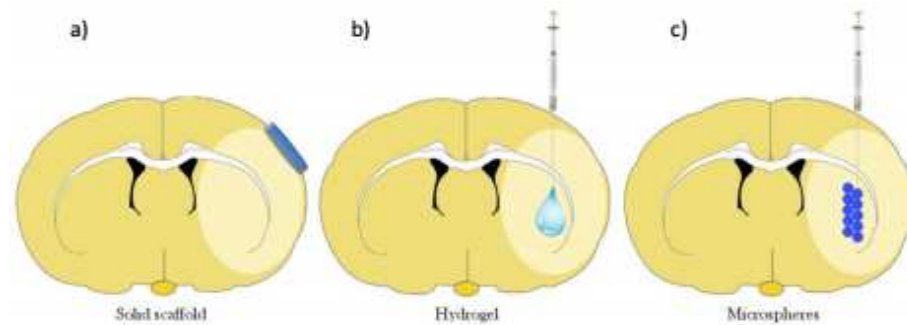




# AVC

## De la science au lit du malade



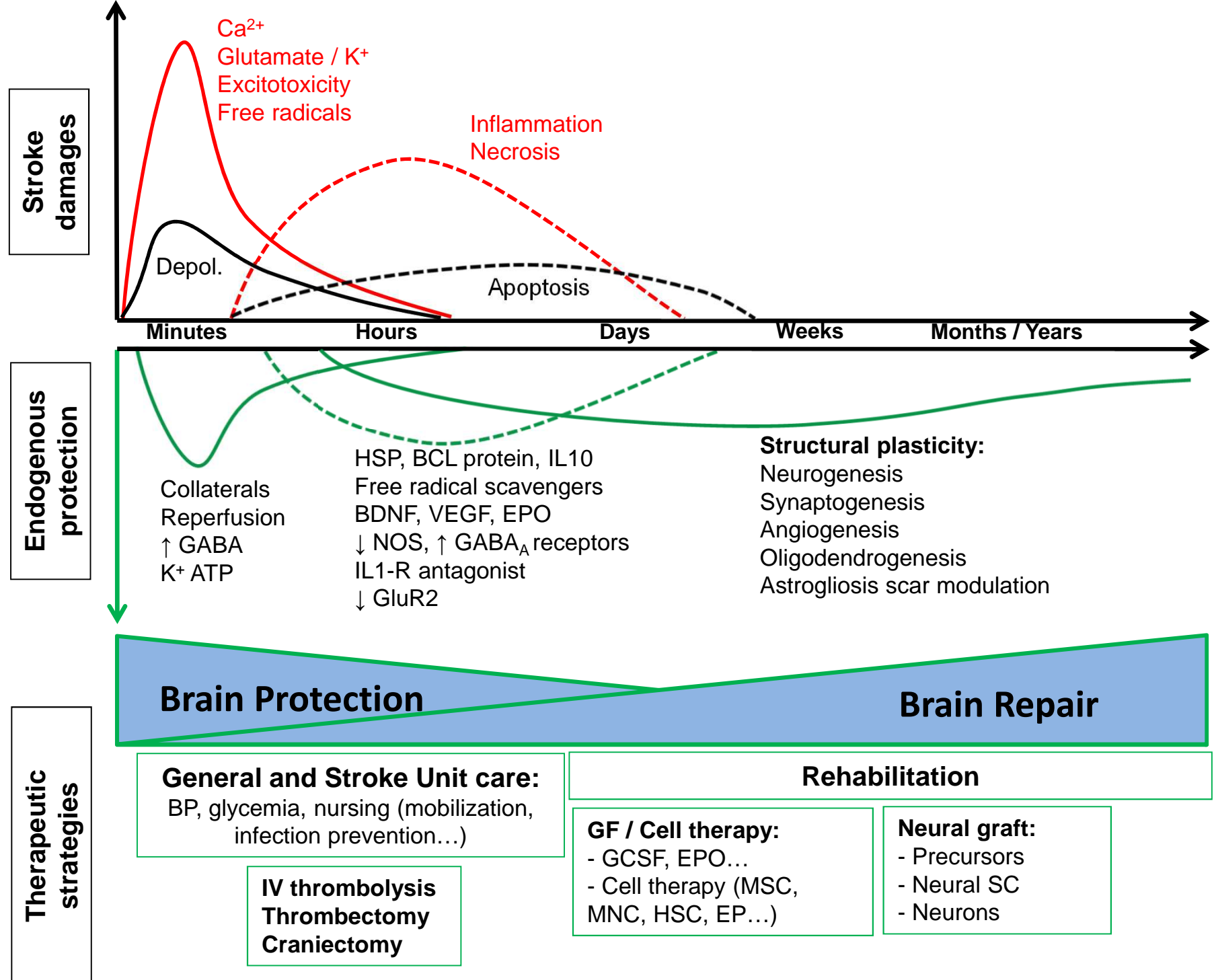
**Pr Olivier DETANTE**  
*Unité Neuro-Vasculaire, CHU Grenoble Alpes  
Grenoble Institut Neurosciences - GIN*

**RENAU AVC, Paris, 2019**



# Disclosures

Company / Name	Honoraria / Expenses	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity position	Employee
Boehringer-Ingelheim	X	X	X				
Bayer	X	X					
Daichi-Sankyo		X					
Bristol Myers Squibb	X						
AMGEN	X						
OTR3		X	X				



