

Stem cell therapy on retinal degenerative diseases

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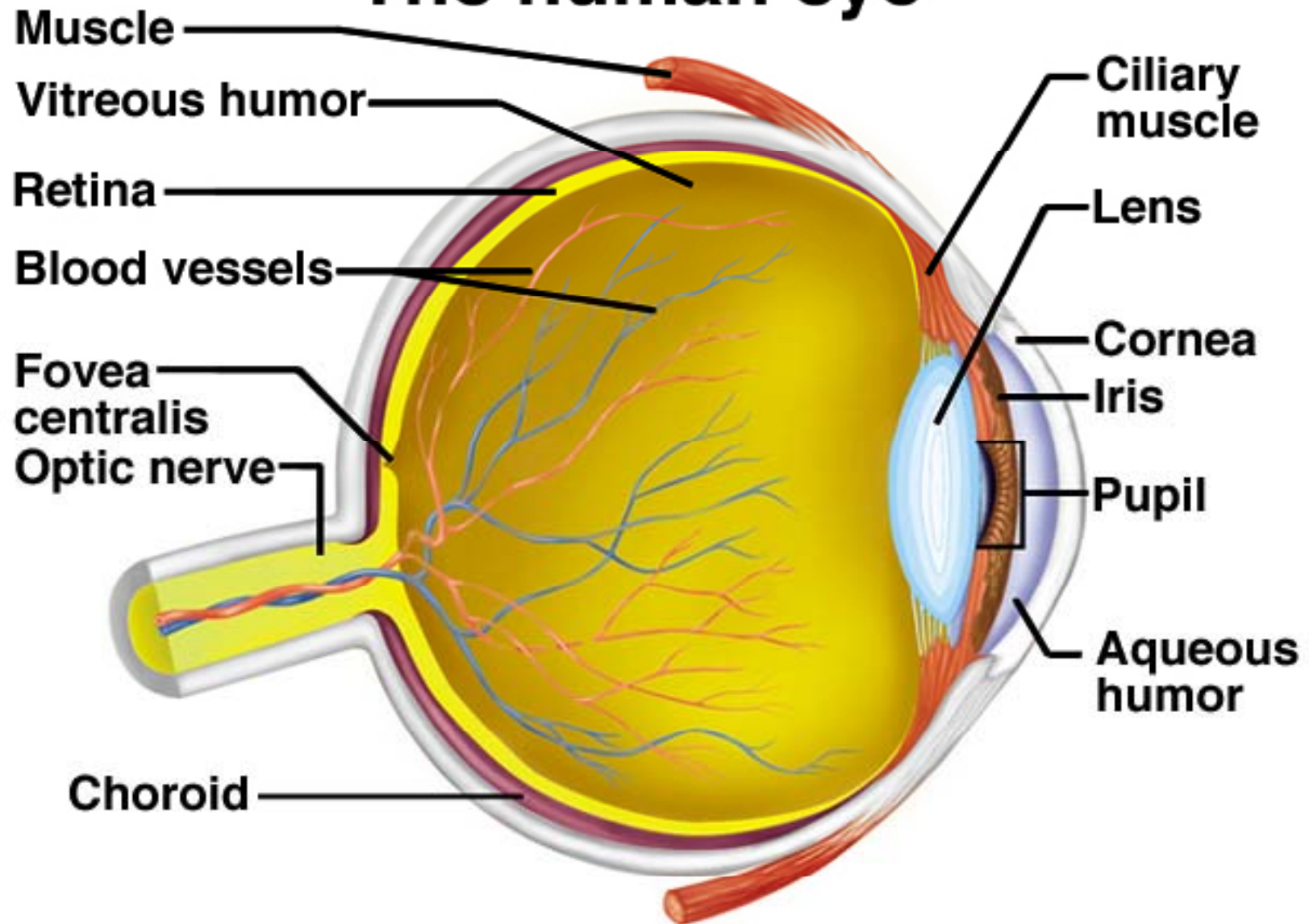
Fu Jen Catholic University
School of Medicine



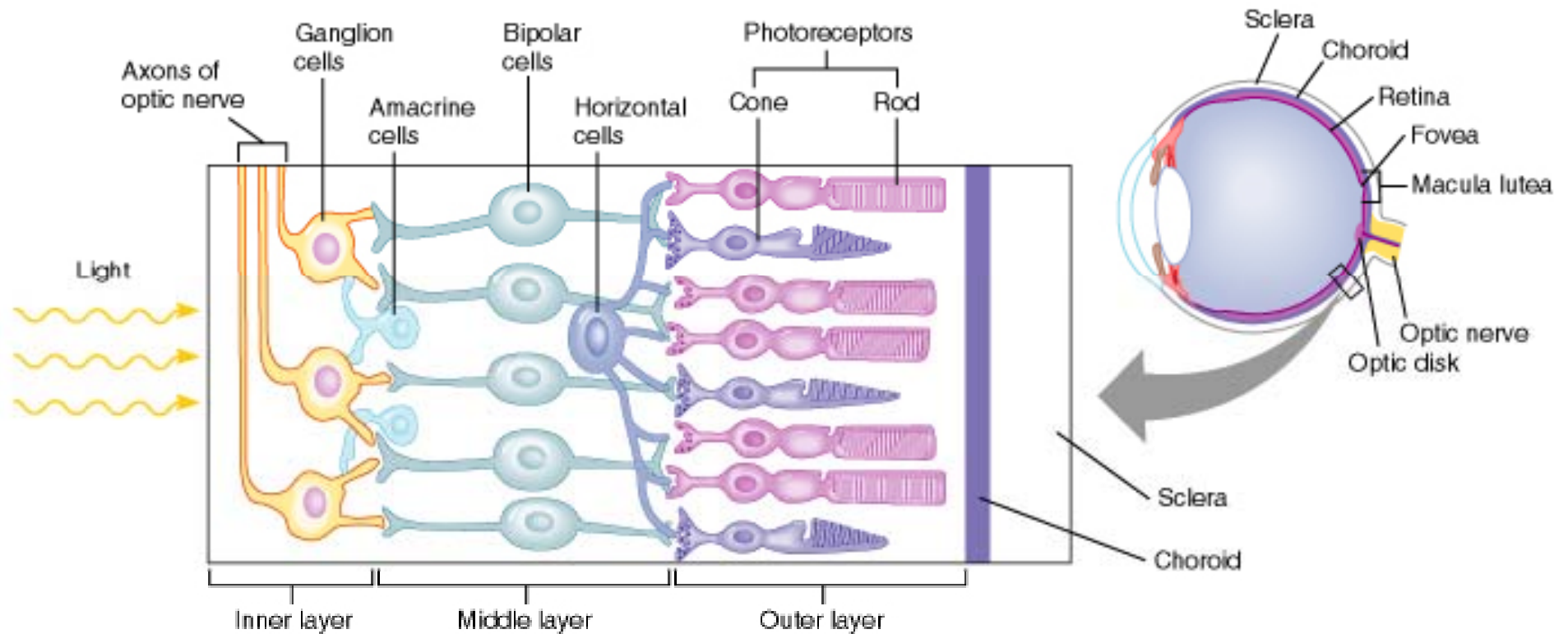
失明的主要原因

- 依據世界衛生組織的統計，失明的主要原因依序為
 - 白內障(Cataract) 46.8%
 - 青光眼(Glaucoma) 12.3%
 - 老年黃斑性病變(Age-related macular degenerative disease, ARMD) 8.7%
 - 糖尿病視網膜病變(Diabetic retinopathy) 4.8%
 - 色素性視網膜炎(Retinitis pigmentosa) 3.9%
- ARMD是西方國家五十歲以上老人造成不可逆視力喪失的原因。

