Potentiels de la Thérapie Cellulaire pour le Traitement des Anévrysmes Intracrâniens

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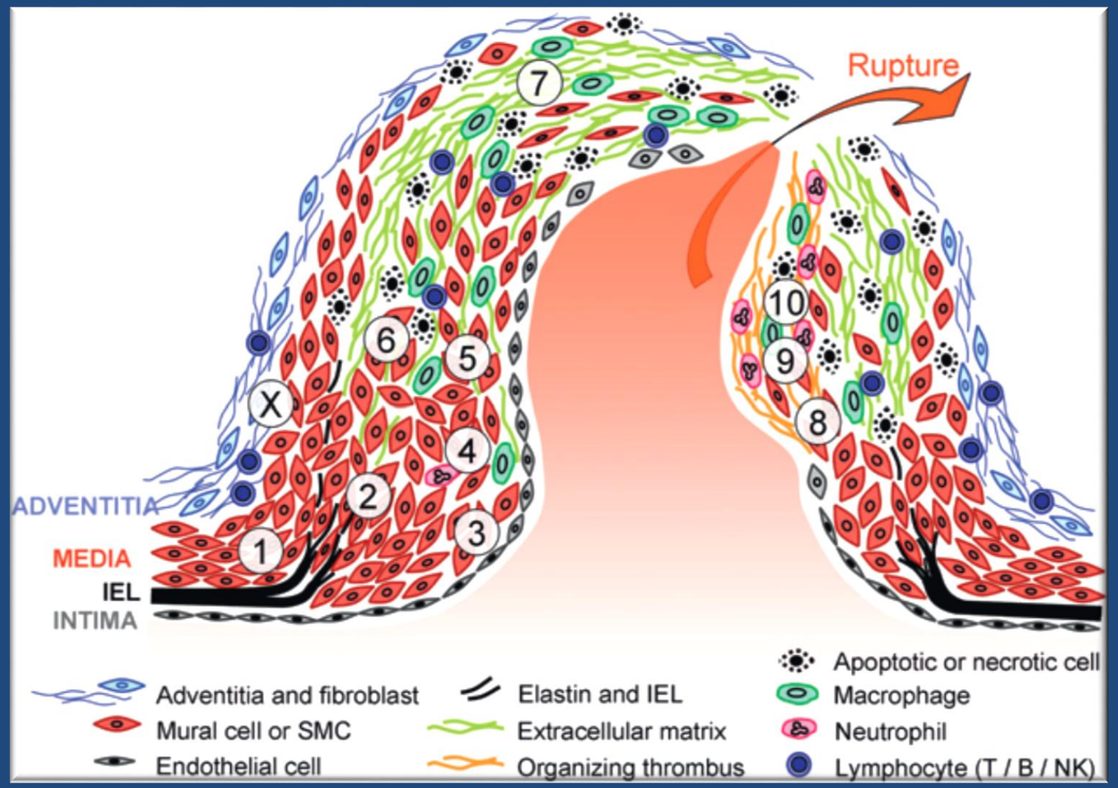
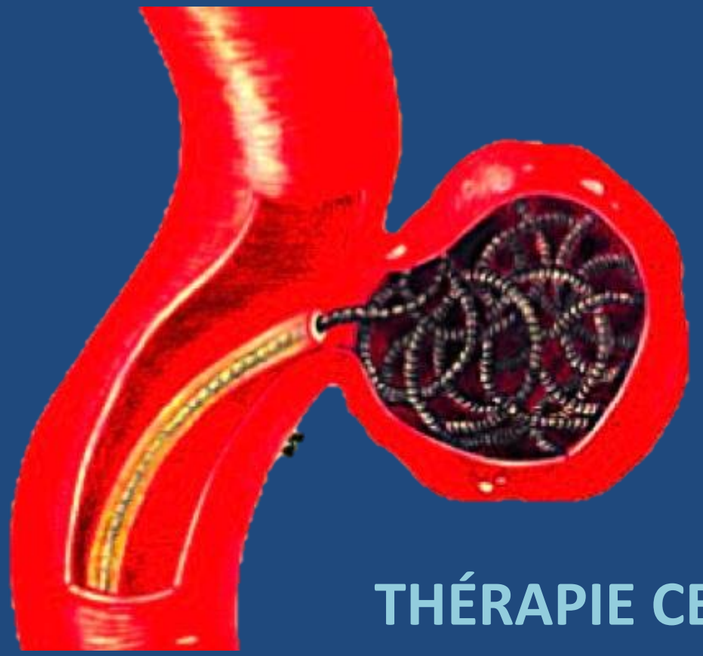
43ème CONGRÈS ANNUEL de la SFNR SOCIETE FRANCAISE DE NEURORADIOLOGIE

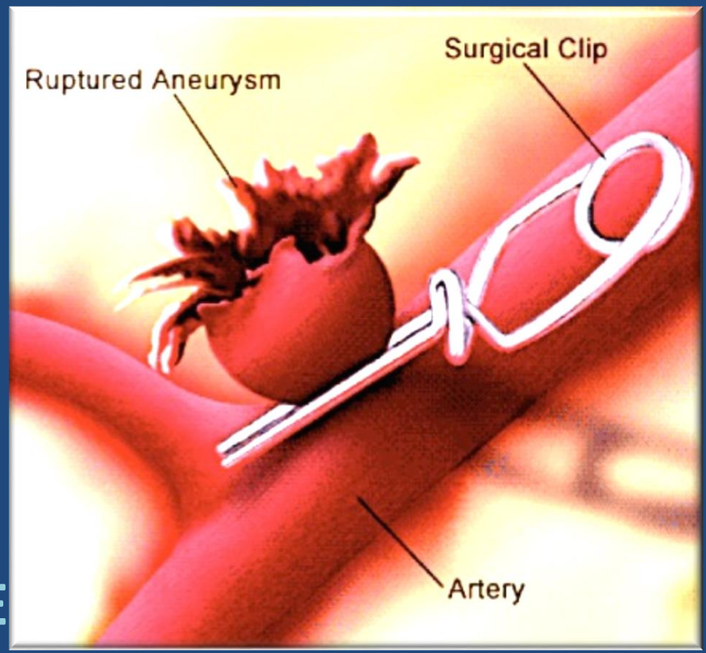
Du 30 mars au 1er avril 2016

Novotel Paris Tour Eiffel

Objectifs







THÉRAPIE CE

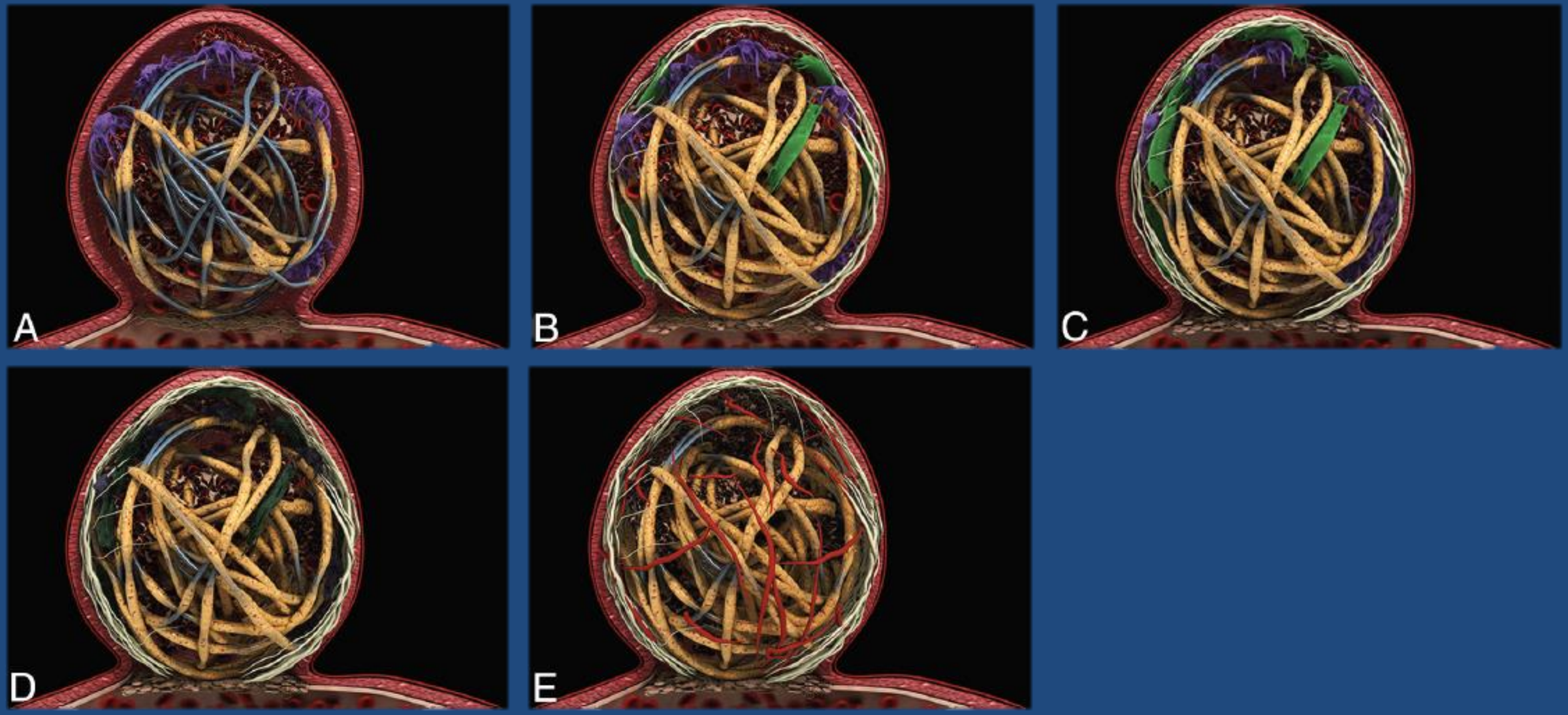
- Inhiber la dégradation protéolytique de la média.
- al.