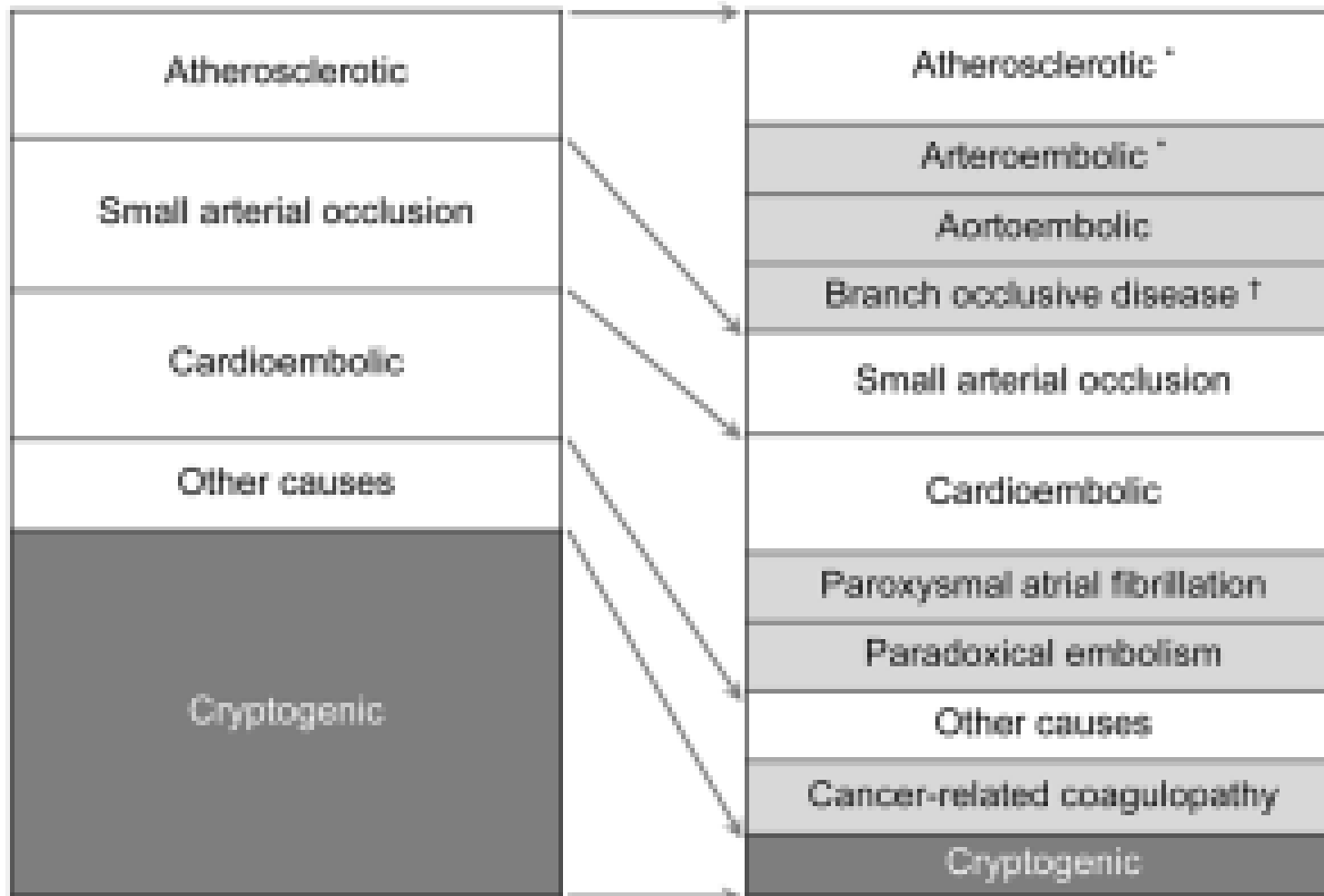
# Diagnostic

# Evaluation of Cryptogenic Stroke With Advanced Diagnostic Techniques

Oh Young Bang, MD, PhD; Bruce Ovbiagele, MD; Jong S. Kim, MD, PhD

## Conventional classification

## Incorporation of advanced technique



# « Intelligence artificielle »

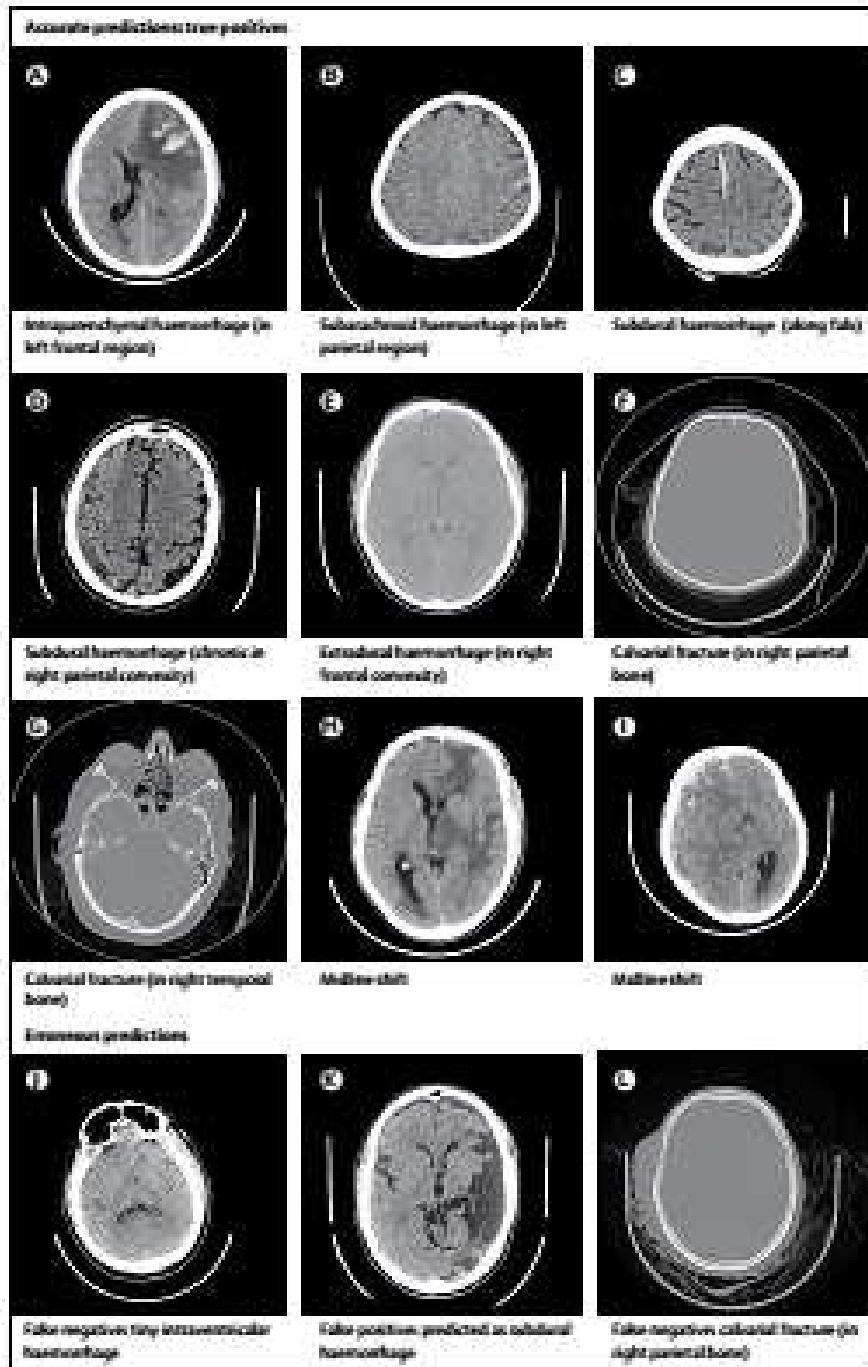


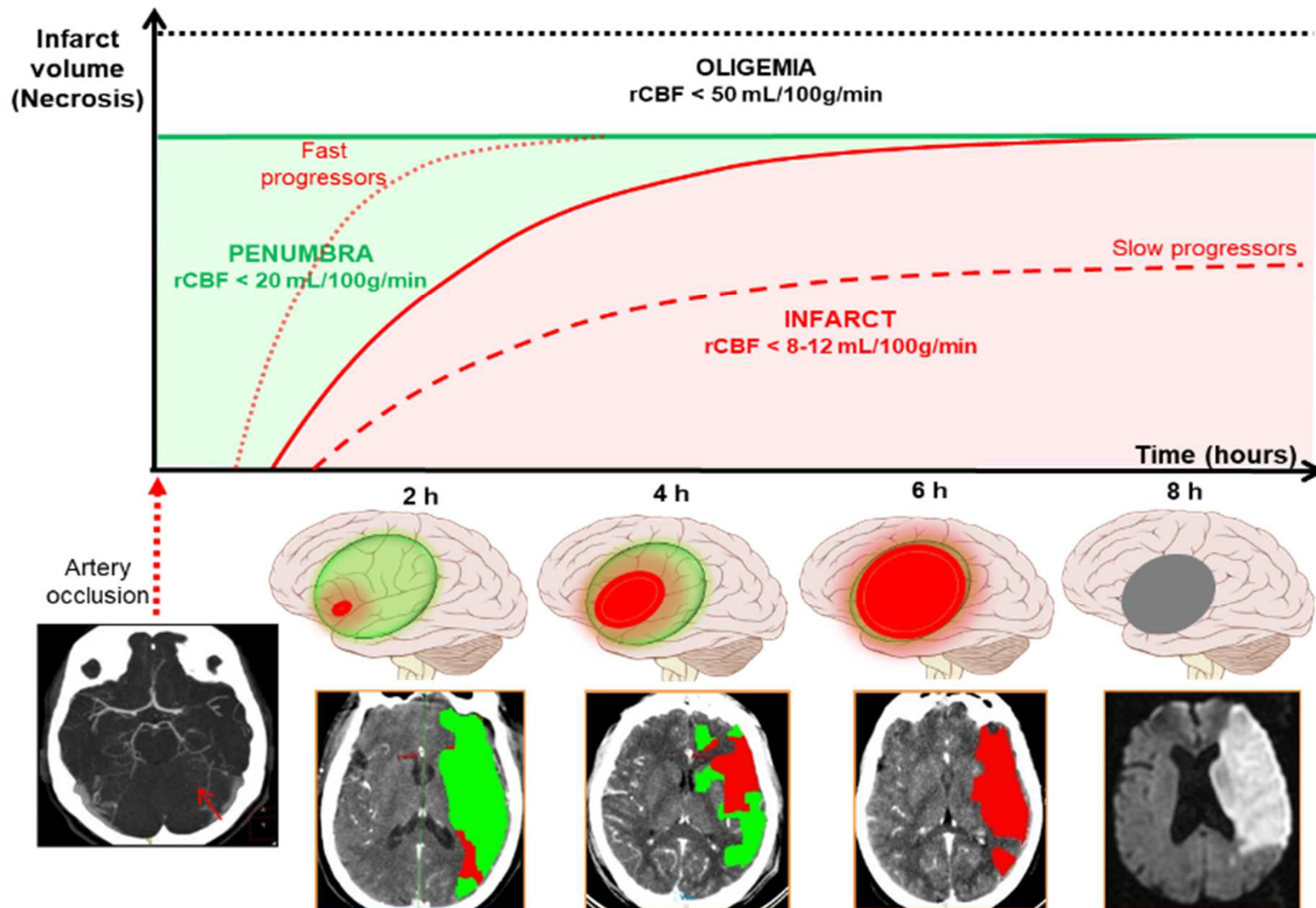
Figure 3: Some accurate and erroneous predictions of the algorithm

- **Deep learning** sur TDM « stroke » ou « trauma » avec hémorragies

- 313 000 TDM !
- AUC > 90%

# **Thrombolyse / Thrombectomie**

# « TIME IS BRAIN »



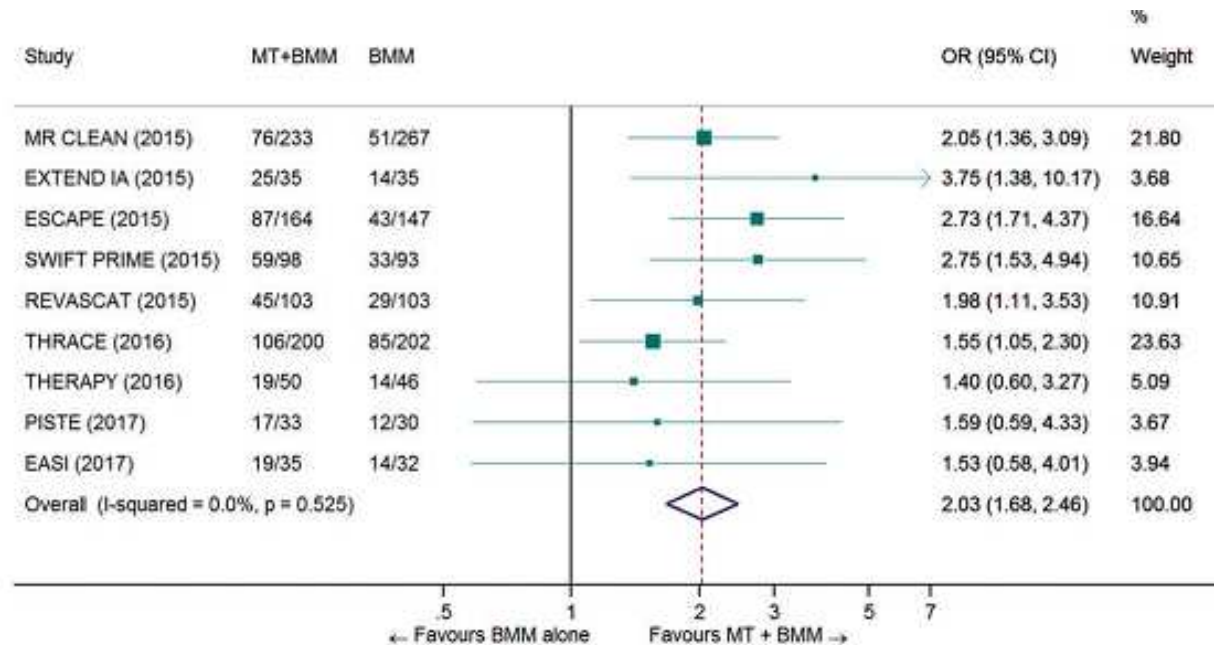
- **1 minute =**
  - **1.9 millions de neurones**
  - 12 km de fibres myélinisées