The human eye

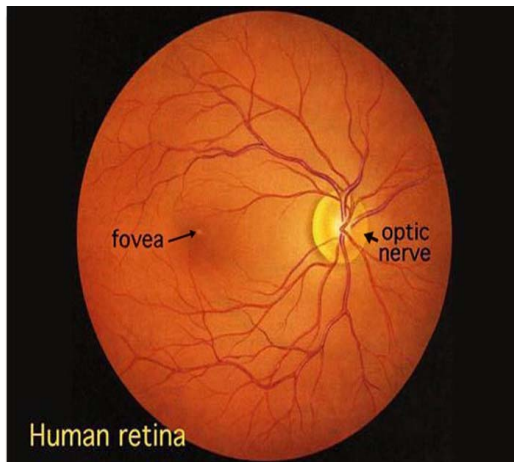


Retina

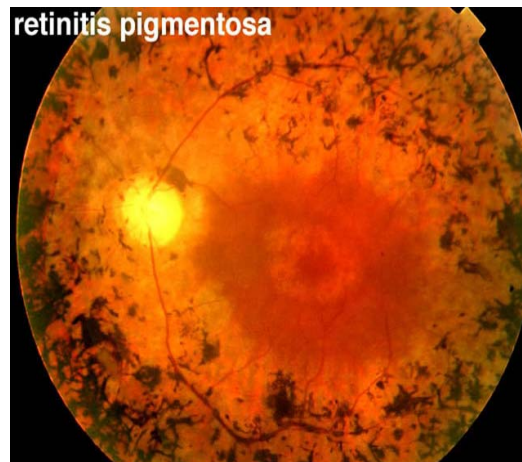


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Normal Vision



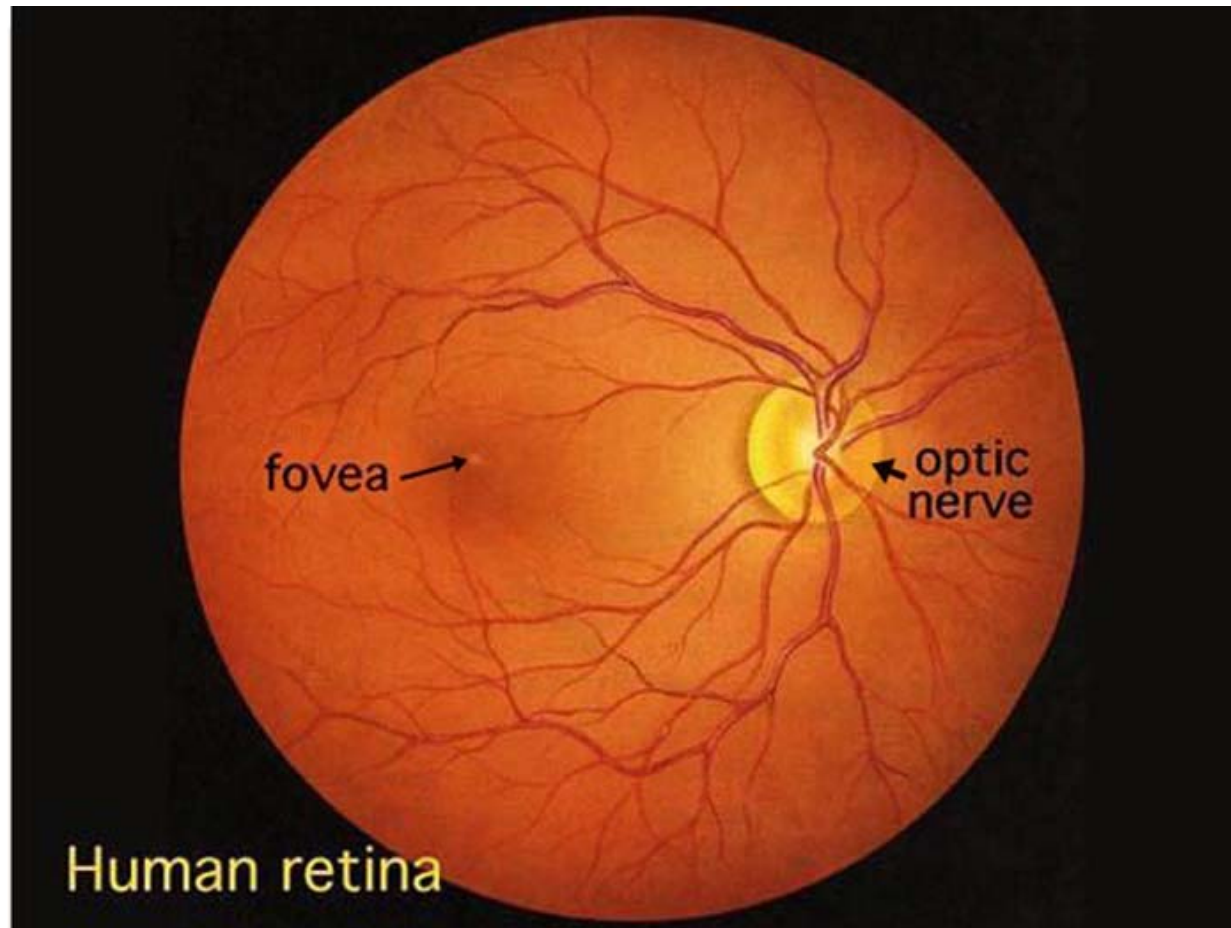
Retinitis Pigmentosa



Age-related Macular Degeneration

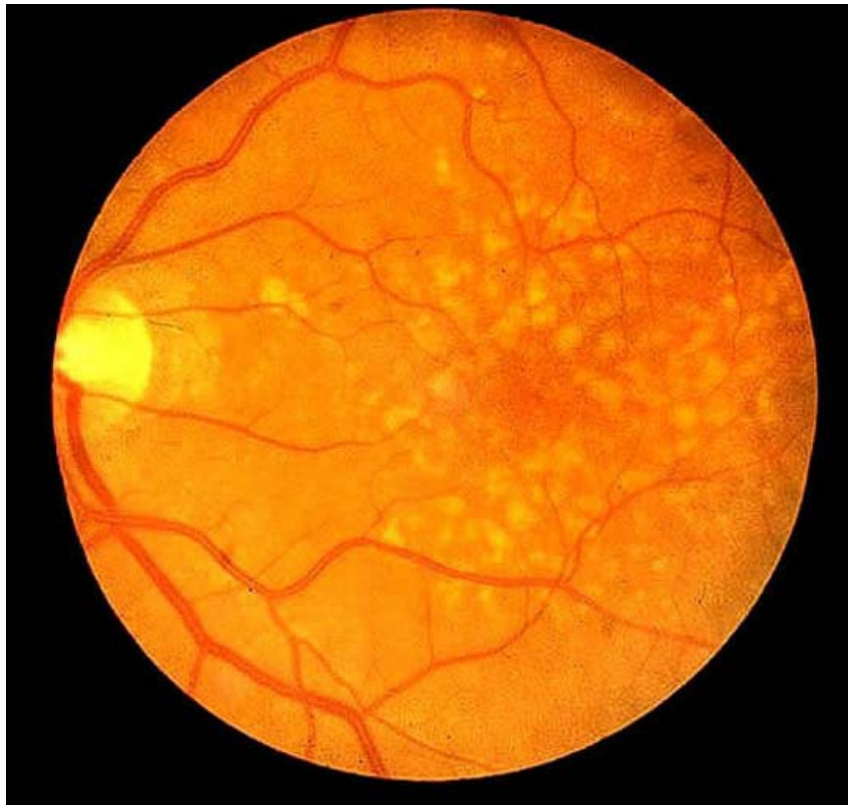


Normal human retina



Age-related macular degeneration

老年黃斑病變



- The macular area and fovea become compromised due to the pigment epithelium behind the retina degenerating, forming drusen 脈絡膜小疣.
- The cones of the fovea die, causing central visual loss.