RÉPARATION AD INTEGRUM

de la paroi artérielle.

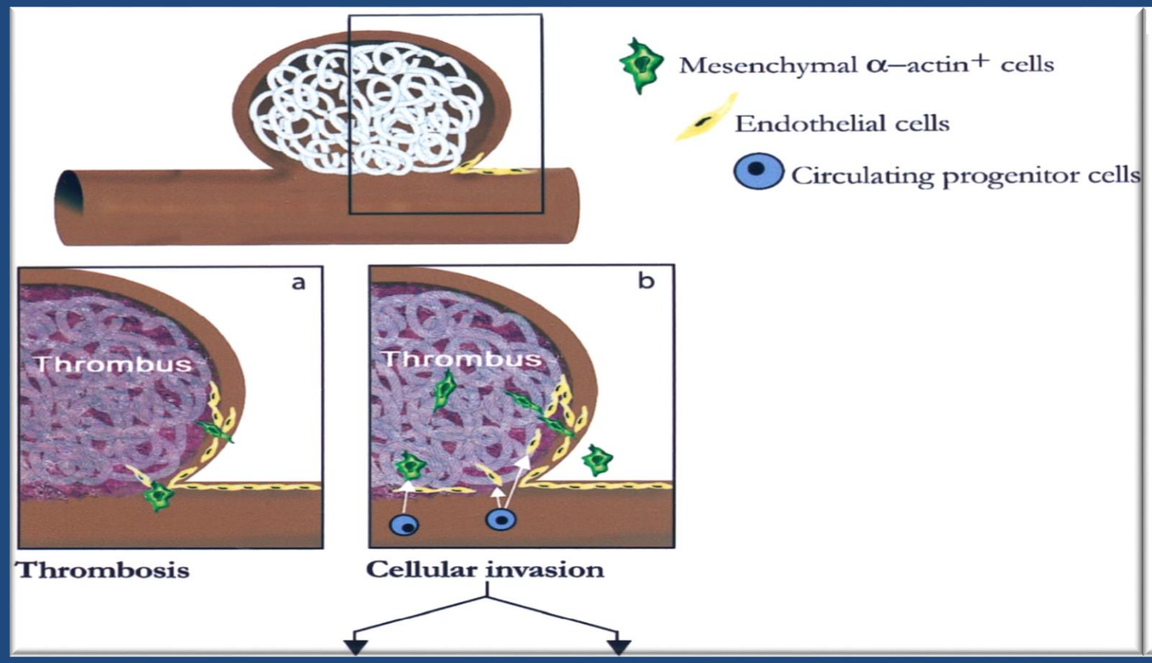
Tulamo et al., *JNIS* 2010; (2):120-130 .

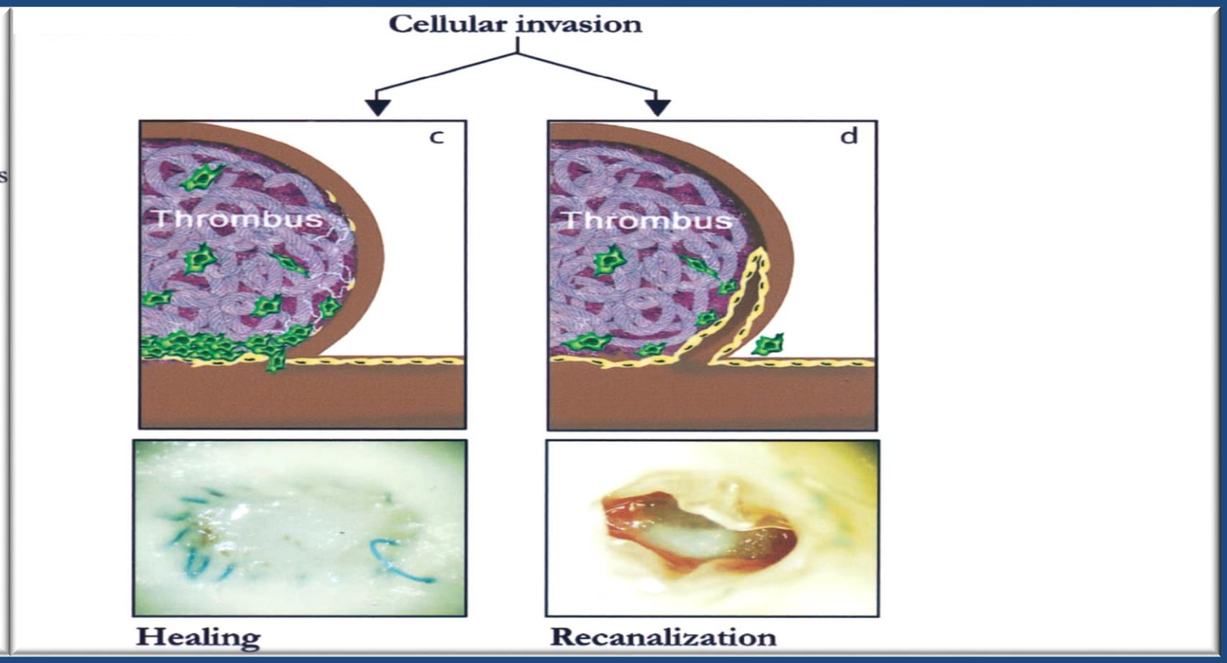
Cicatrisation des Anévrysmes Coilés

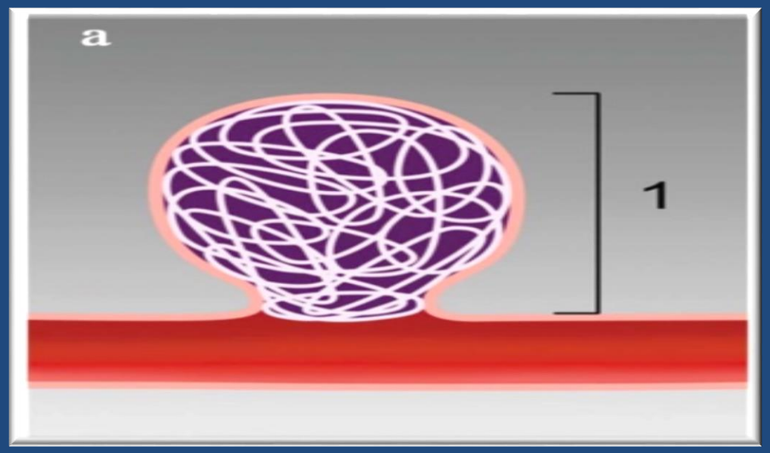


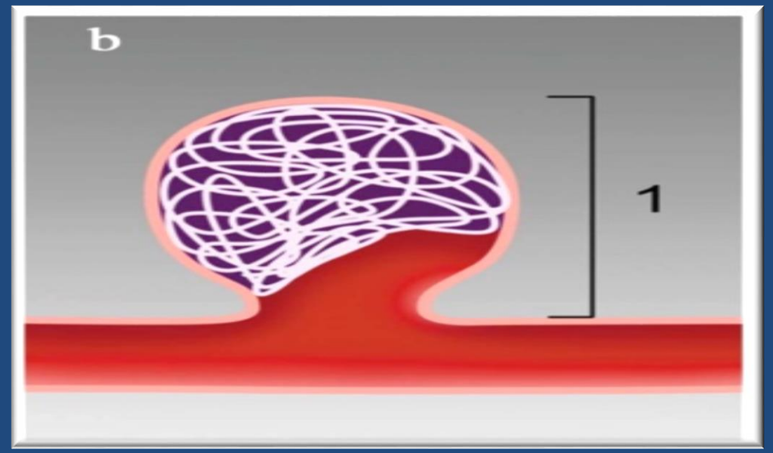
Brinjikji et al. AJNR, 2015. 36(7): 1216-22.