Saver J., *Stroke* 2006

Detante, *EMC* 2014



# ESO-ESMINT Guidelines 2019



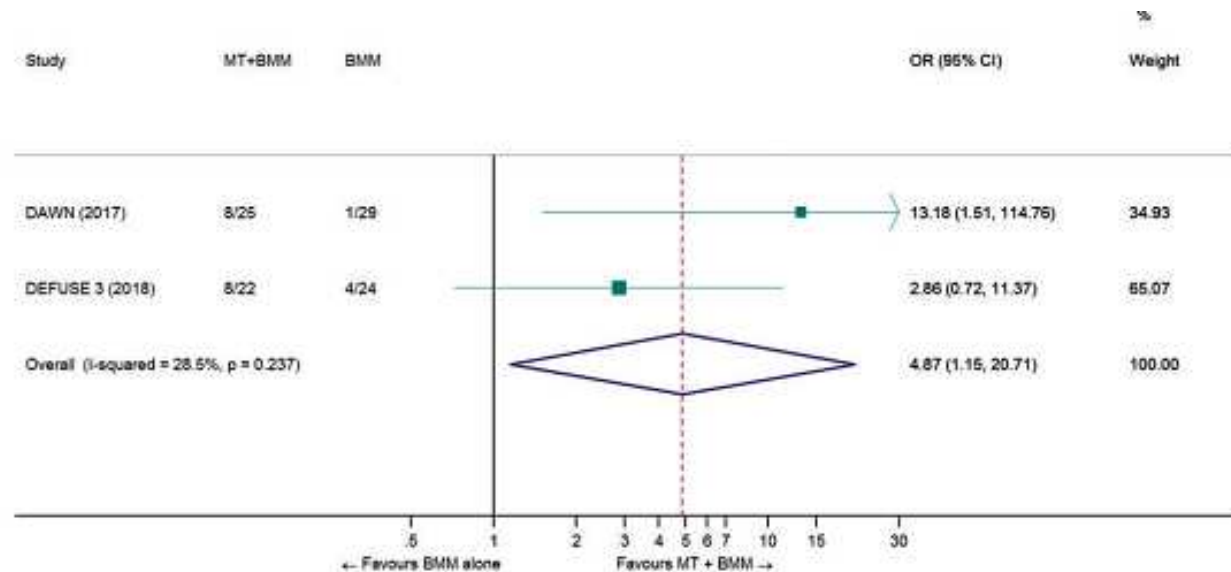
Recanalisation

< H6

**Figure 2.** Pooled odds ratio for functional independence in patients treated with MT + BMM vs. BMM alone in the 0–6 h time window. Random-effects meta-analysis.

Recanalisation

H6 à H24



**Figure 5.** Pooled odds ratio for functional independence in elderly patients treated with MT + BMM vs. BMM alone in the 6–24 h time window. Random-effects meta-analysis.

# Pronostic post-thrombectomie

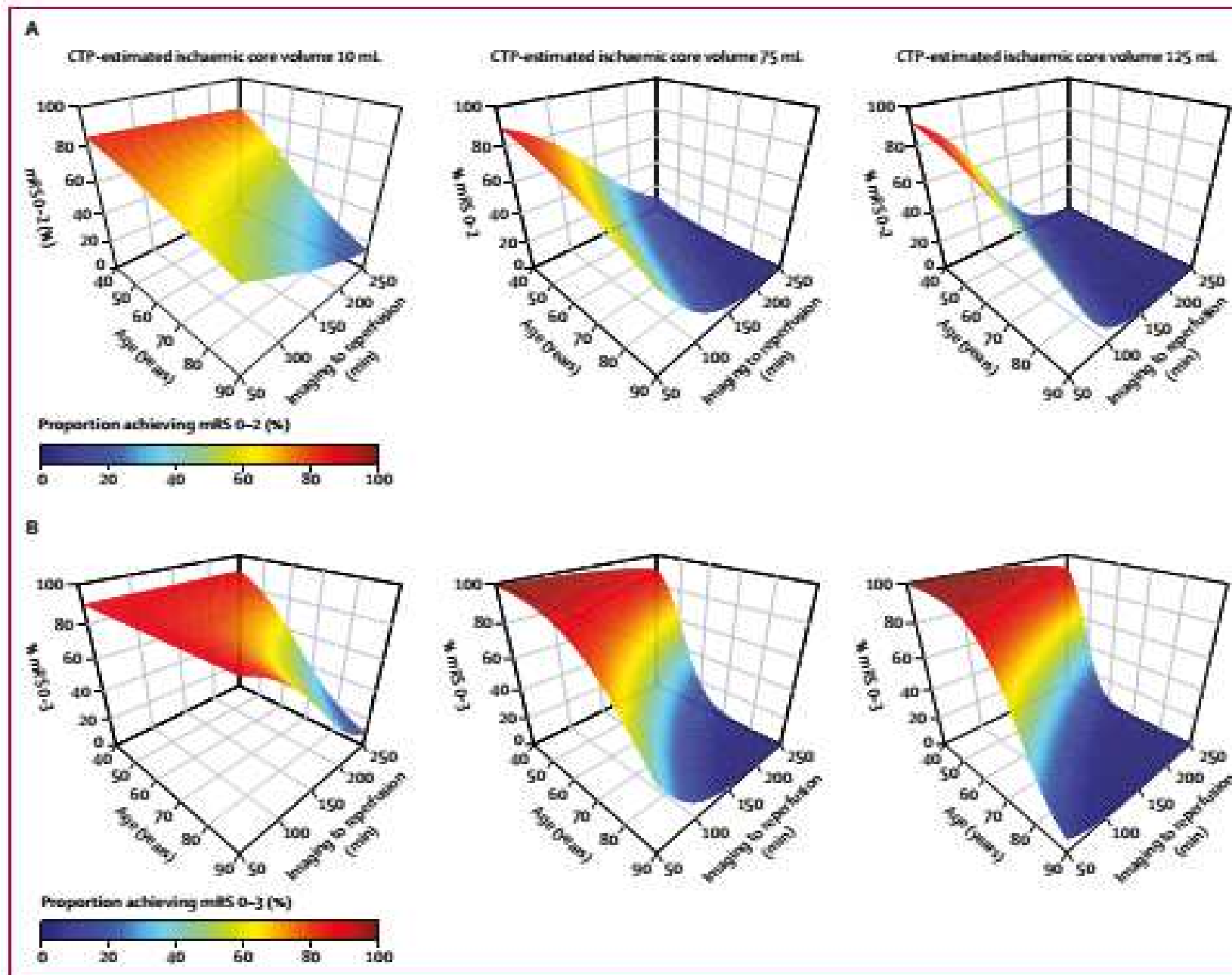


Figure 3: Effect of ischaemic core volume estimated by CT perfusion, age, and imaging-to-reperfusion time on functional outcome in the 186 patients with more than 50% endovascular reperfusion