Age-related Macular Degeneration (AMD)

What It's Like

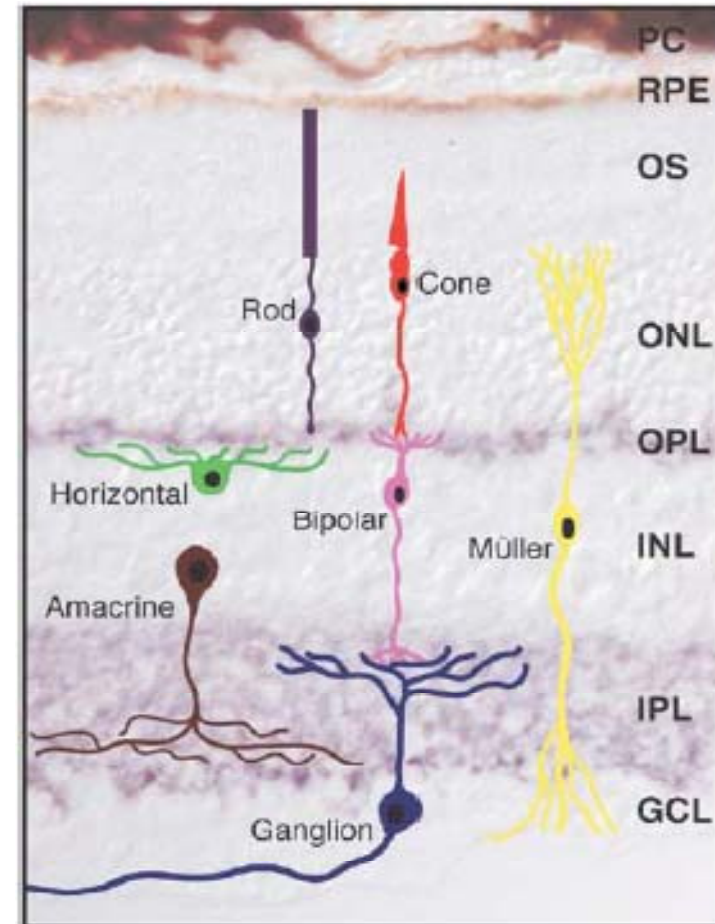
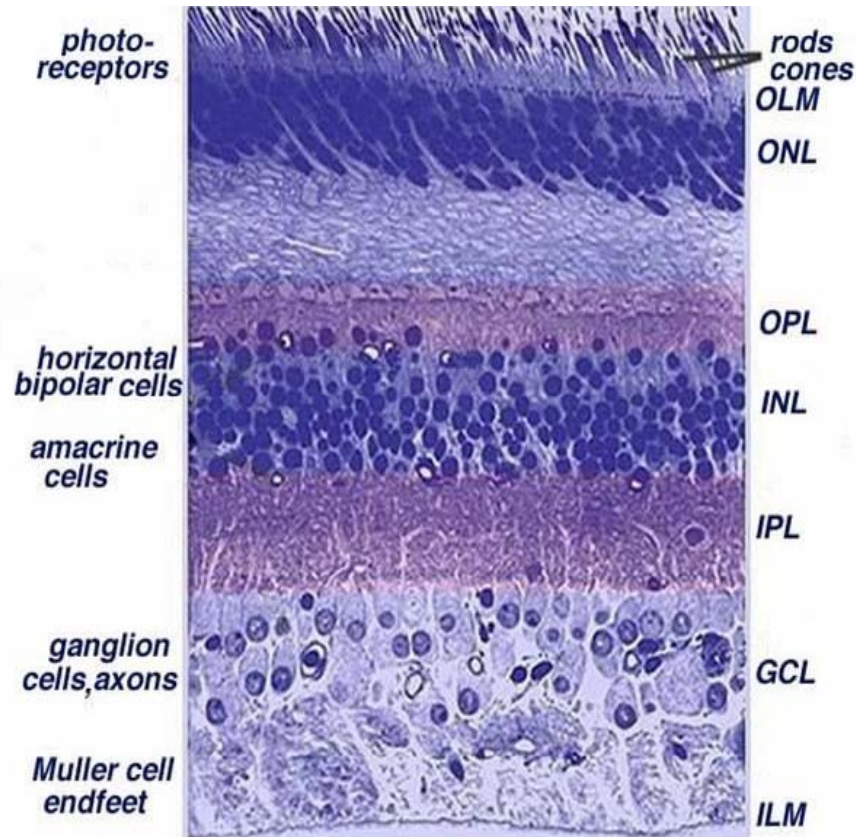


This is how a street scene looks with normal vision.