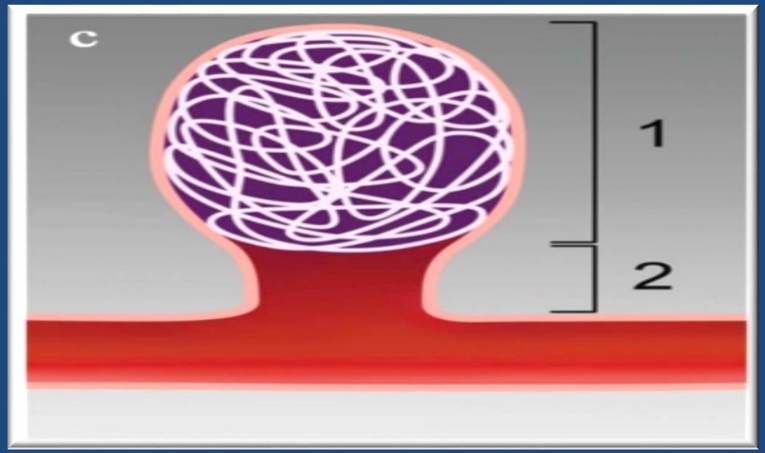
Cicatrisation des Anévrysmes Coilés











Ribourtout et al. Stroke. 2004;35:786.
Ogilvy et al. Neurosurgery , 2015. 77:168.

Différents types cellulaires

- Fibroblastes
- Cellules musculaires lisses
- Cellules endothéliales
- Cellules stromales

Différentes sources cellulaires

- Hétérologue
- Homologue
- Autologue

Différentes voies d'administration des cellules

- Intraveineux
- Intra-artériel
- Intra-anévrysmal
- Sur coils ou stents (bio-ingénierie)

Chalouhi et al. J Cereb Blood Flow Metab, 2012. 32:1659.

Principales Etudes

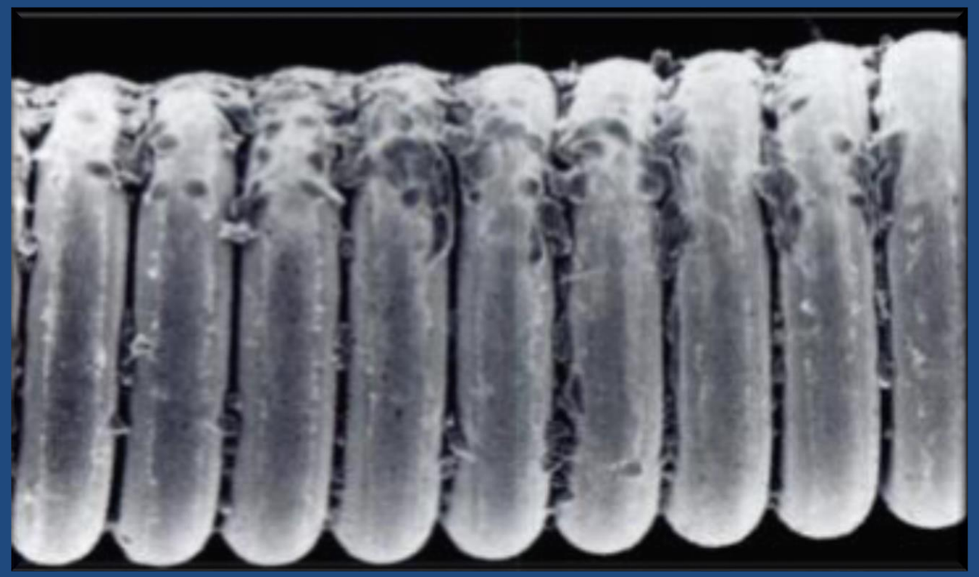
Table 1. Preclinical Cell Therapy Studies for the Treatment of Brain Aneurysms

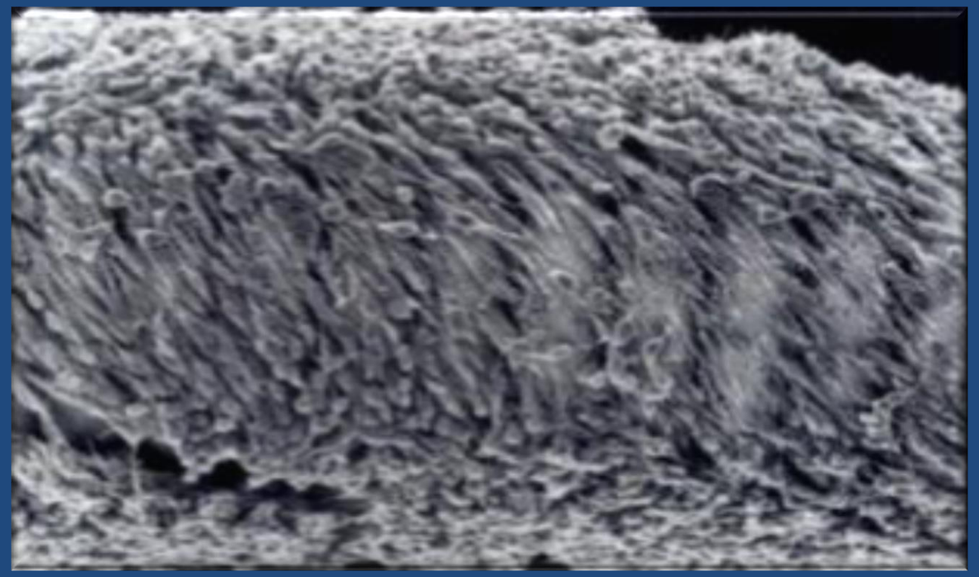
Study	Year	Aneurysm Model	Cell Type	Assumed Mechanism of Action	Source of Cells	Number of Cells	Delivery	Number of Animals
Raymond et al.[35]	1999	Venous pouch carotid aneurysm in dogs	VSMCs	ECM synthesis by transplanted cells	Left femoral artery explants	2×10^6	Fibrin glue	31
Marbacher et al.[34]	2014	Microsurgical side-wall aneurysm in rats	VSMCs	ECM synthesis by transplanted cells	Abdominal aorta explants	Not reported	Fibrin glue	81
Kawakami et al.[37]	2005	Venous pouch carotid aneurysm in rabbits	Fibroblasts	Differentiation into myofibroblasts/collagen deposition	Abdominal skin	$\sim 5 \times 10^5$	Coils	42
Dai et al.[36]	2007	Elastase-induced carotid aneurysm in rabbits	Fibroblasts	Differentiation into myofibroblasts/collagen deposition	Tendon explants	Not reported	Coils	36
Marx et al.[38]	2001	Elastase-induced carotid aneurysm in rabbits	Fibroblasts	Differentiation into myofibroblasts/collagen deposition	HIG-82 cell line	Not reported	Coils	8
Aronson et al.[39]	2012	Elastase-induced carotid aneurysm in rabbits	EPCs	Endothelium regeneration	Peripheral blood	3.4×10^5–4.5×10^5	Fibrin glue	32
Li et al.[41]	2013	Elastase-induced carotid aneurysm in rabbits	EPCs	Endothelium regeneration	Peripheral blood	$\sim 3.2 \times 10^6$	Intravenous	16
Zhang et al.[42]	2014	Aortic pouch aneurysm in rats	EPCs	Endothelium regeneration	Bone marrow	5×10^5–1×10^6	Intra-arterial	15
Rouchaud et al.[44]	2013	Elastase-induced carotid aneurysm in rabbits	MSCs	Paracrine effect/engraftment of transplanted MSCs	Bone marrow	5×10^6	Intra-arterial	13
Kuwabara et al.[43]	2014	Elastase-hypertension induced intracranial aneurysm in mice	MSCs	Paracrine effect of transplanted MSCs	Bone marrow	1×10^6	Intravenous	26

VSMC, vascular smooth muscle cell; EPC, endothelial progenitor cell; MSC, mesenchymal stem/stromal cell.

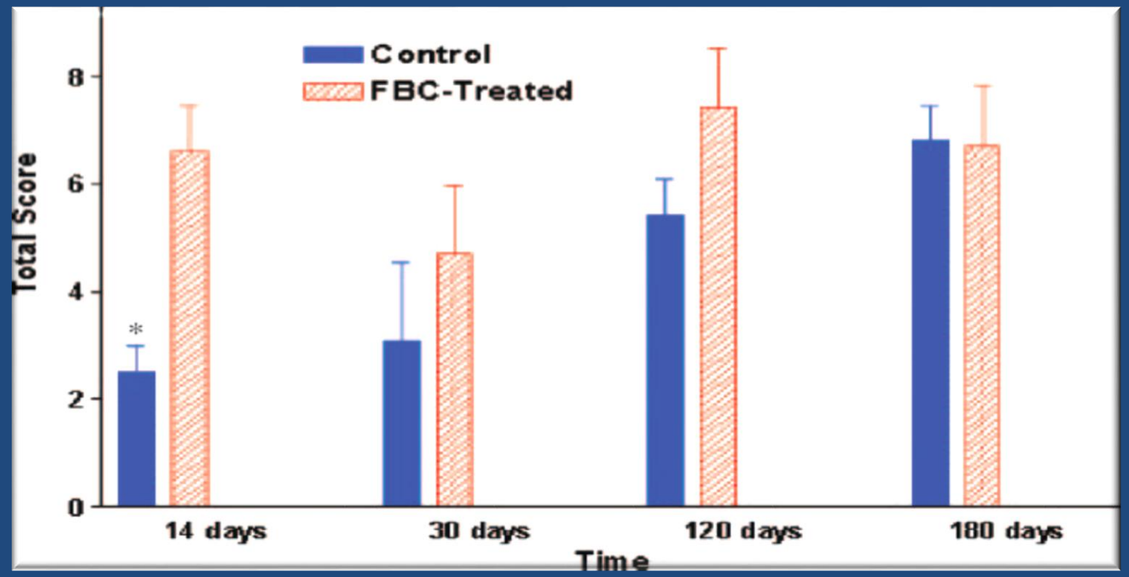
Adibi et al. World Neurosurgery. 2016; 86: 390-398.