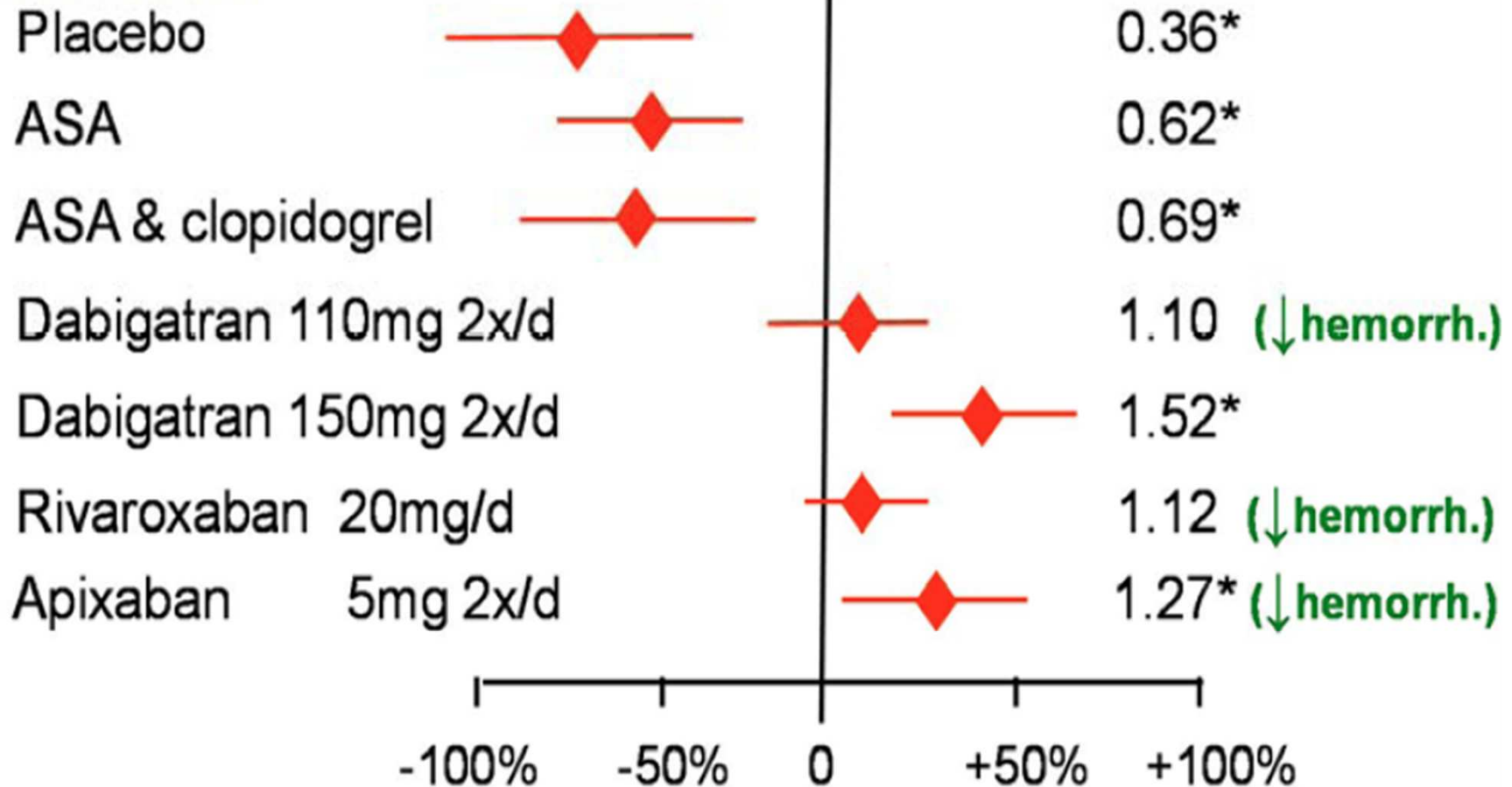
90-day functional outcome dichotomised at mRS 0-2 (functional independence; A) and mRS 0-3 (B). mRS=modified Rankin Scale.

# **Prévention secondaire**

# Fibrillation atriale : AOD mieux que les AVK

AVK vs. :

RR or HR



AVK better

Alternative better

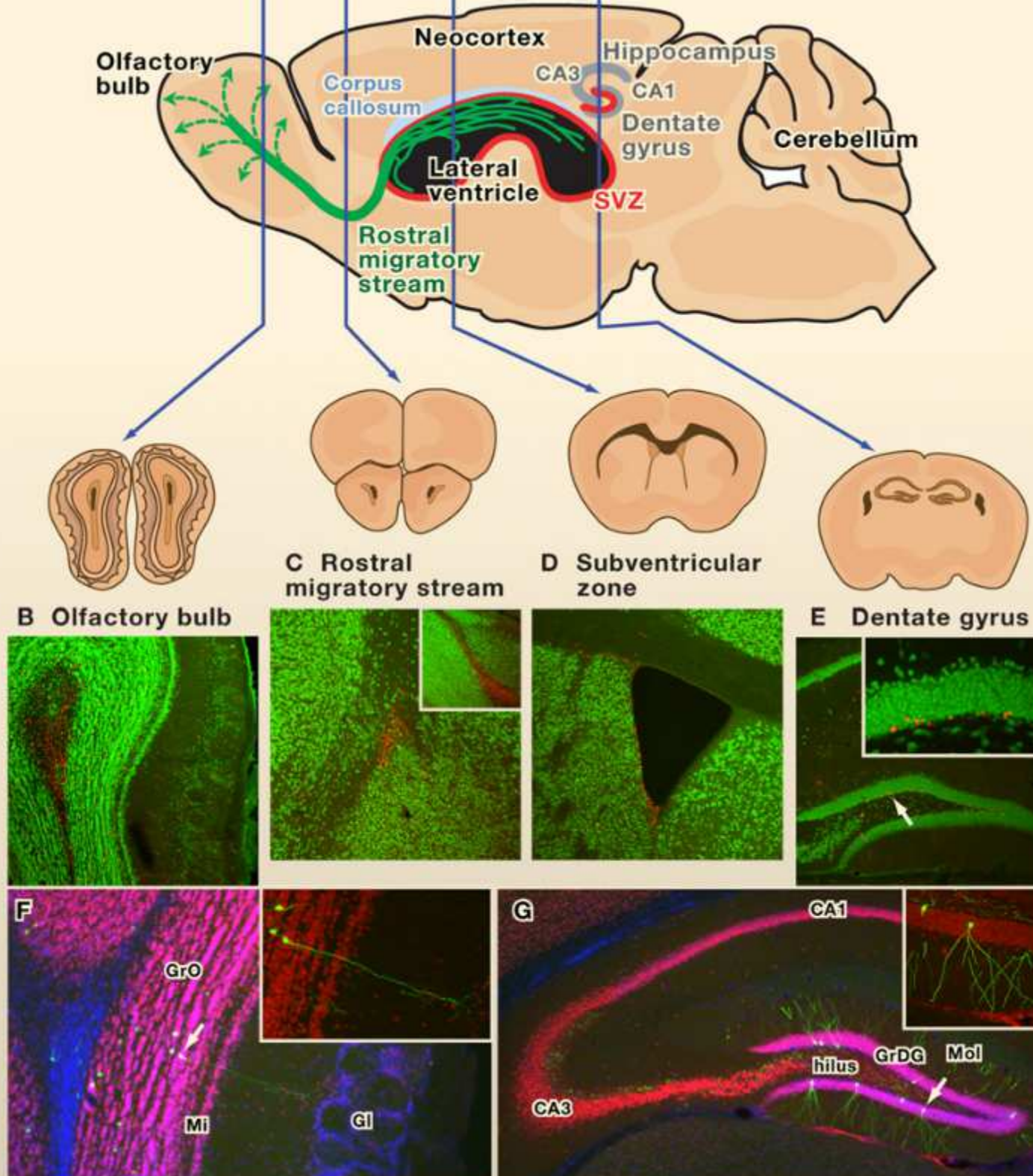
Review: Hankey and Eikelboom Lancet Neurology 2010; Meta-analysis: Hart Ann Int  
Med 2007; RELY: Connolly NEJM 2009; Rocket-AF Mahaffey AHA 2010; ARISTOTLE  
Granger NEJM 2011

**Médecine régénératrice**

**Thérapie cellulaire**



# Neurogenèse adulte



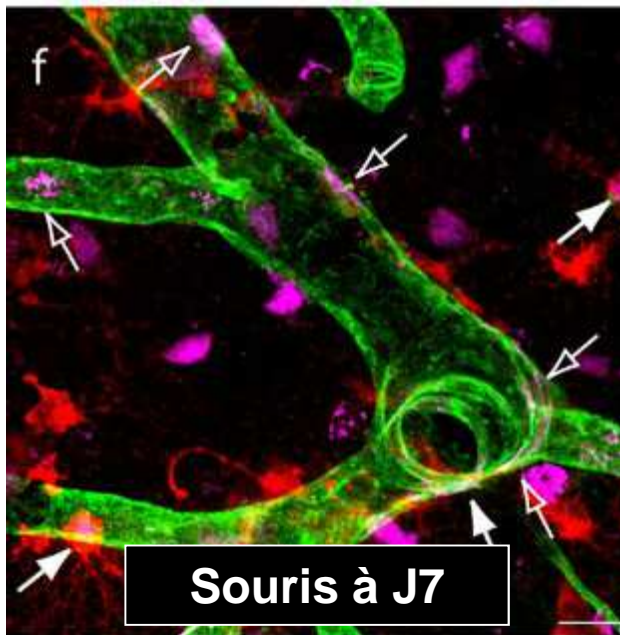
BrdU

GFP

NeuN

# Plasticité post-AVC

- Fonctions du **tissu survivant**
- **Réorganisation** des circuits lésés, croissance des fibres
- Processus cellulaires :
  - **Cellules neurales** : neurones, astrocytes, microglie et oligodendrocytes
  - **Synaptogenèse et activation** de connexions inactives
  - **Angiogenèse / vasculogenèse**