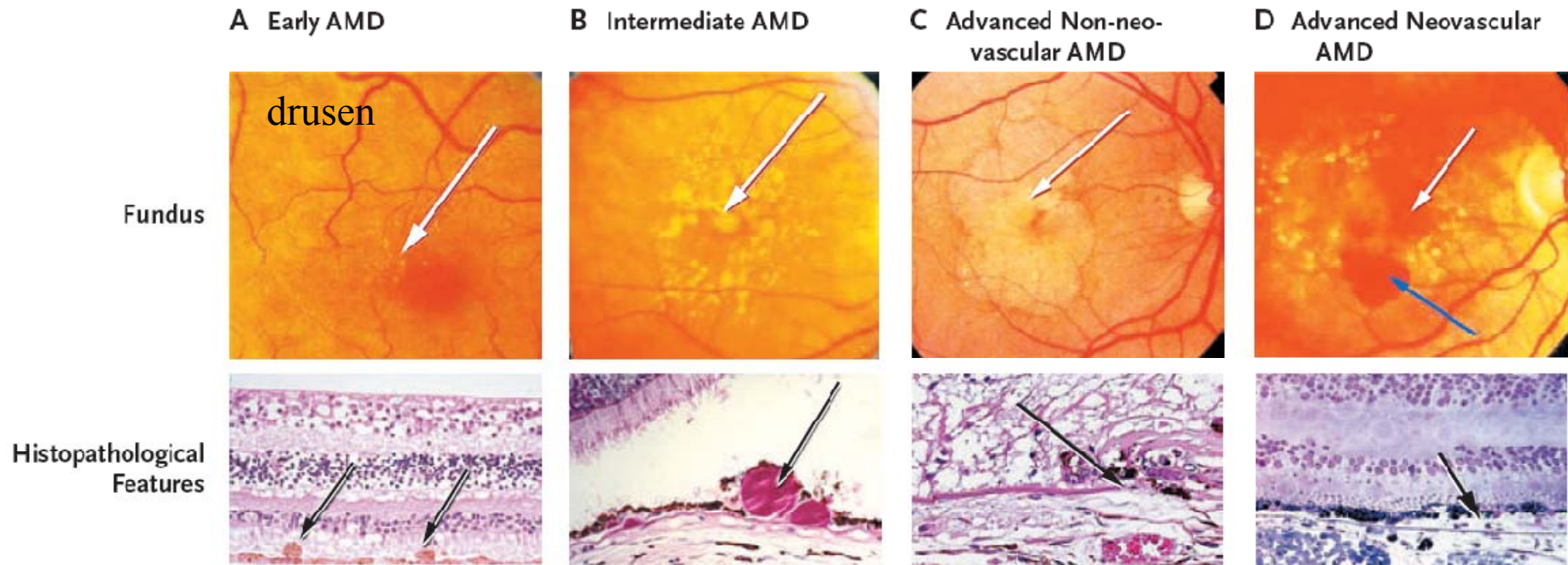


Example of a Macular Degeneration

Human retina



Age-related Macular Degeneration



Jager et al., 2008

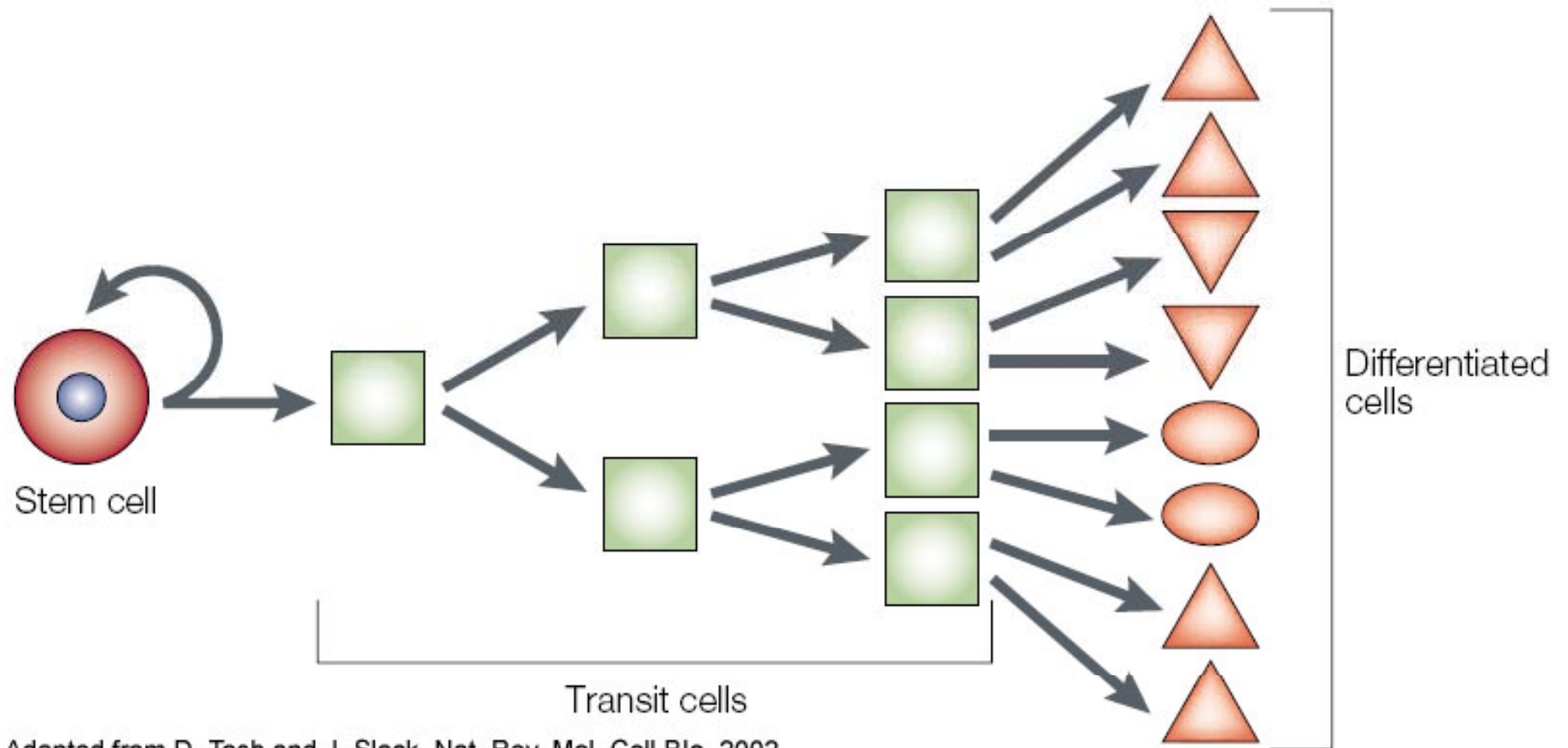
Age-related Macular Degeneration

- At this point in time, **no effective** vision-restoring treatments are available for patients with ARMD.
- For those who have already lost their sight, **cell-replacement** therapy may be the best way for the vision restoration.

What Are Stem Cells ?

- Stem cells are unspecialized cells that have two defining properties:
 - the ability to **differentiate** into other cells
 - the ability to **self-regenerate**

Self Renewing and Differentiation



Adapted from D. Tosh and J. Slack, Nat. Rev. Mol. Cell Blo. 2002

Classification of Stem Cells

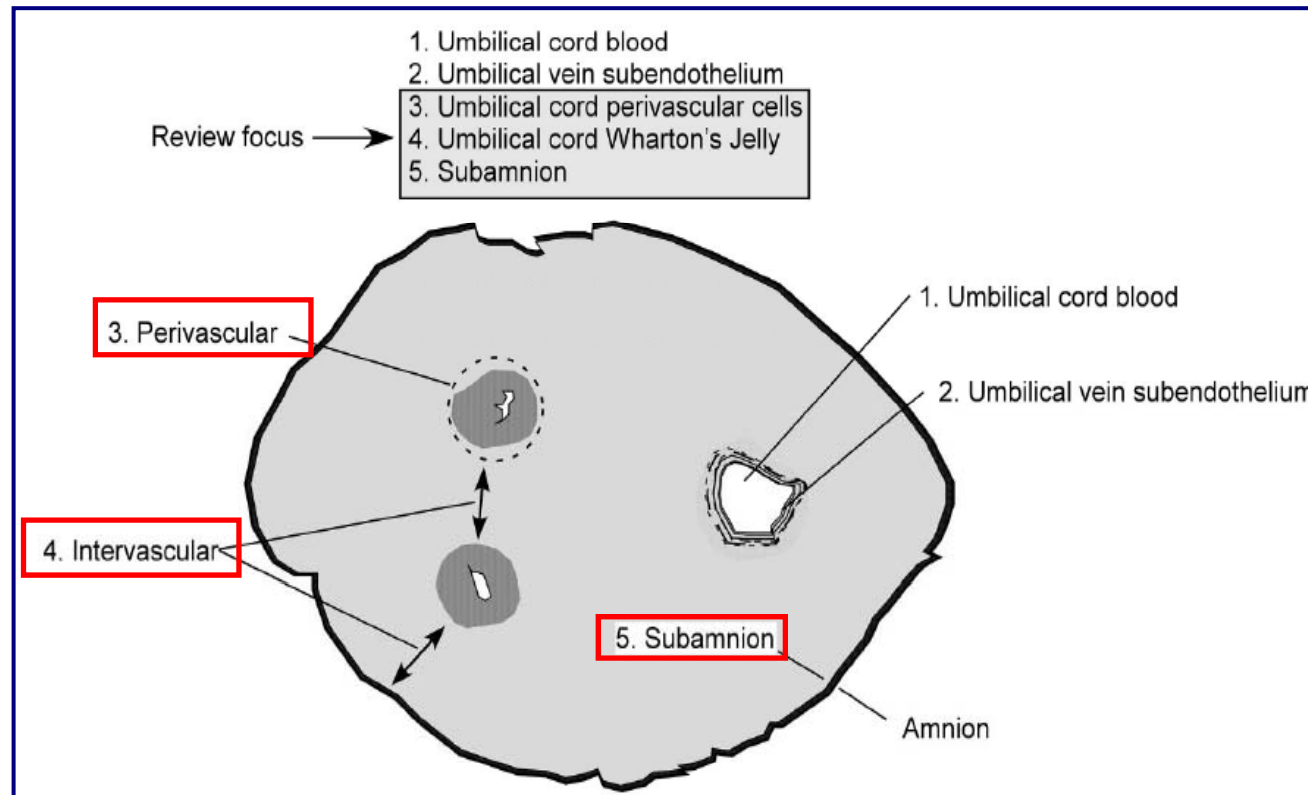
- Embryonic stem cells
 - from blastocyst in the embryo
 - *Mouse* embryonic stem cell, for more than 20 years in research.
 - *Human* embryonic stem cell, from 1998.
- Adult stem cells
 - bone marrow stem cells
 - tissue-specific stem cells, such as neural stem cells.
 - peripheral stem cells
- Cord blood cells, placental cells, amniotic cells, amniotic fluid cells, Wharton's Jelly cells.

Application of stem cell

- For Parkinson's disease, embryonic stem cells may provide a plenty source of dopamine neurons that needed for transplantation. (Kim et al., 2002; Perrier et al., 2004)
- Transplantation of human neural stem cell and neural progenitor cell could improve motor function in a rat model of Huntington's. (McBride et al., 2004; Visnyei et al., 2006)
- Retinal stem cells and retinal progenitor cells have their capacity to generate photoreceptor like cells in vitro or after transplantation, but the number of photoreceptors generated is too low. (Coles et al., 2004; Qiu et al., 2005)