Fibroblastes





Scale	Gross Neck	Micro Neck	Neck Compaction	Dome
0	No Coverage	Unorganized Clot	Macro-Concave	Blood Clot (all)
1	<50%	Fibrin	Micro-Concave	Organized Tissue in <1/3 of Area
2	50%-75%	Fibrin with Organized Tissue	Flat	Organized Tissue in 1/3-2/3 of Area
3	>75%	Completely Organized Tissue, thickness ≤1/3 Coil Diameter	Convex	Organized Tissue in >2/3 of Area
4	N/A	Completely Organized Tissue, thickness >1/3 Coil Diameter	N/A	Completely Organized Loose Tissue
5	N/A	N/A	N/A	Completely Organized Dense Fibrous or Cellular Tissue

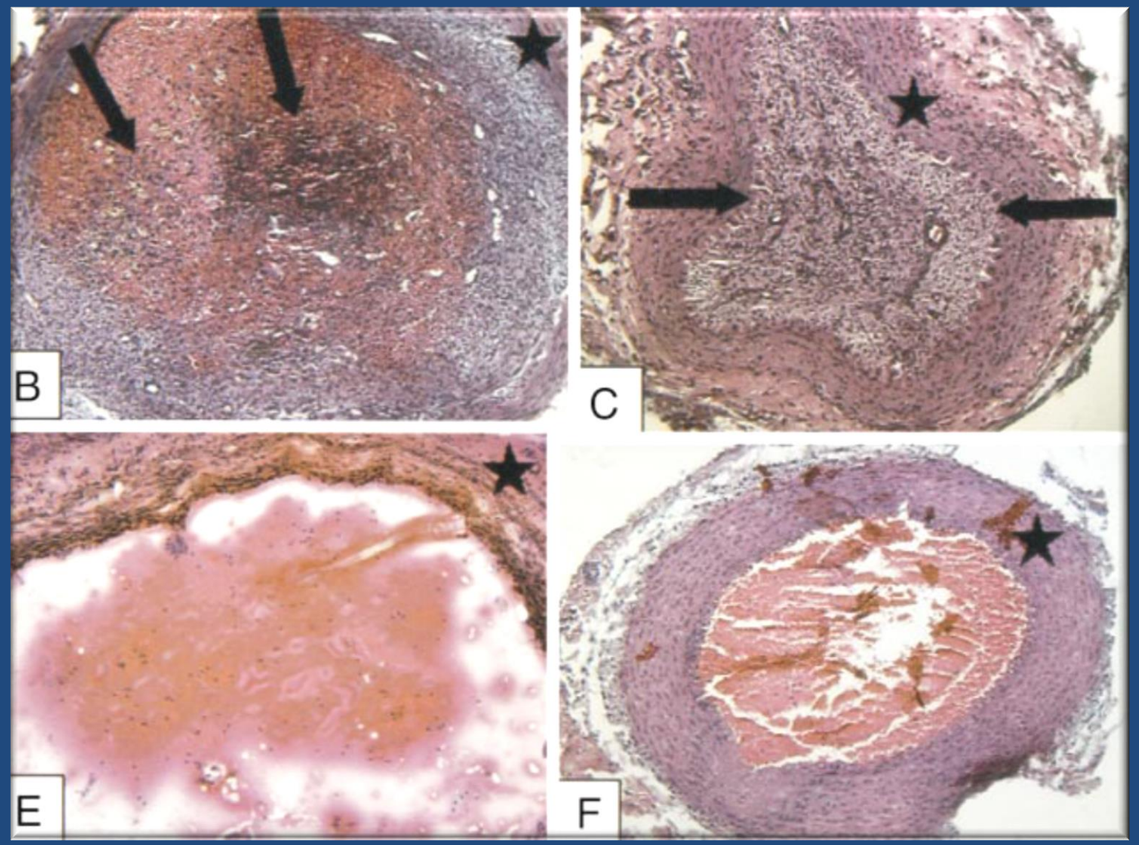


Kallmes et al. Radiology 1998; 206:237-243

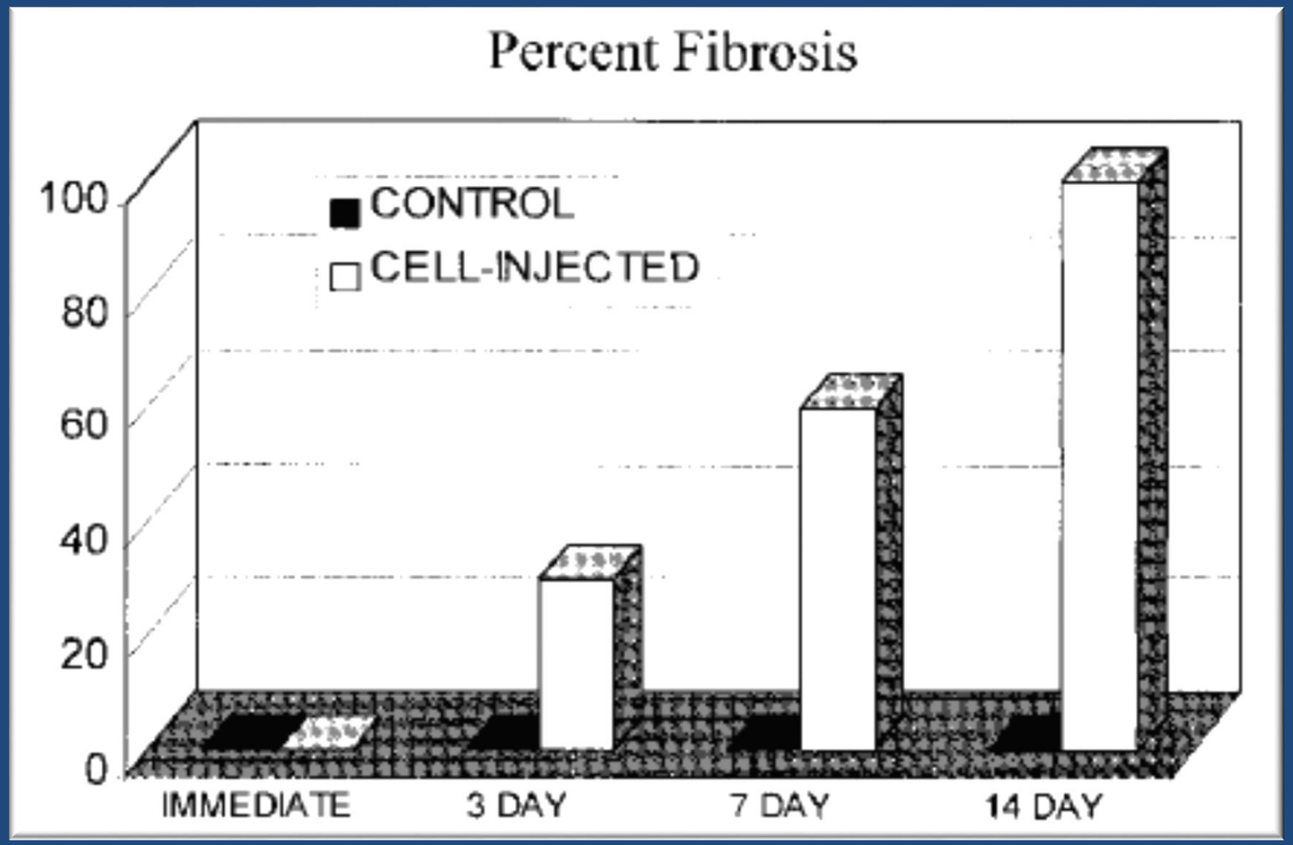
Dai et al. Stroke. 2007;38:170-176.