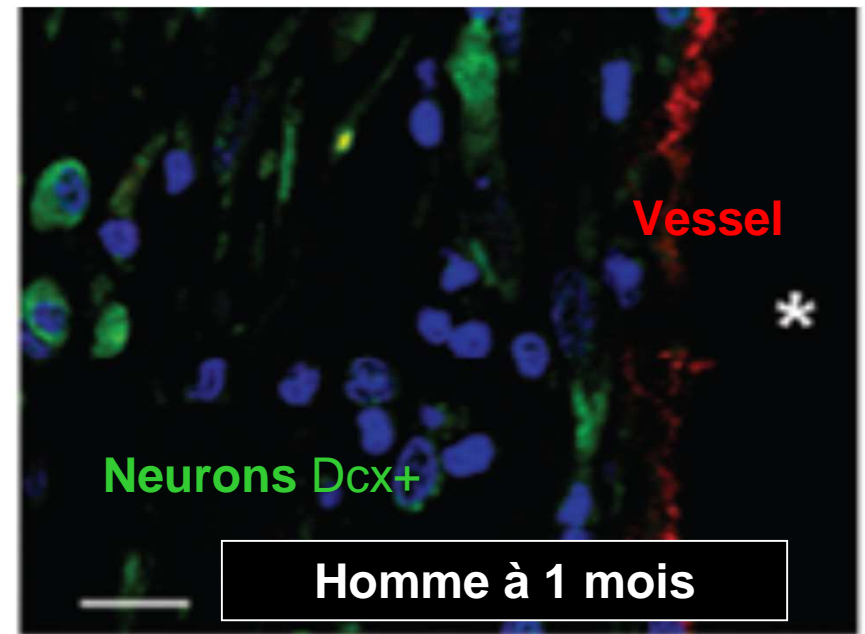


Ohab, *J Neurosc* 2006

**Niche glio-  
vasculaire pour  
neurogenèse**

**BrdU**

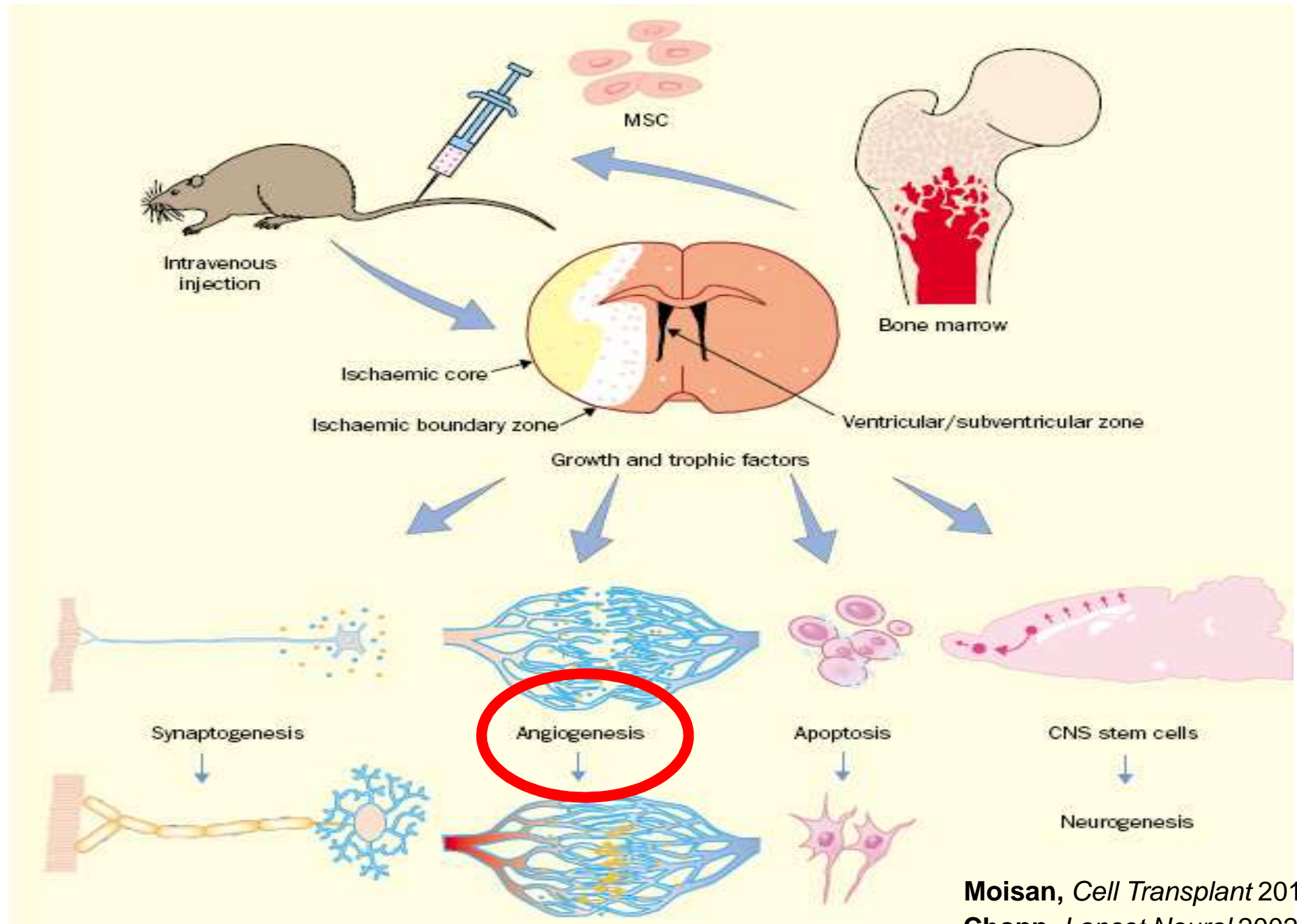
**DCX =  
neuroblastes**



Jin, *PNAS* 2006



# IV injection of MSC – Mechanisms for stroke?





# Intravenous Stem cell therapy for Ischemic Stroke ISIS-HERMES trial (2010-2016)



- Ethics committee 2008 / Regulatory Agency 2009
- 3 parallel groups, controlled, randomized, opened
- Autologous MSC (*from bone marrow*)
- Objective: Feasibility and safety of IV MSC after stroke
- Inclusion: 18 to 70 yo (mean = 52 yo) / Ischemic stroke < 14 days (**NIHSS  $\geq 7$** ) (mean = 18; n=21 left stroke)
- 31 patients in 3 groups (already recruited):
  1. 100 million of MSC (n=10)
  2. 300 million of MSC (n=10)
  3. Controls (n=11)



# Safety and efficacy of multipotent adult progenitor cells in acute ischaemic stroke (MASTERS): a randomised, double-blind, placebo-controlled, phase 2 trial

David C Hess, Lawrence R Wechsler, Wayne M Clark, Sean I Savitz, Gary A Ford, David Chiu, Dileep R Yavagal, Ken Uchino, David S Liebeskind, Alexander P Auchus, Souvik Sen, Cathy A Sila, Jeffrey D Vest, Robert W Mays

- **Dose-escalation, 3 groups (400 or 1200 million MAPC), randomized vs placebo**
- 33 centers (USA, UK)
- **IV injection of allogenic** MAPC (*from bone marrow*), 24h-48h post-stroke
- **Objective: safety and efficacy**
- **Inclusion:** 18 to 83 yo / **Ischemic stroke (NIHSS = 8 - 20)**
- Non inclusion: splenectomy
- **8 patients (safety) + 129 patients** (2011 to 2015)
- Safety at 7 days and efficacy at 3 months (NIHSS, Rankin, Barthel) / 1-year follow-up
- **No cell related adverse events**
- Trend for benefit ? Decrease of infection (at 1 year)

# RESSTORE 1 trial (phase 1, 139 patients)



- « **Toxicity** » (phase 1a): 15 patients (8 patients included)

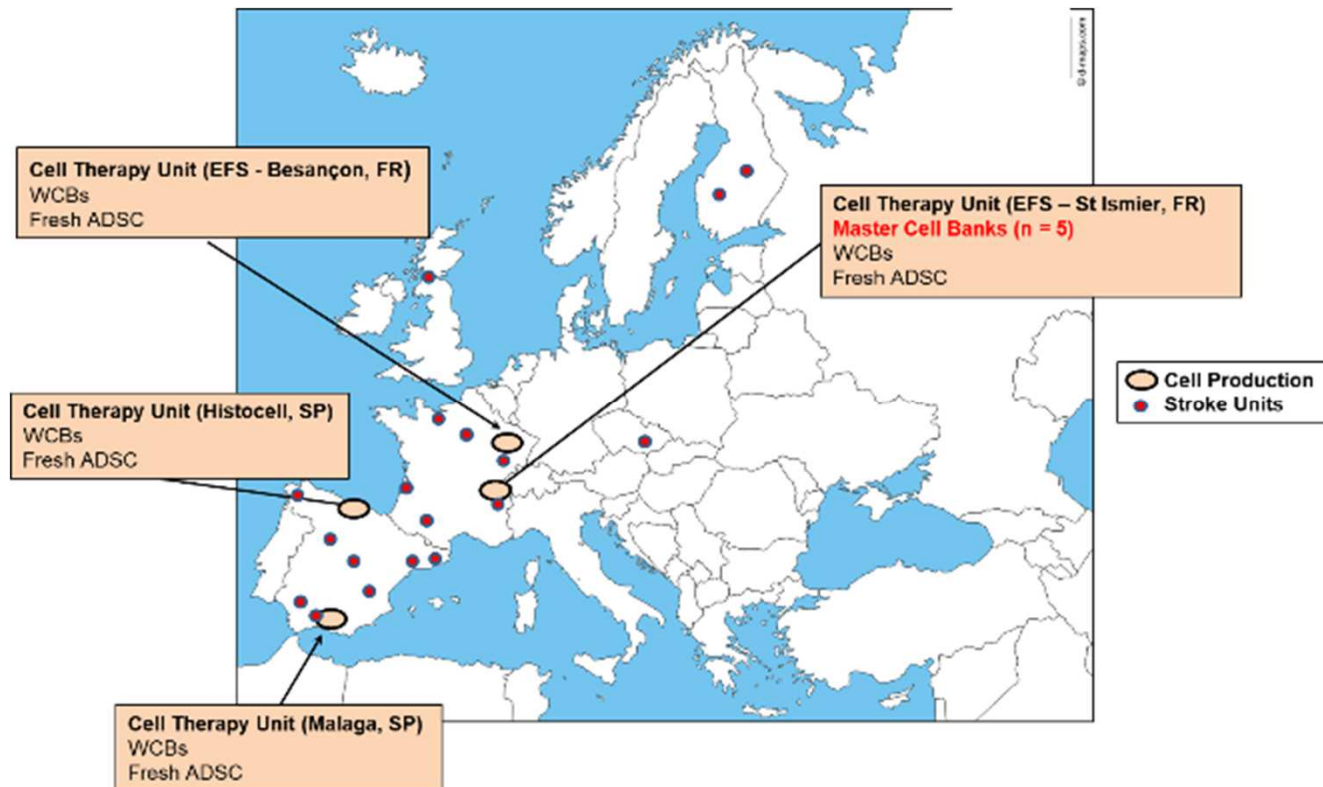
4 doses: 1 / 1.5 / 2 / 3 million of allogenic ADSC /kg