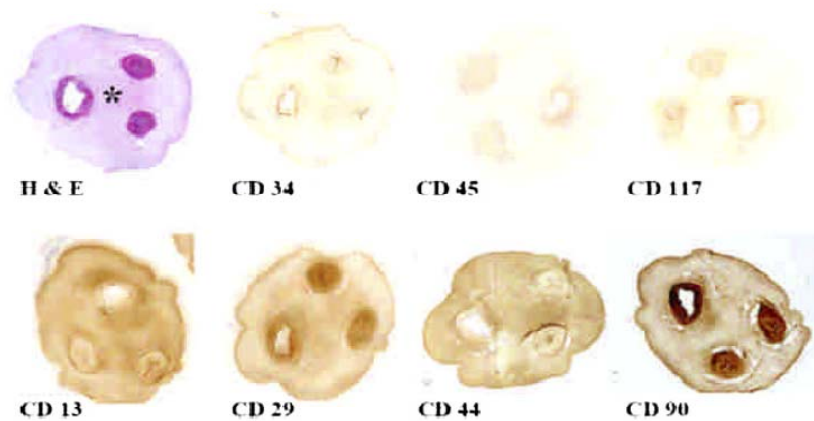
Umbilical Cord

Troyer et al., 2008

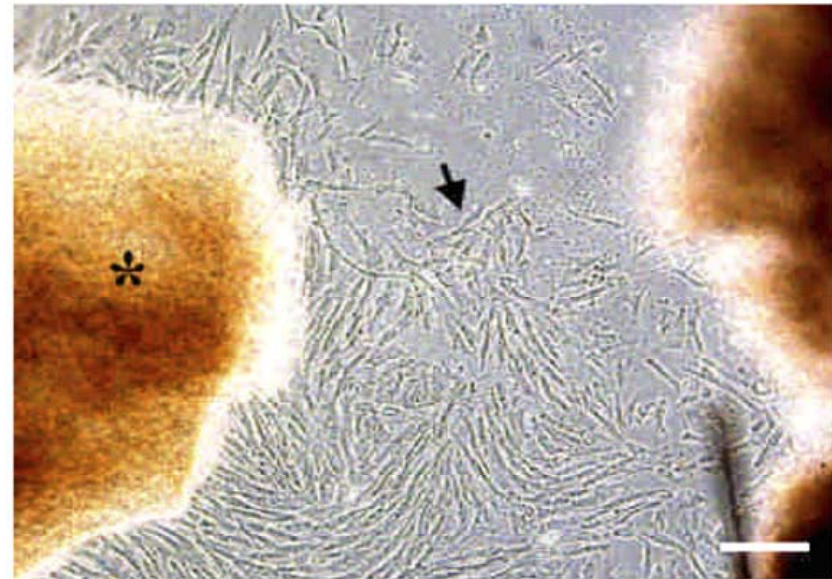


Wharton's Jelly (WJ) includes zones 3, 4 and 5.

Application of stem cell



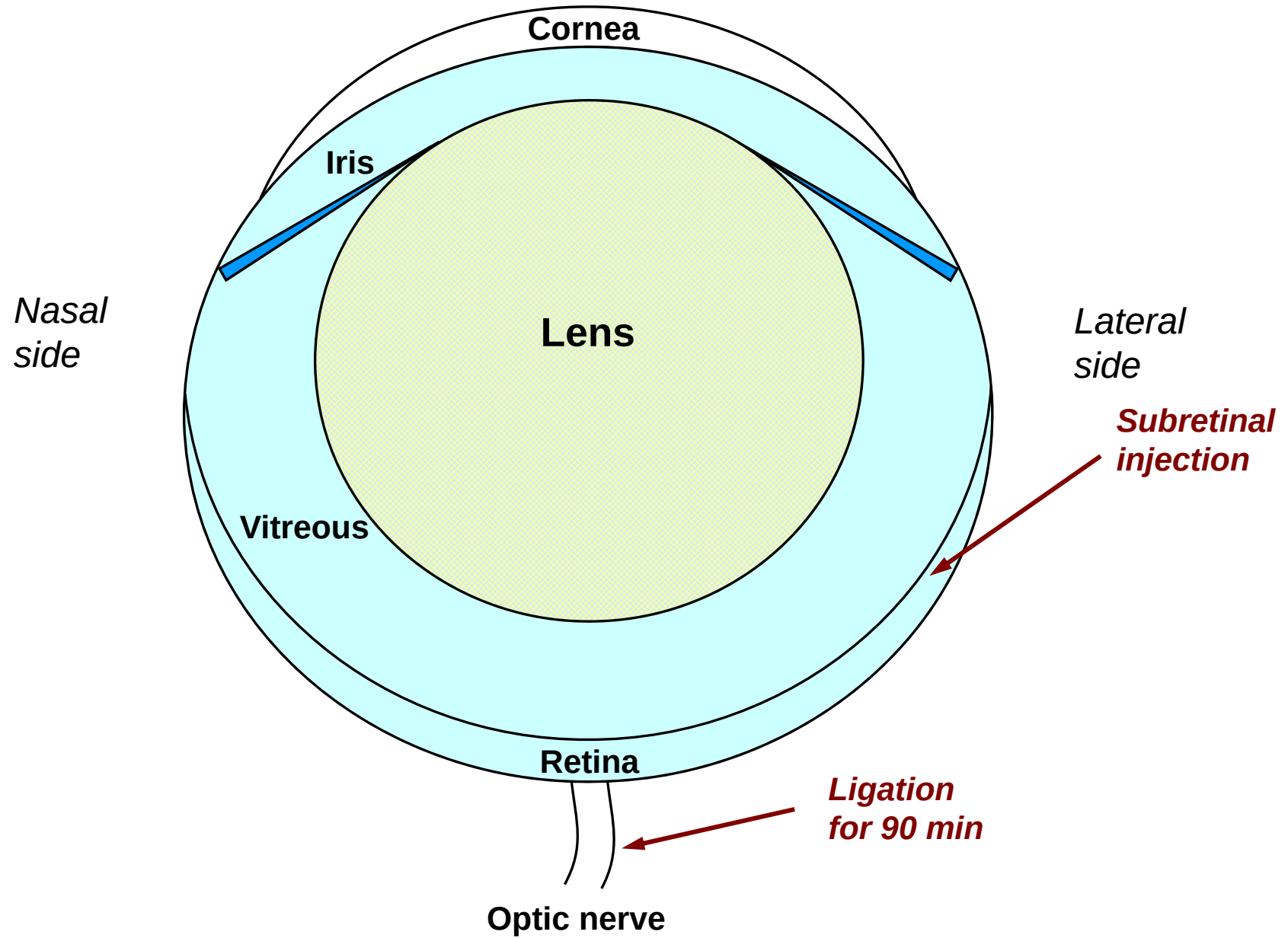
CD 13 — myelomonocytic cells
CD 29 — β 1 integrin
CD 44 — leukocyte, erythrocytes
CD 90 — Thy-1
HLA — Class II human leucocyte antigens



Ding et al., 2007

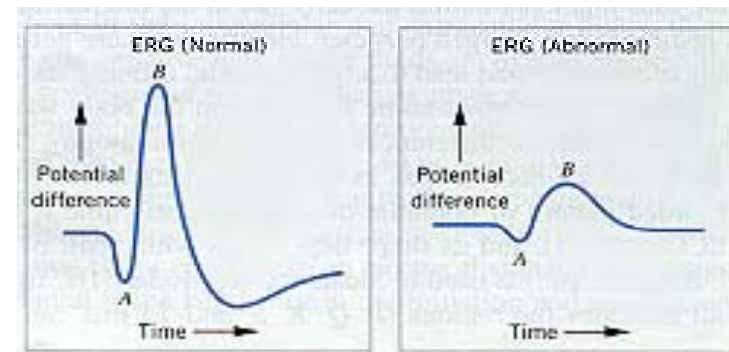
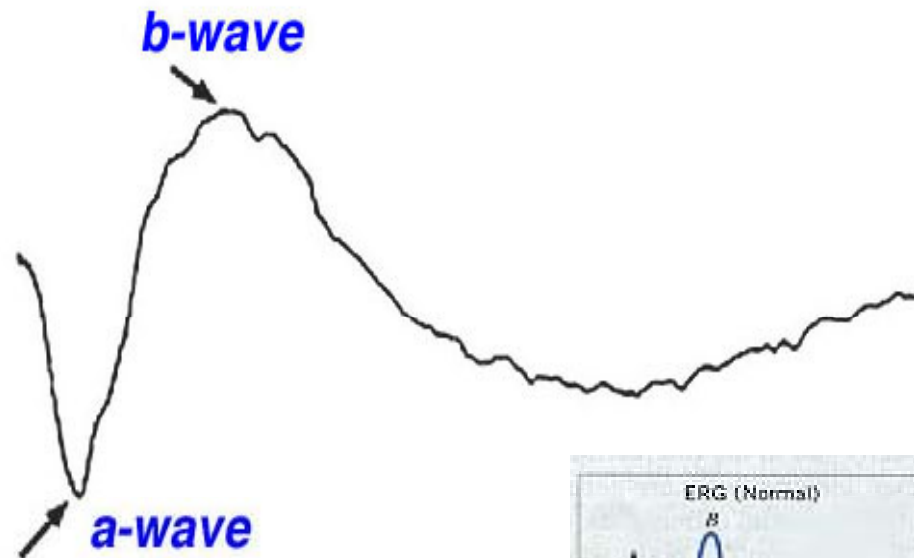
Application of stem cell

- In stroke rats, transplantation of human umbilical cord-derived stromal cells showed enhancement of neuroplasticity of the ischemic brain. (Ding et al., 2007)
- We used Wharton's jelly cells (WJC) as the therapeutic material for ARMD animal models.