Fibroblastes

Fibroblastes



Contrôles



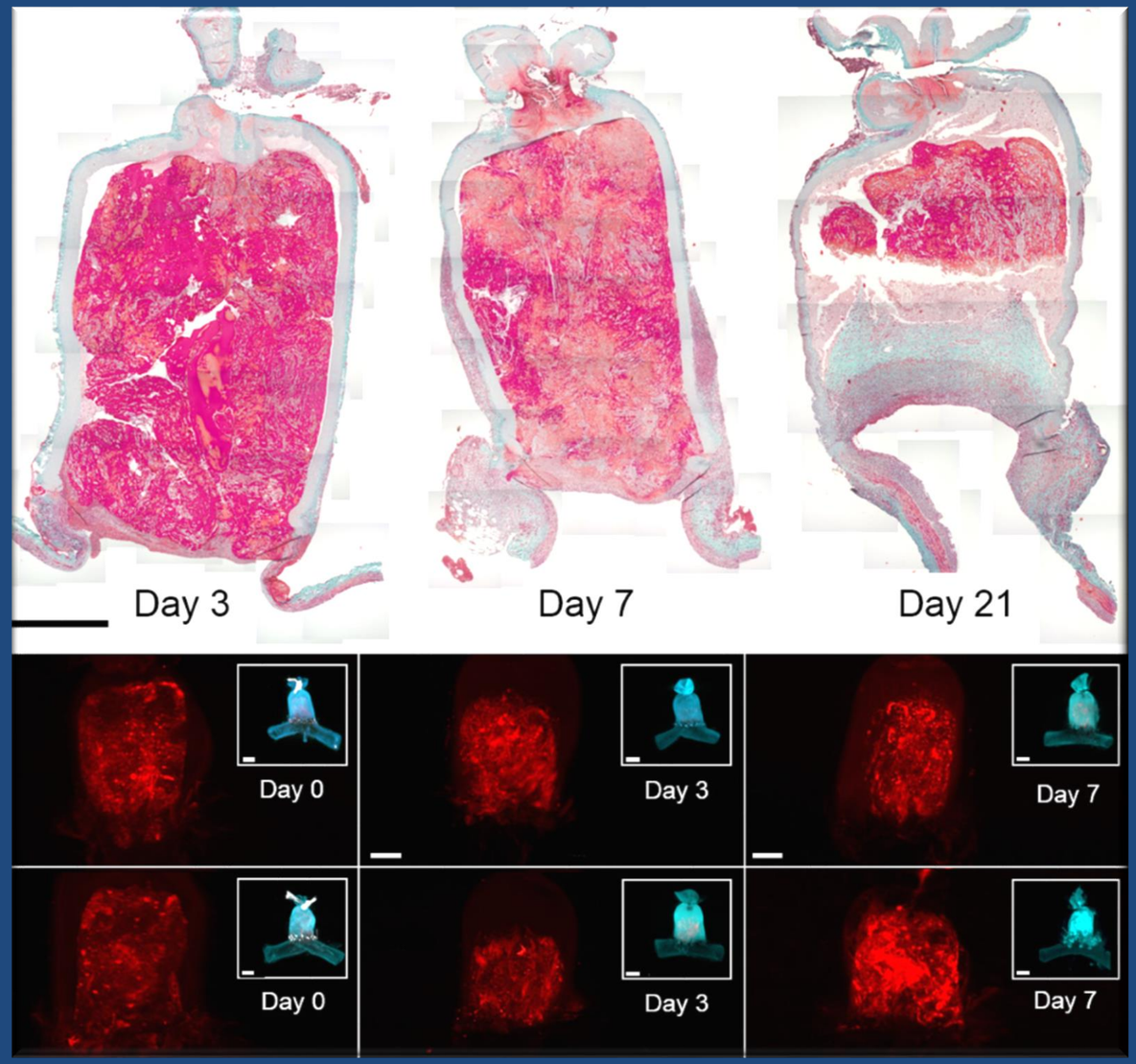
N = 8

Hétérologue

Marx et al. AJNR Am J Neuroradiol. 2001. 22:323.

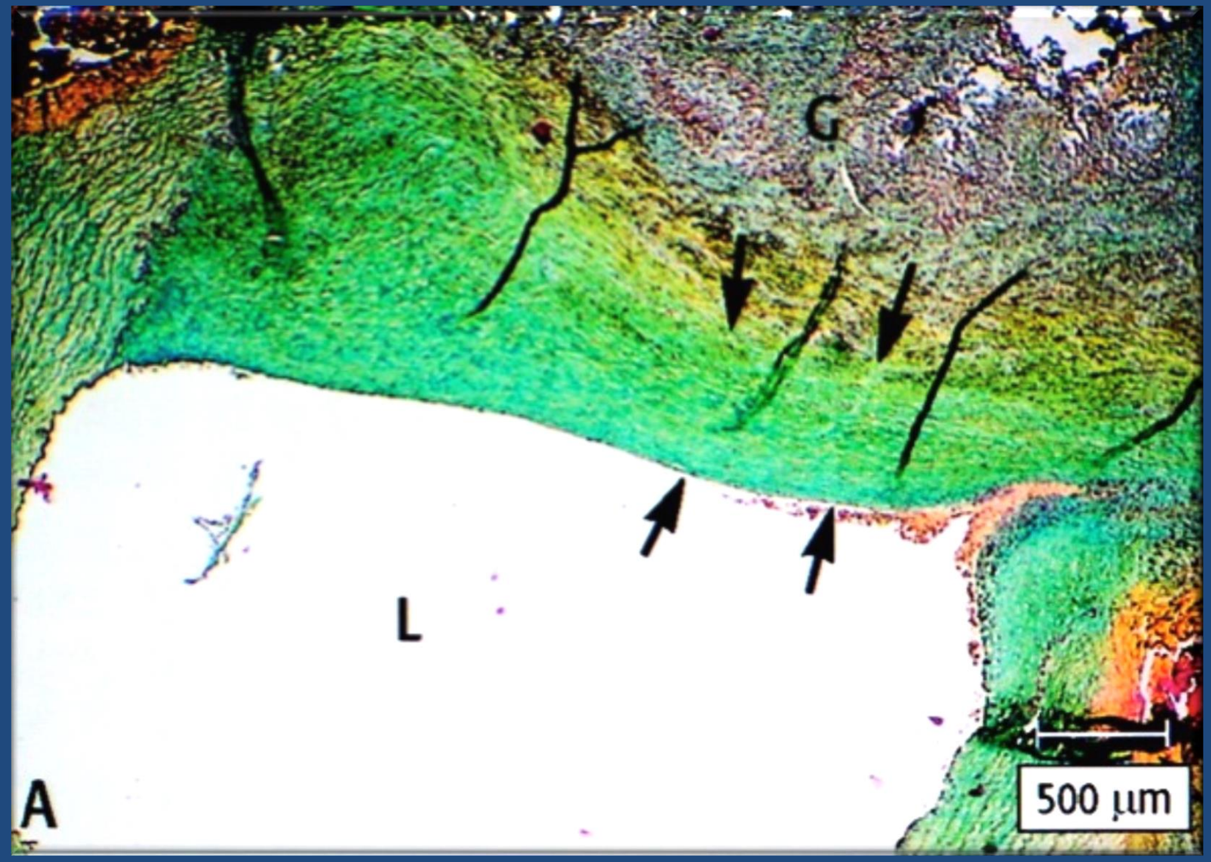
Cellules Musculaires Lisses

- Anévrysmes chez le rat en position aortique (n=81)
- Traitement avec fibrine +/- CML (homologue).
- Moins de récurrence dans le groupe traité avec CML (**P** =0.037).
- Meilleurs résultats histologiques (formation néo-intimale) (**P** =0.002).



Marbacher et al. Stroke. 2014. 45:3684.