**Primary endpoint:** life-threatening **adverse events at 7 days** after injection

- « **Dose-effect** » (phase 1b): 124 patients / 4 groups

3 doses, double blind, vs placebo

**Dose-effect « curve »:** motor **NIHSS at 6 months** / activation fMRI



# RESSTORE Data Analysis



- **Clinical database**
- **BioBank**: Barcelona (Spain)
- **MRI database**: ShaNoir (France)
- **Health economics**
- **Experimental studies:**
  - Effect of intensive **rehabilitation and co-morbidities**
  - Explore neurobiological **mechanisms**
  - **Safety** of IV infusion of human ADSC in mice

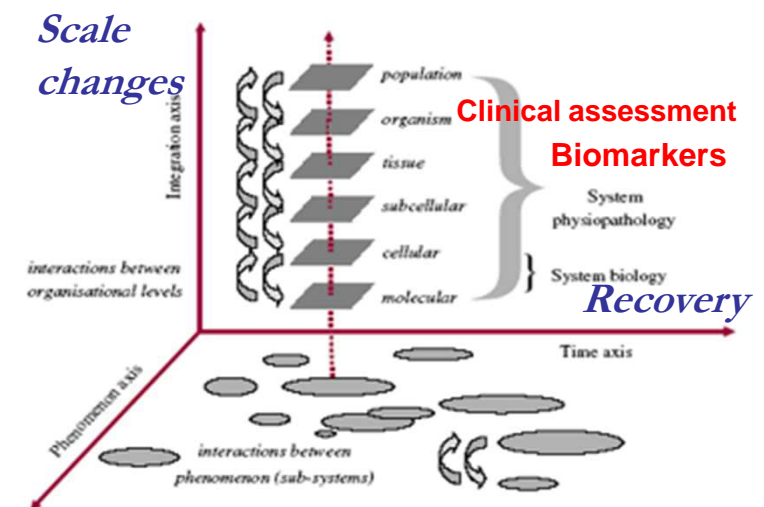
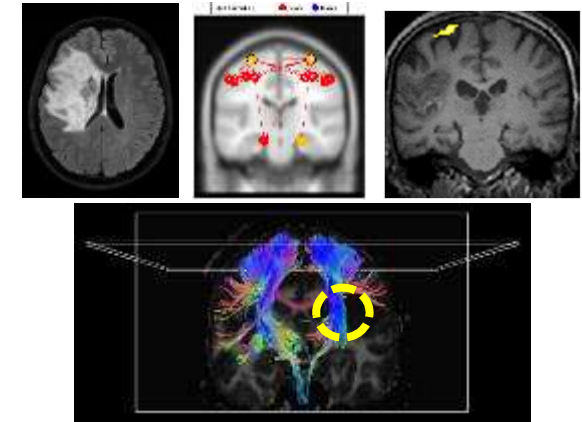
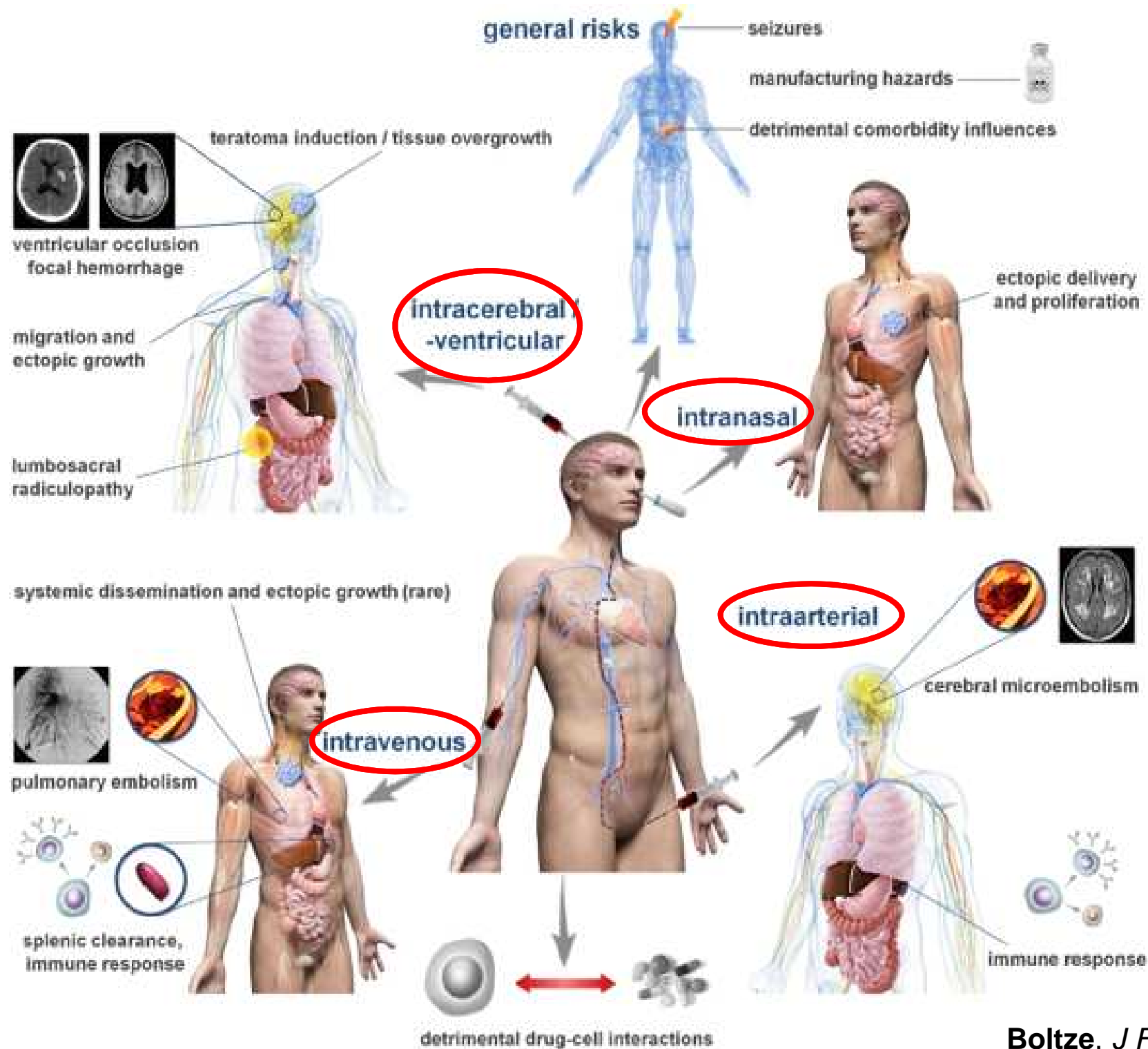


Fig. 1. Complexity of systems physiopathology and systems biology.





# Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study

Gary K. Steinberg, MD, PhD; Douglas Kondziolka, MD; Lawrence R. Wechsler, MD;  
L. Dade Lunsford, MD; Maria L. Coburn, BA; Julia B. Billigen, RN, BS;  
Anthony S. Kim, MD, MAS; Jeremiah N. Johnson, MD; Damien Bates, MD, PhD;  
Bill King, MS; Casey Case, PhD; Michael McGrogan, PhD; Ernest W. Yankee, PhD;  
Neil E. Schwartz, MD, PhD

**18 patients**  
**MSC San Bio SB623 Notch1+**

Steinberg, *Stroke* 2016

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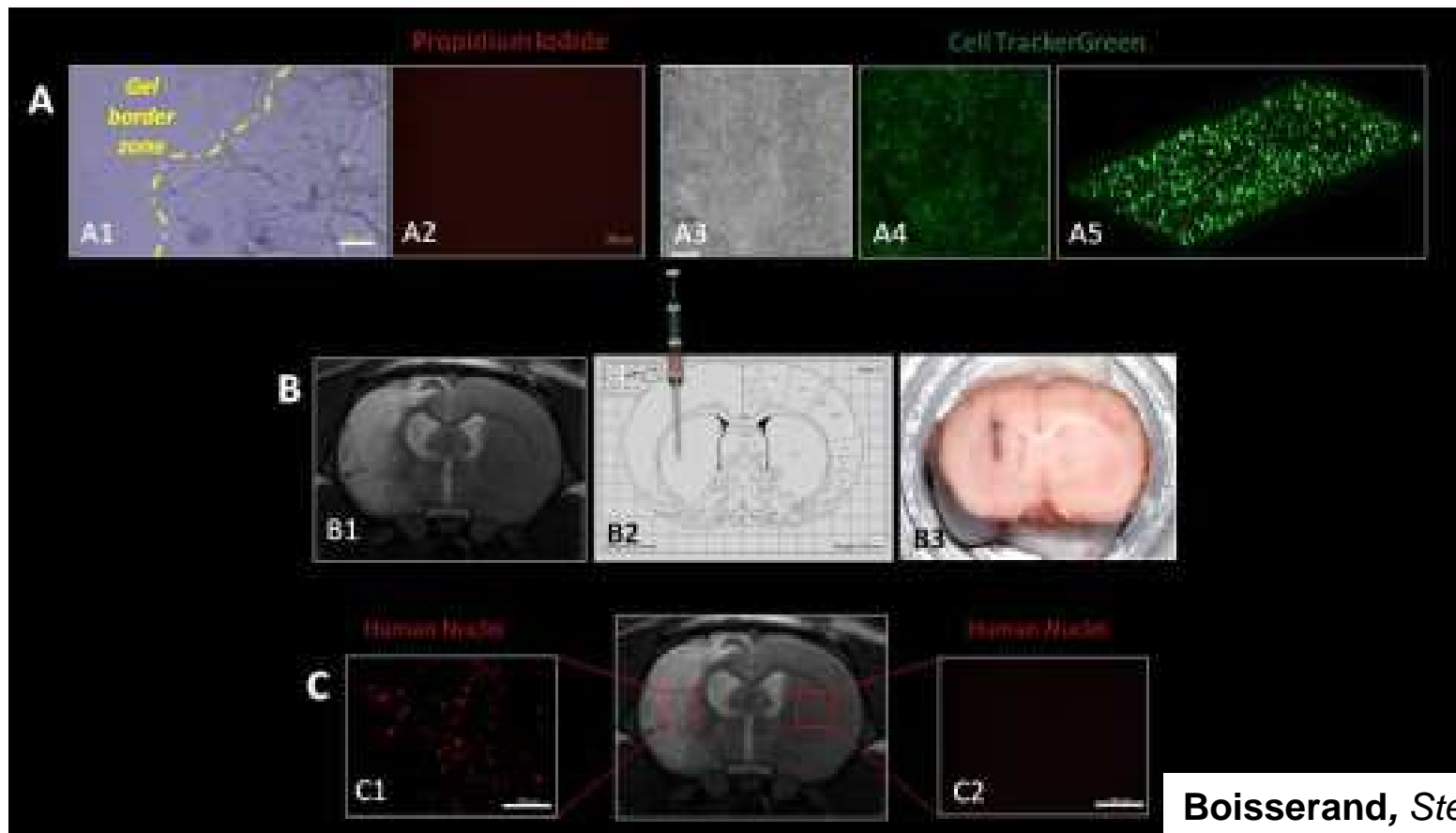
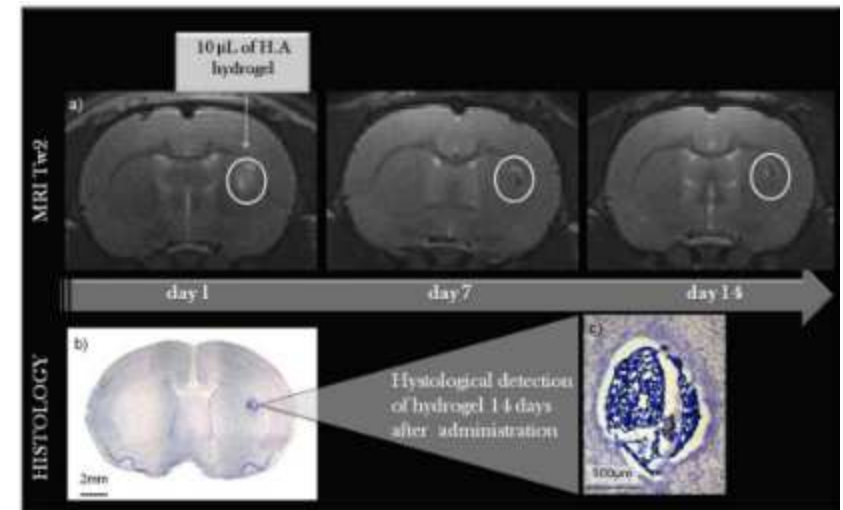
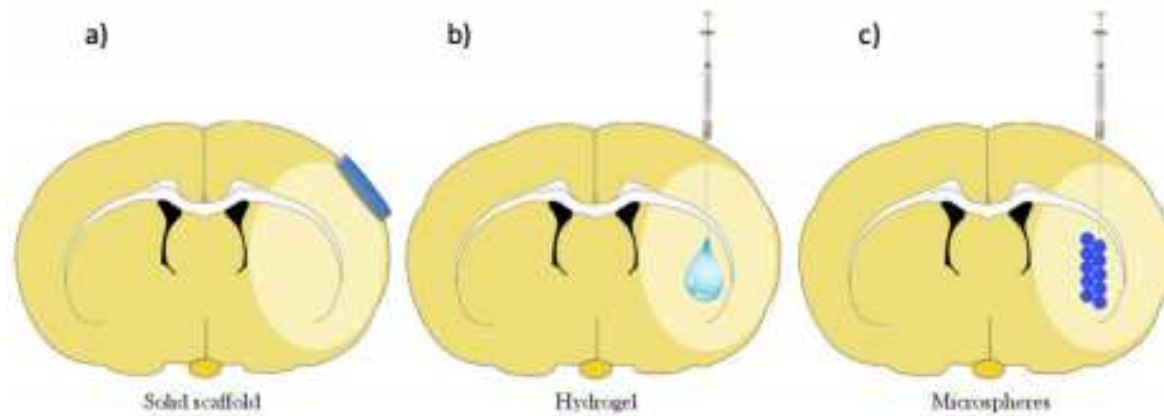
## Human neural stem cells in patients with chronic ischaemic stroke (PISCES): a phase 1, first-in-man study

Dheeraj Kalladka, John Sinden, Kenneth Pollock, Caroline Haig, John McLean, Wilma Smith, Alex McConnachie, Celestine Santosh, Philip M Bath, Laurence Dunn, Keith W Muir

**13 patients**  
**Cell line CTX 0E03 from fetal neuroepithelium**

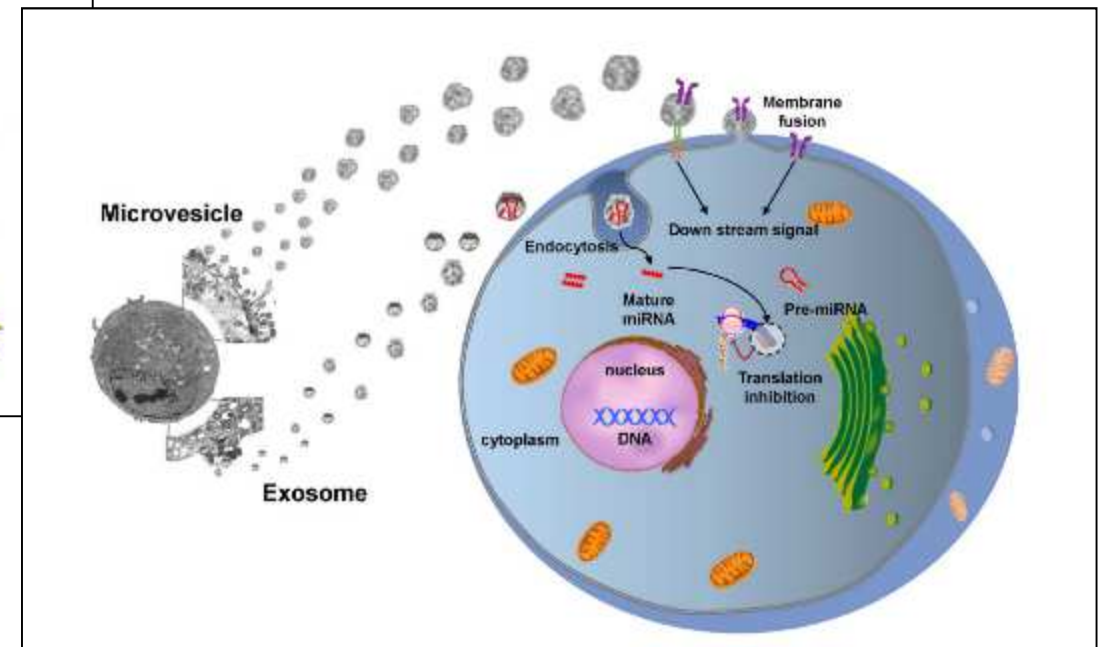
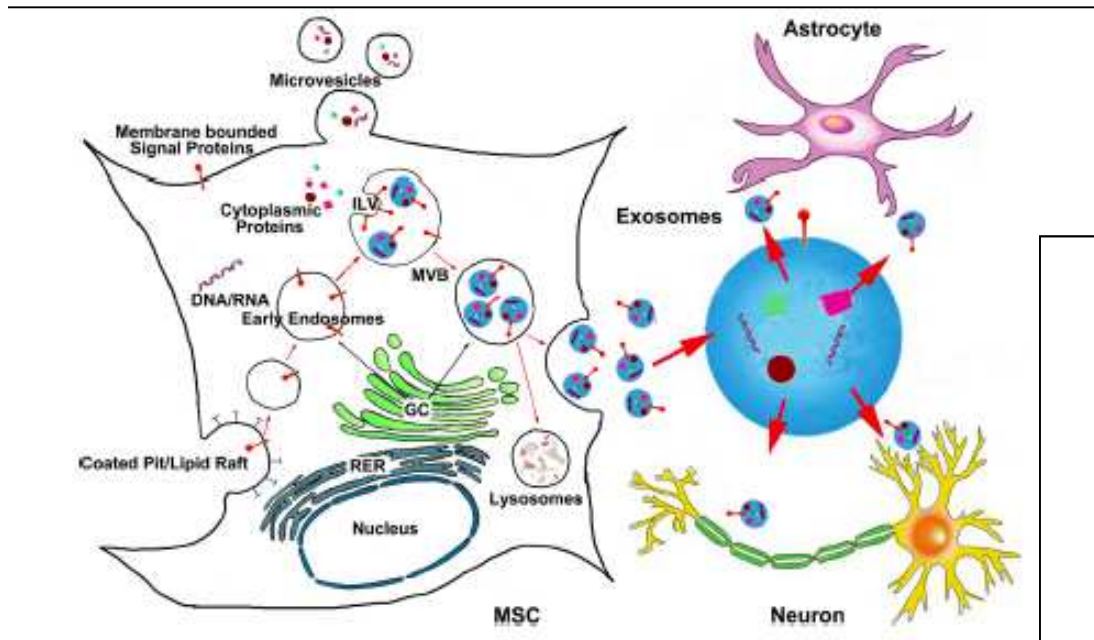
Kalladka, *Lancet* 2016