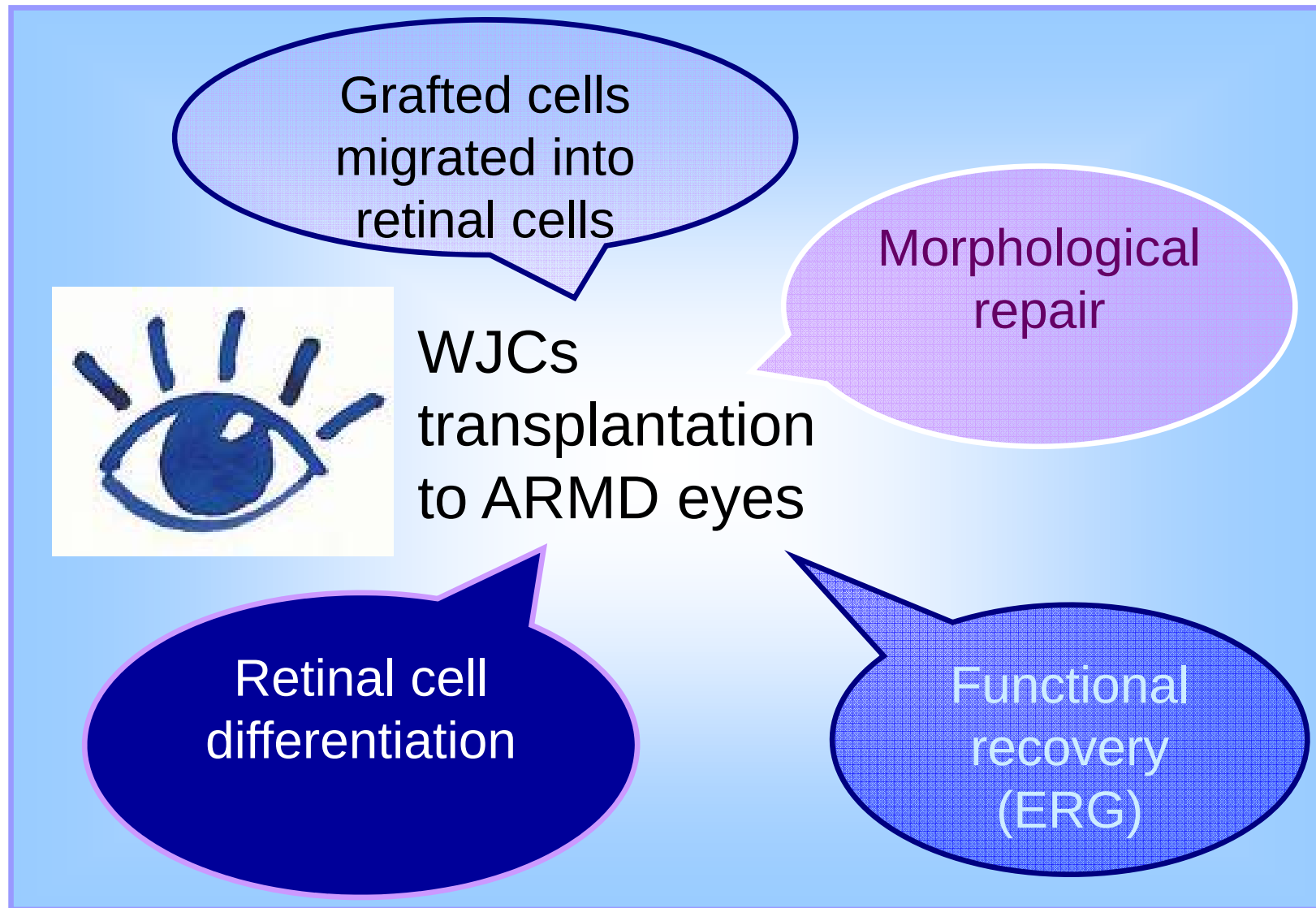


Electroretinogram (ERG)

- A test used to assess the status of the retina in eye diseases in human patients and in laboratory animals used as models of retinal disease.



Conclusion



New Usage of G-CSF

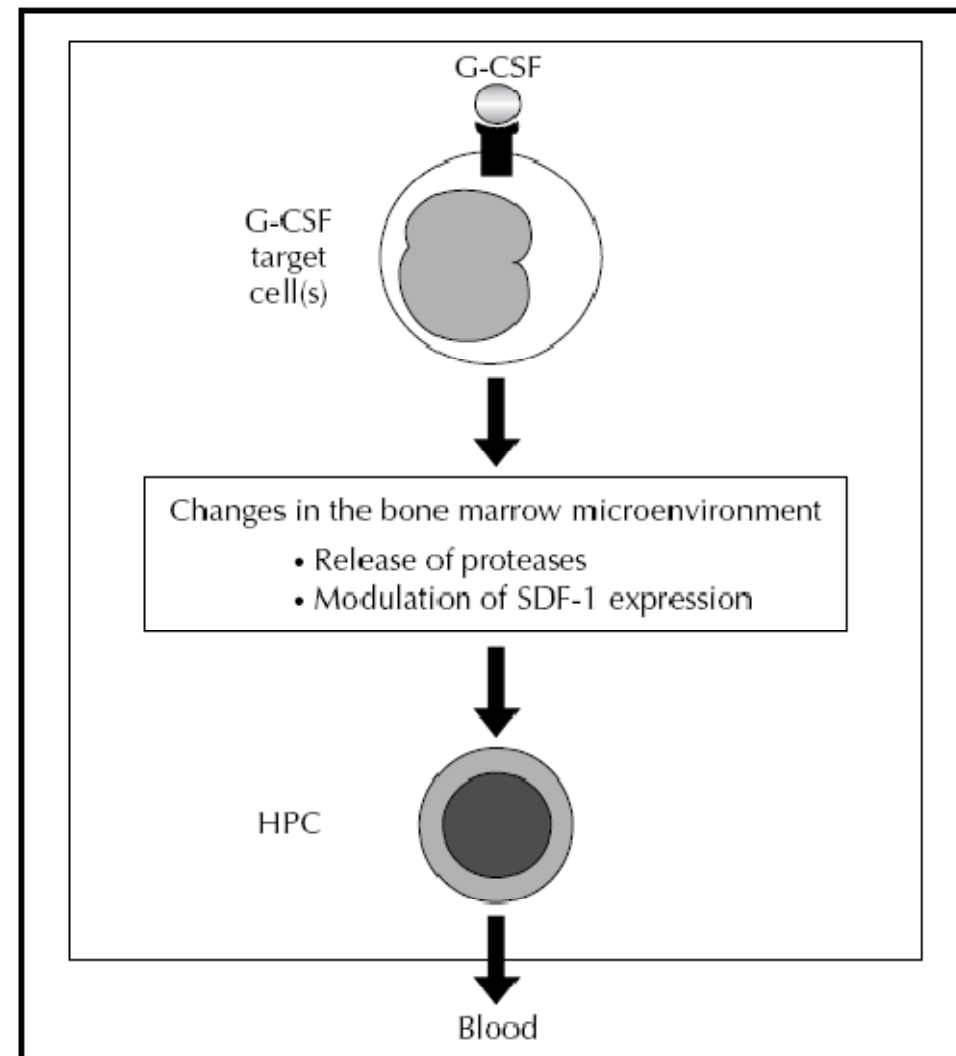
(Granulocyte-colony stimulating factor)

Mechanisms of mobilization of hematopoietic progenitors with granulocyte colony-stimulating factor