Cellules Musculaires Lisses

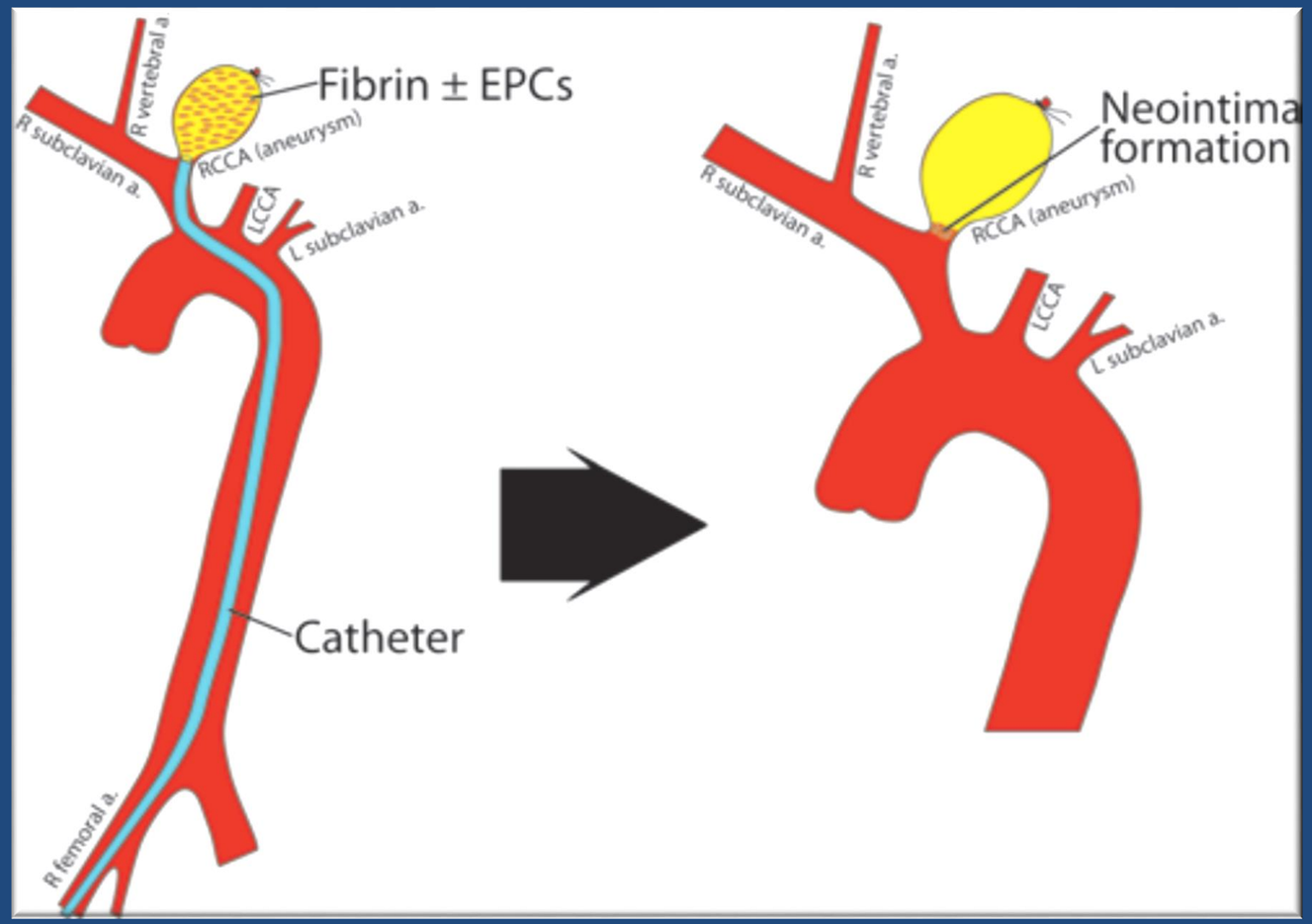


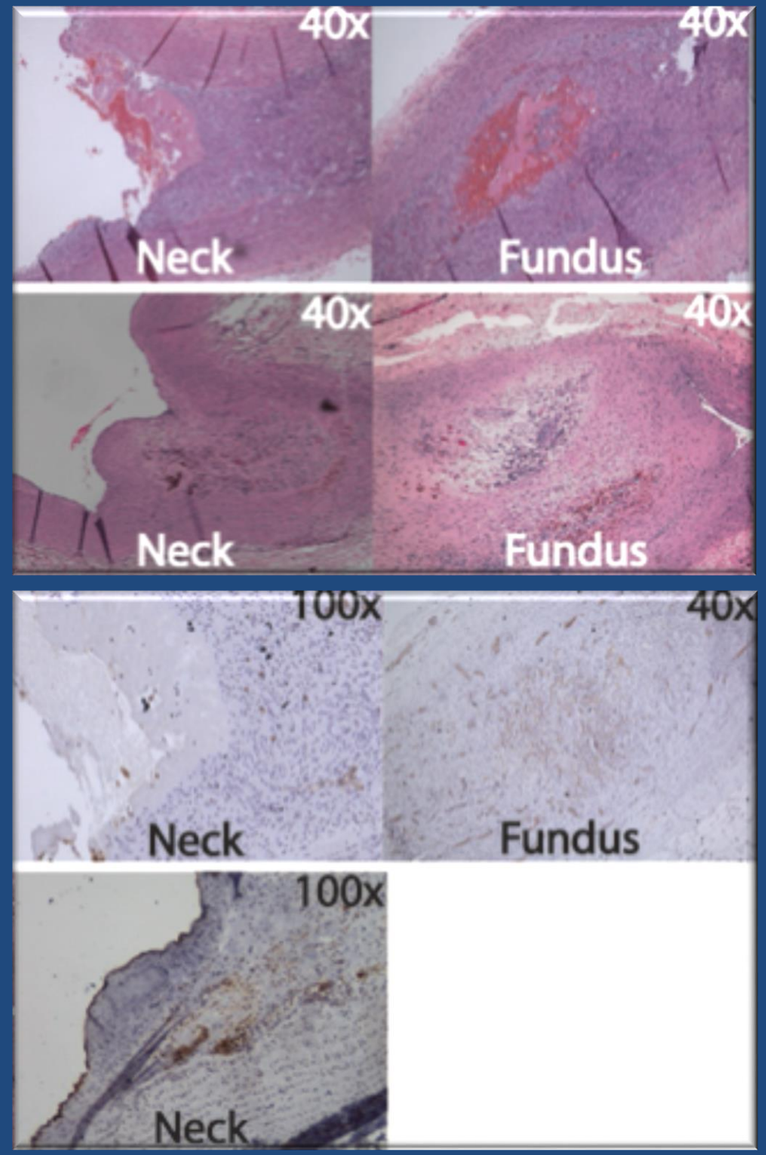
- Poches veineuses chez le chien (n=31)
- Traitement avec éponges de Gelfoam traitées avec fibrinogène +/- CML (autologue).

- Plus d'occlusion complète à 3 mois.
- Néo-intima significativement plus épaisse.

Raymond et al. Stroke. 1999;30:1657-1664

Cellules Progénitrices Endothéliales



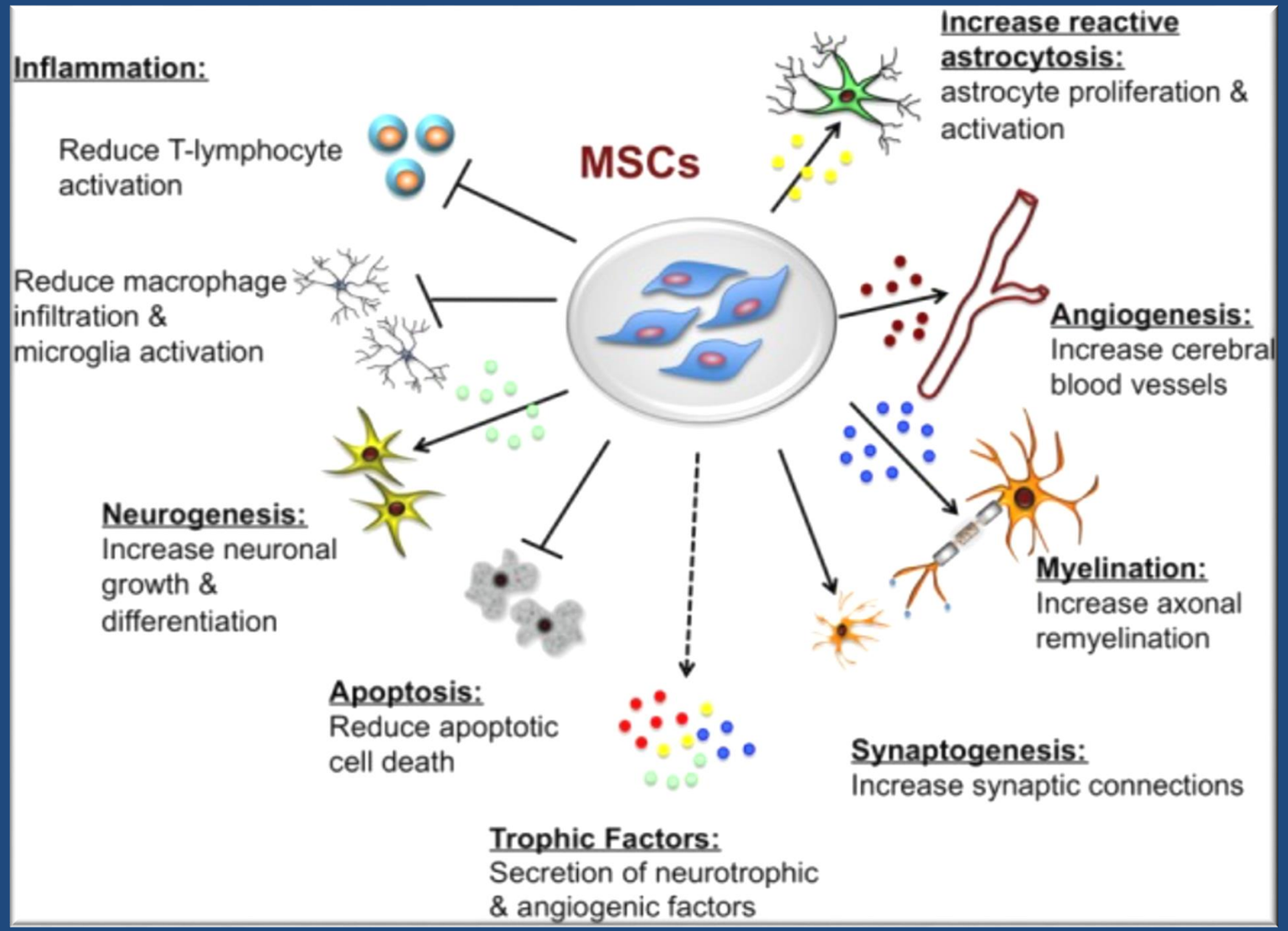


- EPCs autologues extraites du sang circulant.
- Formation néo-intimale +++ dans le groupe progéniteurs endothéliaux.
- Risque ischémique +++

Aronson et al. J Neurosurg. 2012. 117:546.

