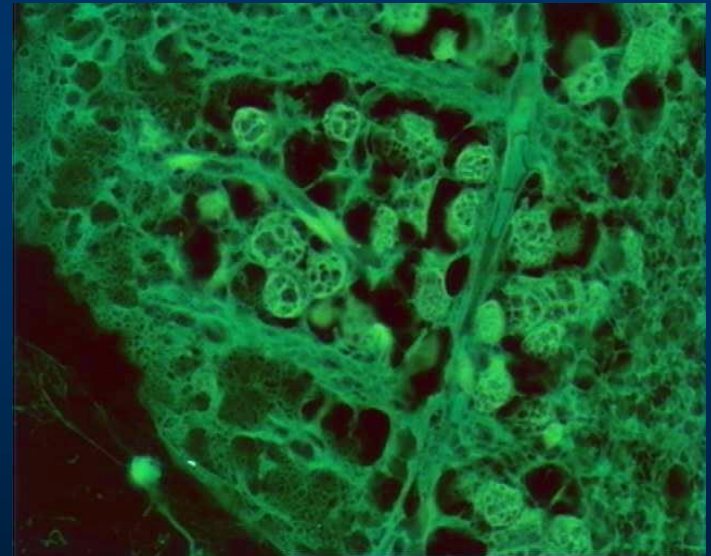
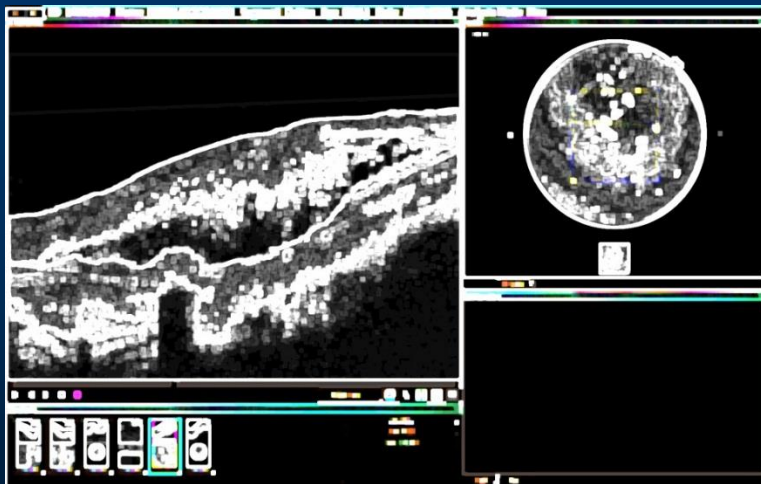
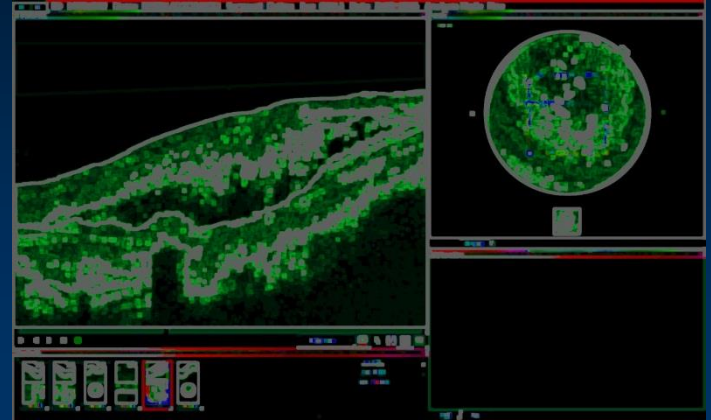
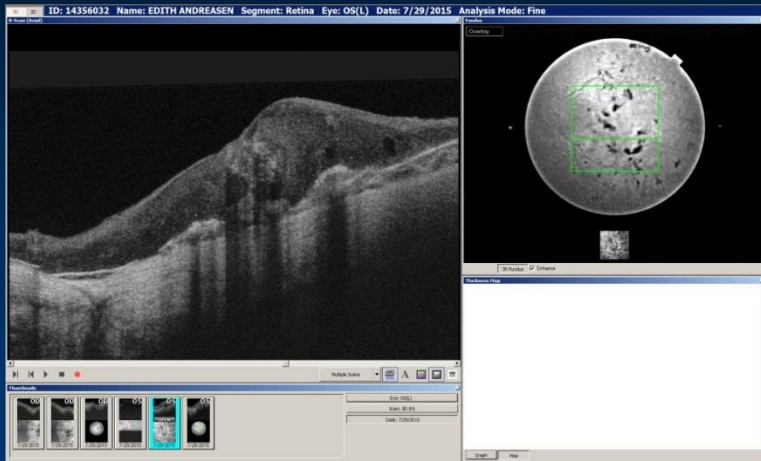
3 months after Treatment



Pre Treatment

3 months after Treatment





Preliminary Results

- After three months of the cellular treatment of a Patient with only Optic Nerve Damage:
 - Recovery of Optic Evoked Potential (OEP).
 - Persistence of the normal values of the Electroretinogram (ERG)
- After three months of the Cellular treatment of two Chronic Blind AMD patients, in the OCT and Digital Biopsy Analysis, was observed:
 - 4 times Enlargement of the Chronic Atrophied Choroidal Vessels.
 - Decreasing of the sub retina and intra retina edema areas.
 - Increasing up to 20 time of the number of Retinal Pigmented Epithelium cells (RPE) in the previous depopulated areas.
 - Retina width Increasing of 20 to 25% in previous atrophied areas.

Conclusions

- Optic Evoked Potentials (OEP) and Electroretinogram (ERG) Registers as Well as OCT and Digital Biopsy Analysis may be effective, accurate and quantitative methodologies to objectively evaluate Safety and Efficacy of Cellular therapies applied for Optic Nerve, Retina and CNS pathologies.
- Clinical results obtained in the Ophthalmologic setting seem be similar to the ones obtained in the treatment of Spinal Cord Injury. This fact may shed light on the Mode of action of MED therapy program.
- Clinical trials are in progress to assess the above preliminary conclusions.