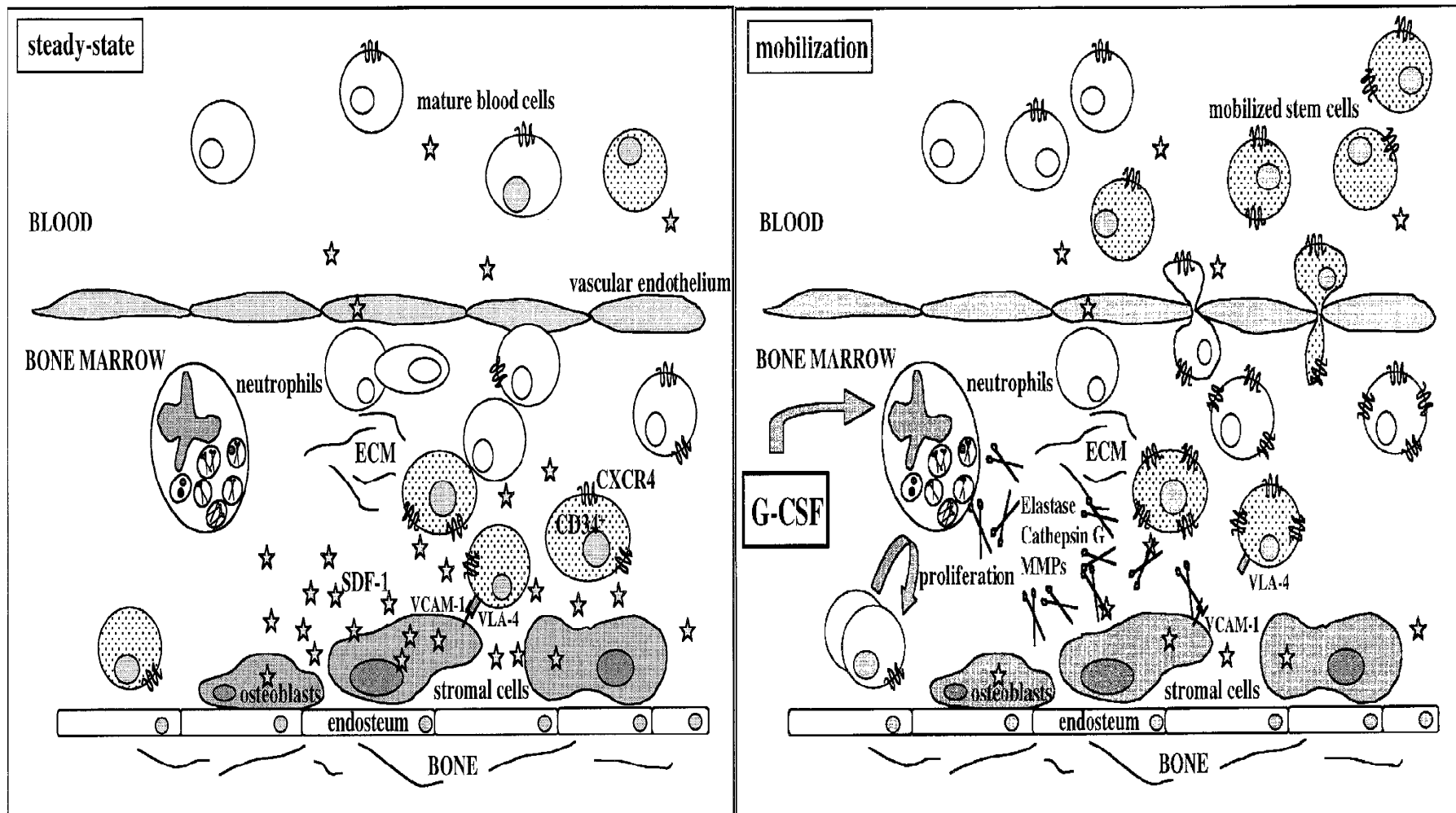
John Thomas, PhD, Fulu Liu, MD, and Daniel C. Link, MD

Current Opinion in Hematology 2002, 9:183-189

Figure 1. Model of hematopoietic progenitor cell mobilization by granulocyte colony-stimulating factor



Stem Cells Mobilized by G-CSF



G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4

Petit et al.

Nature Immunology, 2002 Vol 3(7):687-787

Neuroprotective Effect of Granulocyte Colony–Stimulating Factor After Focal Cerebral Ischemia

W.-R. Schäbitz, MD; R. Kollmar, MD; M. Schwaninger, MD; E. Juettler, MD; J. Bardutzky, MD;
M.N. Schölzke, MD; C. Sommer, MD; S. Schwab, MD

Stroke, 2003 Vol 34:745-751.

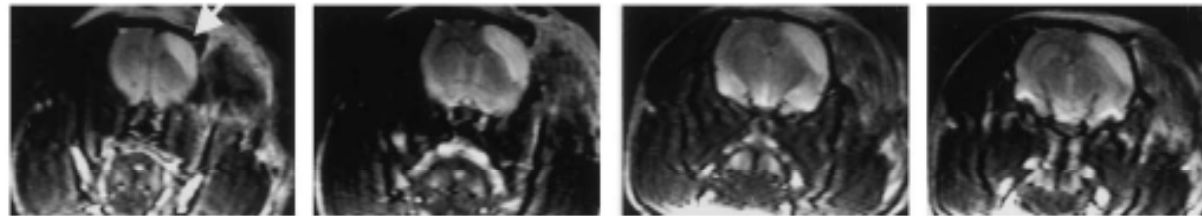
Functional Recovery of Stroke Rats Induced by Granulocyte Colony-Stimulating Factor–Stimulated Stem Cells

Woei-Cherng Shyu, MD, PhD; Shinn-Zong Lin, MD, PhD; Hui-I Yang, BSc; Yi-Shiuan Tzeng, MS;
Cheng-Yoong Pang, PhD; Pao-Sheng Yen, MD; Hung Li, PhD