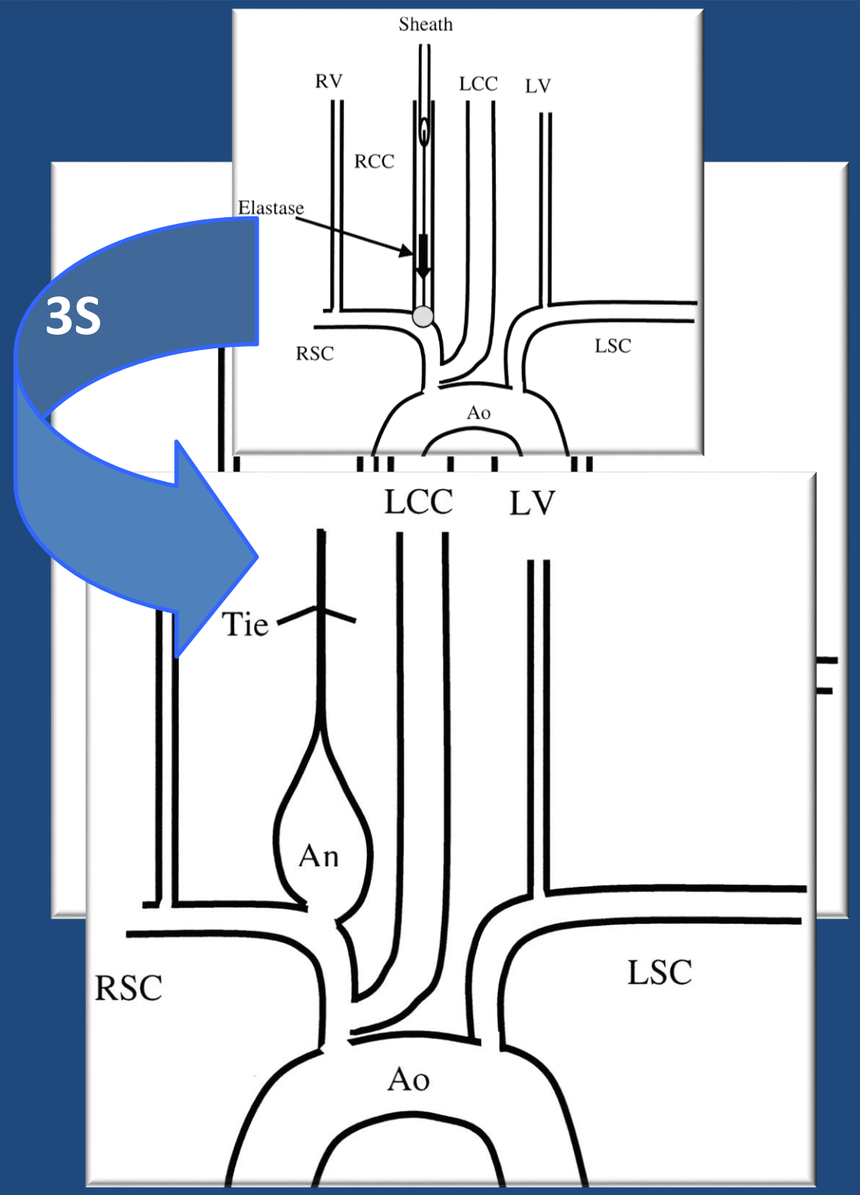
Cellules Stromales Mésenchymateuses

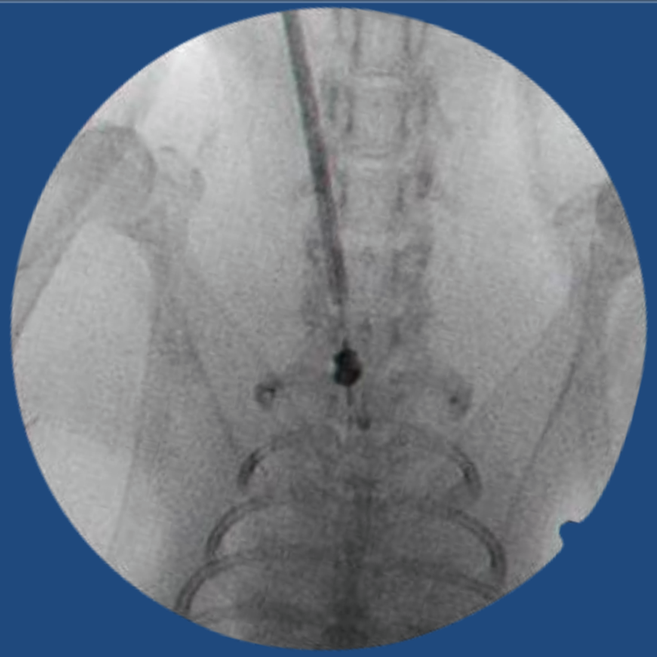
- Localisées dans la moelle osseuse
- Pluripotentes
- Migrent vers les tissus endommagés.
- Augmentent la capacité de survie des cellules.
- Sécrétion de facteurs tissulaires aidant la régénération des tissus.
- Actuellement utilisées dasn plus de 400 essais cliniques.

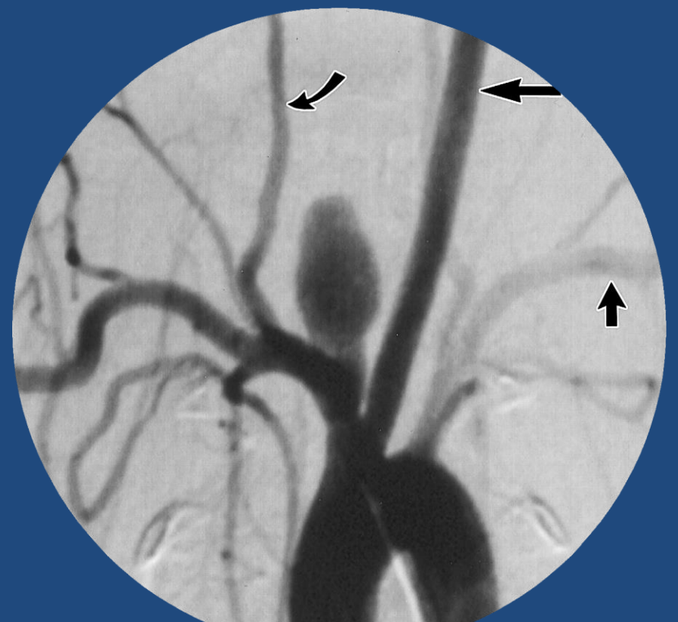


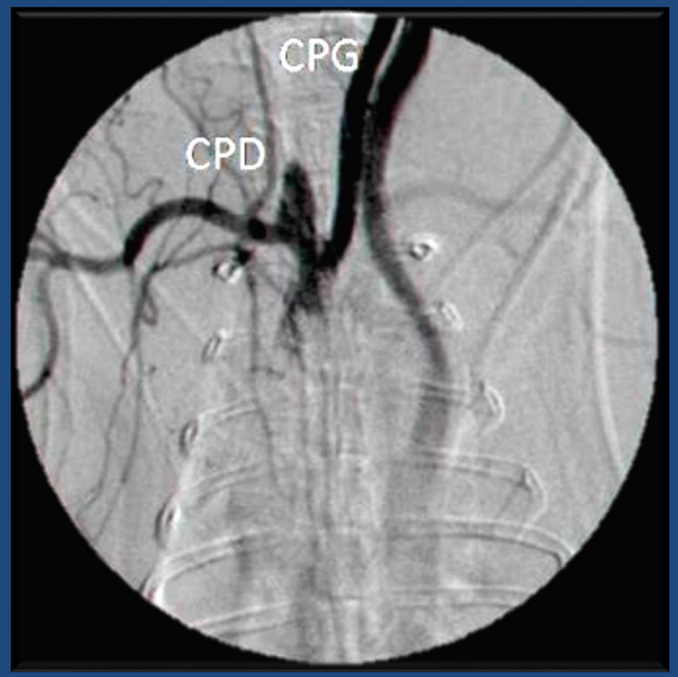
Bianco et al. Nature Med. 2013. 19:35.
Castillo-Melendez et al. Front Neurosci. 2013;7:194.