# Biomaterials: smart or not...



# « No cell » therapies

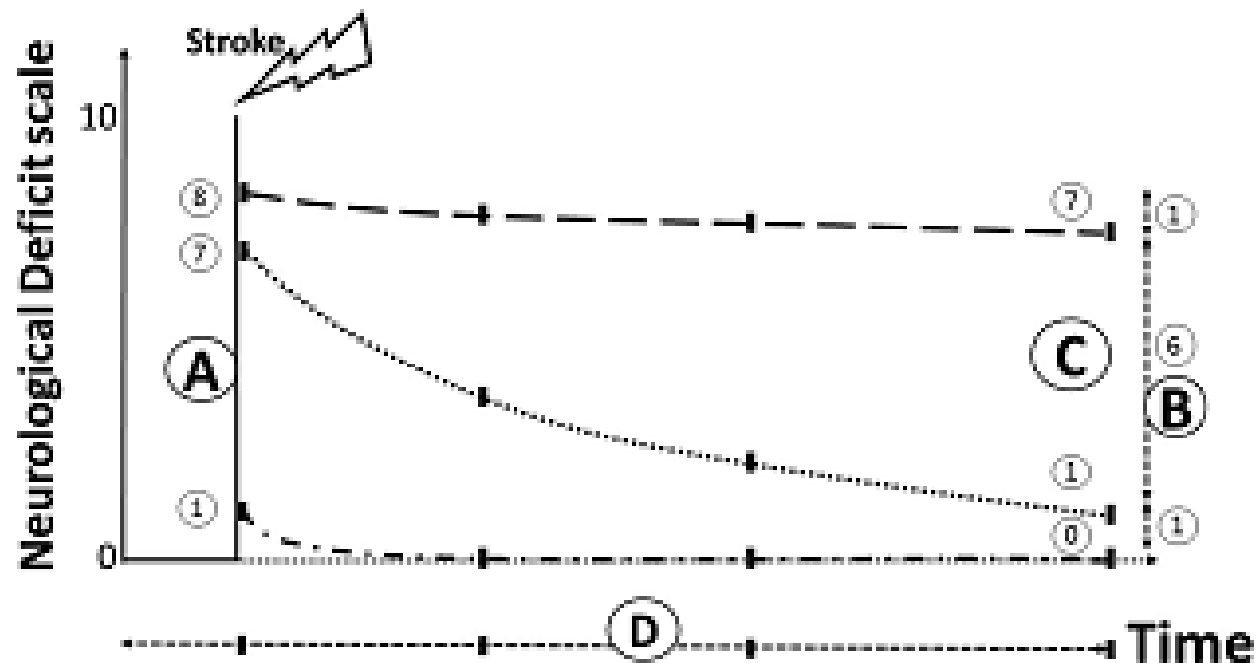
- **Secretome:** cytokines, growth factors...
- Microvesicles (exosomes)
- Extracellular matrix



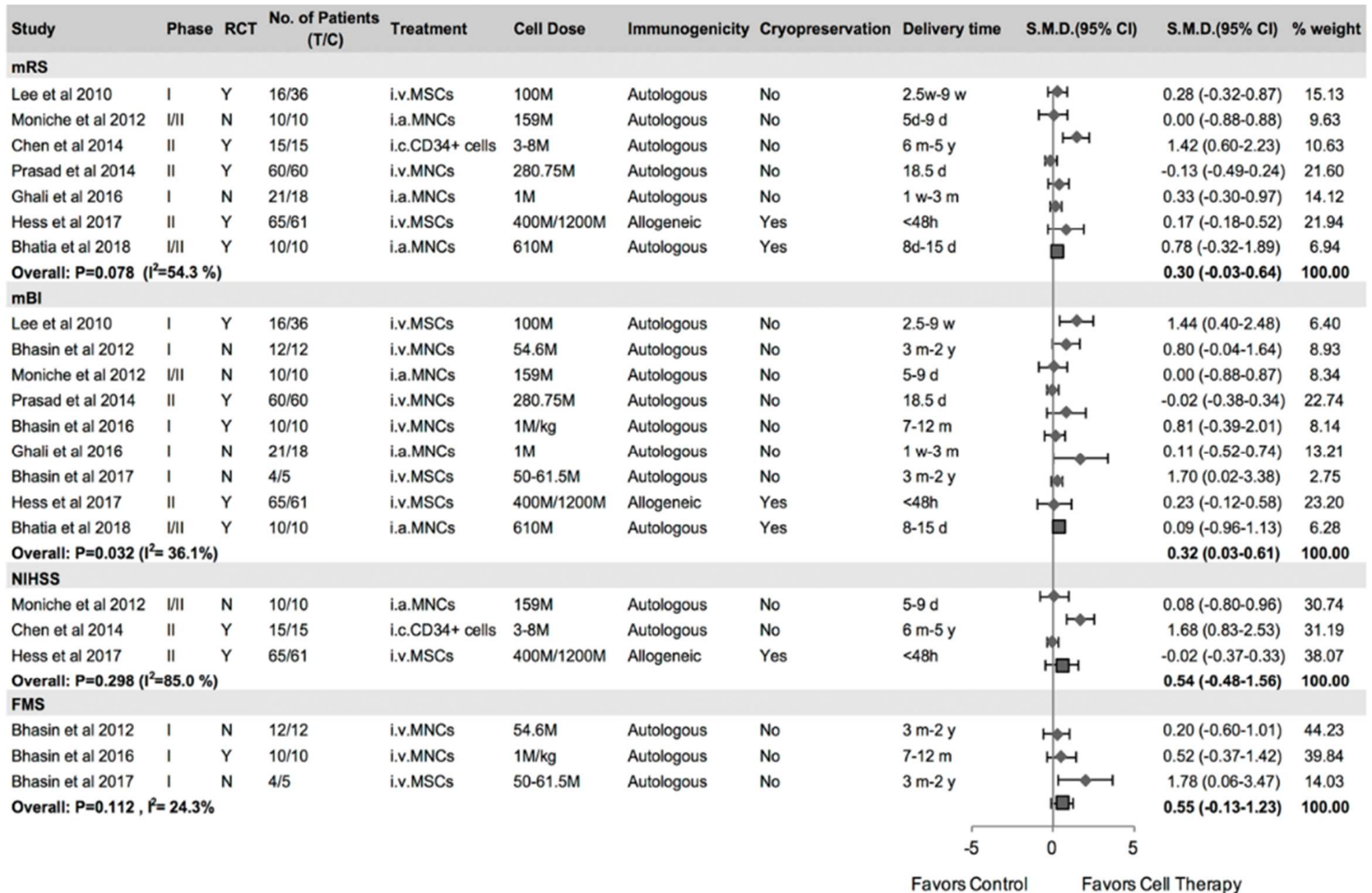


# Qu'est-ce que la récupération ?

- NIHSS / Rankin / Barthel... ICF (functioning) / EuroQoL
- **Récupération « vraie » vs Compensation**
- **Récupération « vraie » + Compensation**
- Quelle mesure ? Quand ?



# Cell therapy in stroke: which score?



# Compensation - Adaptation



*Aimée MULLINS*

Rôle de l'entourage et société pour **limiter la perte d'autonomie**

Difficile à quantifier (médico-sociale) !

*« L'homme augmenté, l'homme réparé ou l'homme amélioré » ?*



1 cm

Rat

Rabbit

Cat

Sheep

Chimpanzee

Human

Dolphin

Rat

Cat

Dolphin

Human

Chimpanzee

Sheep

Rabbit