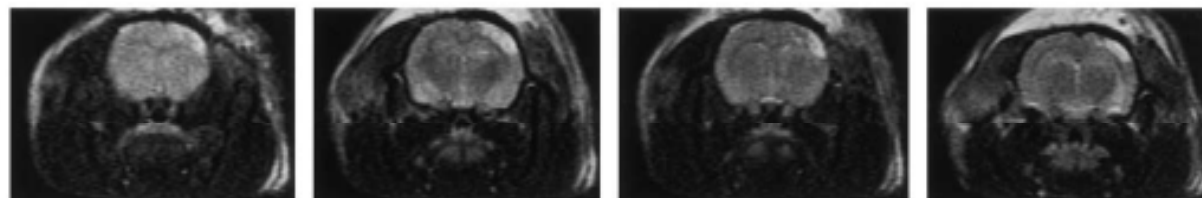
***Circulation*, 2004**

A. G-CSF

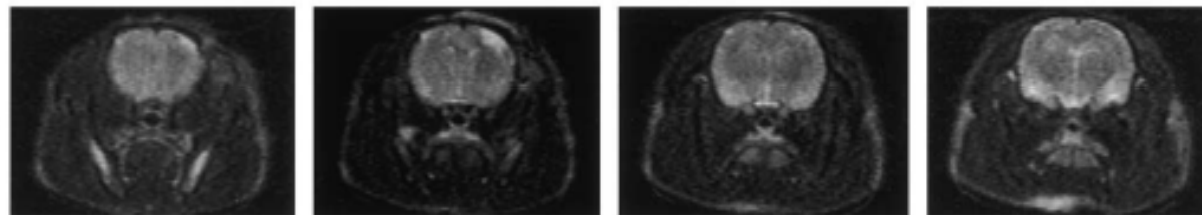
Post 1 day→



Post 7 days→

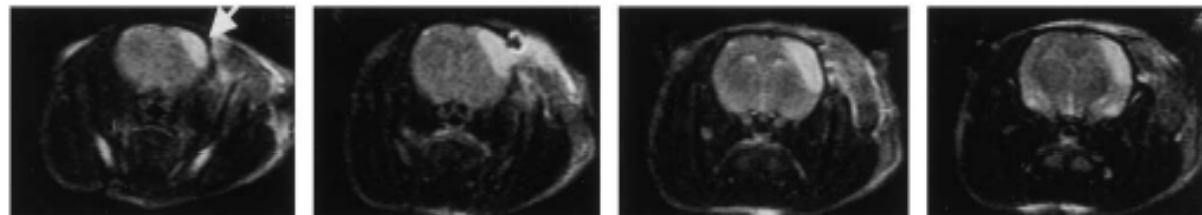


Post 28 days→

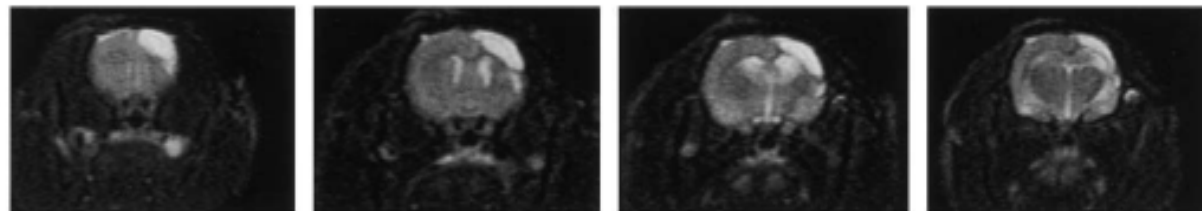


B. Control

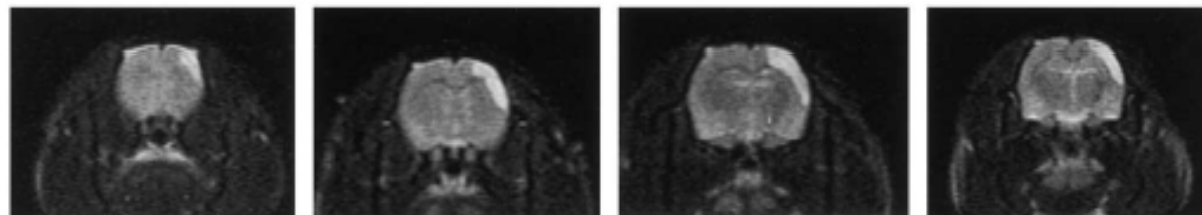
Post 1 day→



Post 7 days→



Post 28 days→



骨髓移植藥物
GCSF
老藥新用

栓塞型中風偏癱 3個月後能走能跳

花蓮慈濟動物試驗 成效顯著 副作用小 目前正徵求花東受試者 為中風治療帶來新契機

記者胡恩惠／報導

●腦中風患者往往須經漫長的復健恢復部分肢體功能，但是，花蓮慈濟醫院將骨髓移植藥物GCSF老藥新用，治療栓塞型腦中風患者，原本半身不遂的病患經過3個月治療，多人恢復行動自如；按照一般療法，患者

復健半年至一年，也不一定站得起來，這項老藥新用法為中風治療帶來新契機。以GCSF治療中風老鼠的動物實驗，已見相當成效；實驗將栓塞型腦中風，半身不遂老鼠，施打GCSF藥劑，14天後發現老鼠腦部受傷的白色區域明顯減少；而中風老鼠半身不遂癱瘓無力，從尾巴提

起時，身體不斷扭向單側，但經過GCSF治療7-10天，老鼠肌肉恢復，被提起時身體可保持平衡，測量其垂直動作時間、次數、品質，也與正常老鼠相近。由於研究結果對中風治療具相當意義，被刊登在排名第一的心臟血管期刊「循環」(Circulation)上。

動物實驗治療效果顯著，慈濟醫院進行人體試驗，8名急性中風患者，。慈濟醫院神經內科醫師徐偉成表示，患者的中風指數平均在14-15分，來院時大多半身癱瘓、講話不清楚，有人甚至已昏迷，若接受一般復健治療半年到一年，能恢復部分肌力就不錯了，不一定能站得起來，但是在中風3天內連續5天注射GCSF後，3個月內可站可走，甚至有人能跑能跳，恢復相當迅速。

徐偉成說，GCSF是血球生長激素，原本用於骨髓移植患者，讓骨髓內的幹細胞跑到周邊血液；而用於腦中風治療時，GCSF將骨髓中的幹細胞運到周邊血管，中風處

會有蛋白質表現，吸引幹細胞到患處修補，分化成腦神經、血管等細胞，因此有助中風患者迅速恢復。此外，GCSF可保護神經，使腦神經不致因中風缺血而壞死，並有抗發炎作用，可抑制中風處的發炎組織及細胞。

不過，GCSF僅對栓塞型腦中風有效，出血型中風仍以手術清除手術為主。徐偉成表示，中風目前無藥可醫，栓塞型中風只能在中風2小時內施打溶血藥物TPA，但此藥有增加出血型中風的危險，而以GCSF治療，患者恢復快，副作用不大，部分患者反映有骨頭痛、皮膚癢、肝功能異常等暫時性副作用，停藥後便停止，用於治療中風前景可期。

慈濟醫院計畫進行10-15個人體試驗，並追蹤一年評估療效。花東地區若有中風7天內，屬中大腦動脈栓塞患者，中風指數在9-20分之間(多為半身不遂)，可至慈濟醫院接受此試驗，但是有心臟病、出血型中風史的患者不適宜，至於已中風1到2年的慢性患者，慈濟亦將進行下一步人體試驗。

注射GCSF一周後 手腳能動了 兩個半月後 竟行動自如... 走過癱瘓 林英享 好幸運

記者胡恩惠／專訪

●住在花蓮的林英享，是接受GCSF治療的第一人，原本中風半身癱瘓的他，注射GCSF約一周後，癱瘓的手腳逐漸恢復活動力。兩個半月後便行動自如，林英享的太太同樣也是中風患者，但因為是二度中風，且未接受試驗，夫妻兩人雖同樣中風，癱瘓卻大不相同。去年12月一個寒冷的早晨，林英享起身後突然跌倒，爬不起來，被兒子、媳婦連忙送往慈濟醫院急診室。他僵及。那時左手左腳無力不能動，雖然意識清楚，還能說話，但嘴巴不自

主地向內一邊，中風指數19分，屬嚴重的患者，對於一向好動、交遊廣闊的他來說，人生頓時陷入黑白。醫院診斷林英享屬急性型腦中風，並未出血，醫師徐偉成向林英享及家屬透露正在研究一種藥物，以前沒有人試過，問他願不願意試一試，當時兒子、女兒、媳婦沒什麼信心，問過其他醫師朋友，說用藥應該沒問題，才答應放手一搏。說也奇怪，一般半身癱瘓患者手腳無力半年以上是常態，但林英享接受一天一劑GCSF注射，連續5天後，他的左手左腳的肌力逐漸恢復，五、六天後左手左腳恢復到

和右邊差不多，便從加護病房轉到普通病房。隨後回家修養，林英享說，可能是地下室空氣比較好，「做田人」又經常活動，兩個半月後他已活動自如，不但手腳活動沒問題，甚至能跑能跳。徐偉成表示，一般像林英享這樣半身癱瘓患者，經過持續復健，半年至一年手腳能恢復一部分力氣就不錯了，通常是以僵硬的手腳，撐著對抗地心引力，像林英享這樣，手腳可恢復到活動自如、能對抗人的拉力，幾乎是不可能的事。林英享並不是唯一恢復迅速的案例，60歲的莊先生送到慈濟時中風指數11分，左

手不能動、左腳微微能抬、講話變大舌頭，而他接受GCSF治療，7天後可撐著扶手行走，近3個月後雙腳控制自如，手負重物也沒問題。林英享說，很感激住院時醫師護士對他無微不至的照顧，但是，他的太太就沒那麼幸運了，今年3月，林英享的太太中風導致右邊癱瘓，由於是二度中風，且當時急診未送到慈濟，錯過了黃金期，林太太至今仍半身不遂，走路需要人攙扶。女兒說，幸好父親恢復得好，才讓家屬負擔減輕，現在幾乎是父親在照顧母親，由於要照顧太太，林英享說，他更要珍惜得來不易的健康。



▲花蓮慈濟醫院神經內科醫師徐偉成(左)以骨髓移植藥GCSF治療中風患者，64歲的林英享如今身體健康，很期待像半年前他曾經半身不遂。(圖／徐偉成醫師提供)

G-CSF treatment on retinal degenerative diseases

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Fu-Jen Catholic University

Summary

- G-CSF reduces cell apoptosis caused by ischemia in retina.
- Administration of G-CSF may mobilize more CD34+ cell to the injured area in retina.
- STAT3 may regulate the protective effect of G-CSF in retinal cell loss after ischemia.
- G-CSF preserves the cell number and the function of retina after ischemia.

Future directions

If we could “treat” or “cure” these diseases in animals, why not the human?

Problems Remain for Stem Cell Therapy

- Clinical trial
- Ethical issue..
- Biomedical issue:
 - How to purify the specific cell lineages in the differentiated populations?
 - Tumor formation?
 - How long the effect of transplanted cell originated remains?