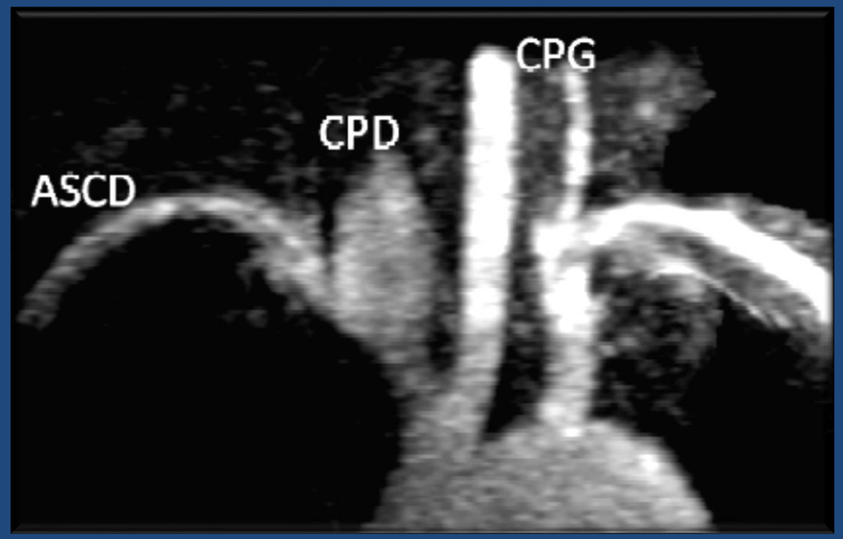
Modèle anévrysmal chez le lapin





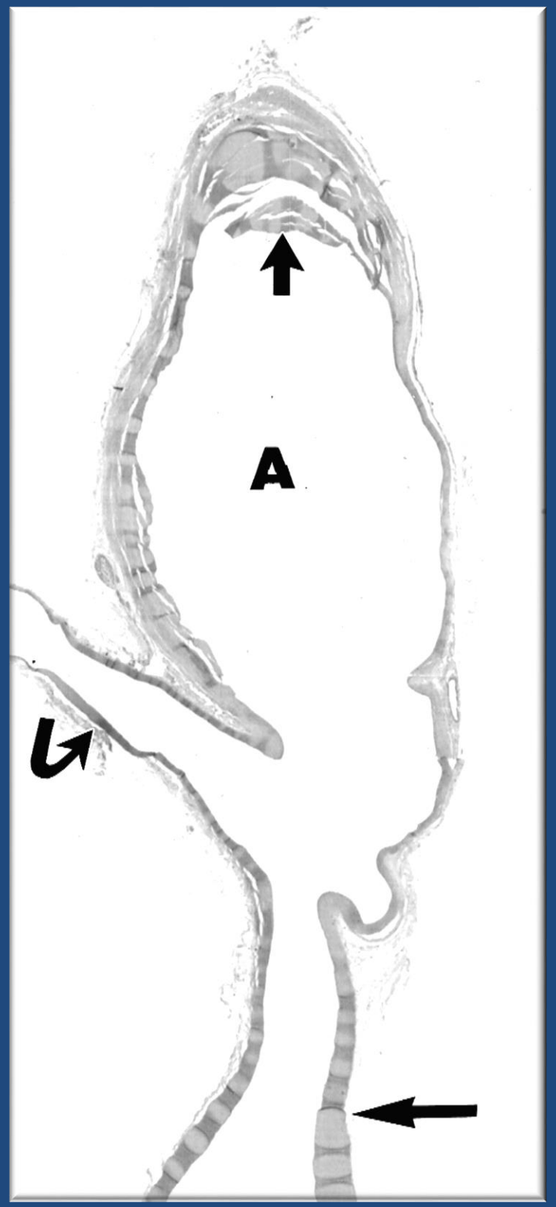


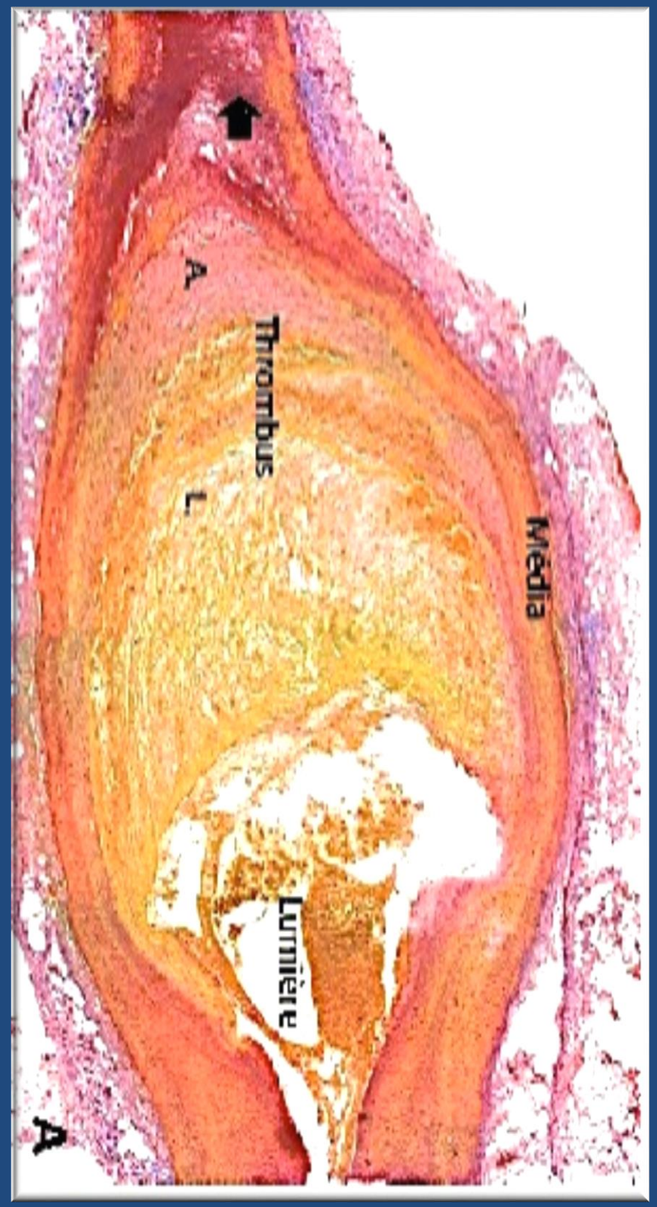




Kallmes et al. Am. J. Roentgenol. 2000;174:349-354

Modèle anévrysmal chez le lapin



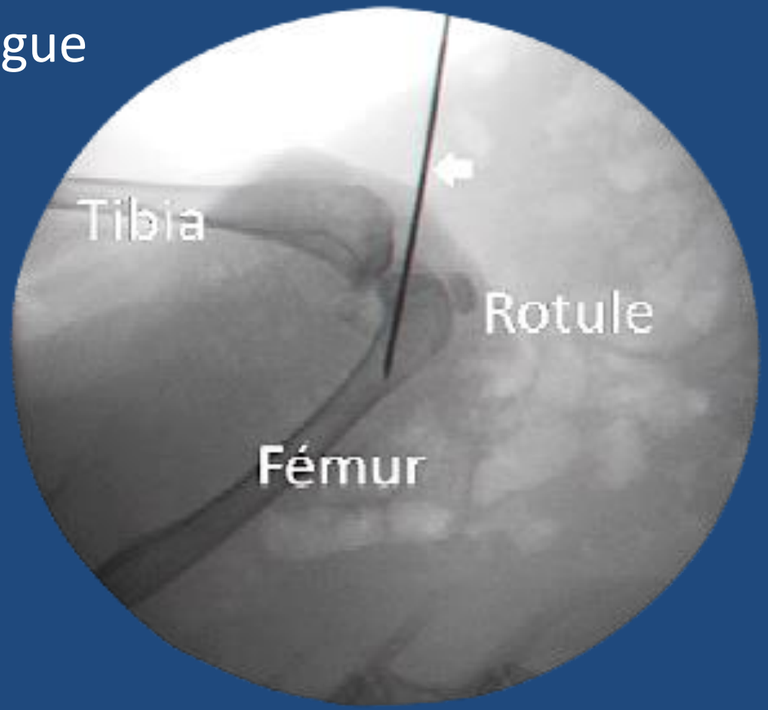


Orcéine-picro-indigo-carmin

Rouchaud et al., Neuroradiology. 2013;55(6):741-9.

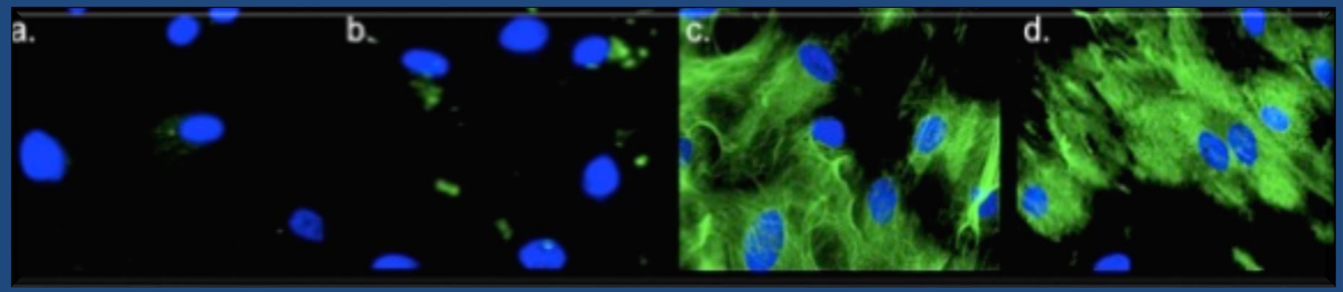
Cellules Stromales Mésenchymateuses

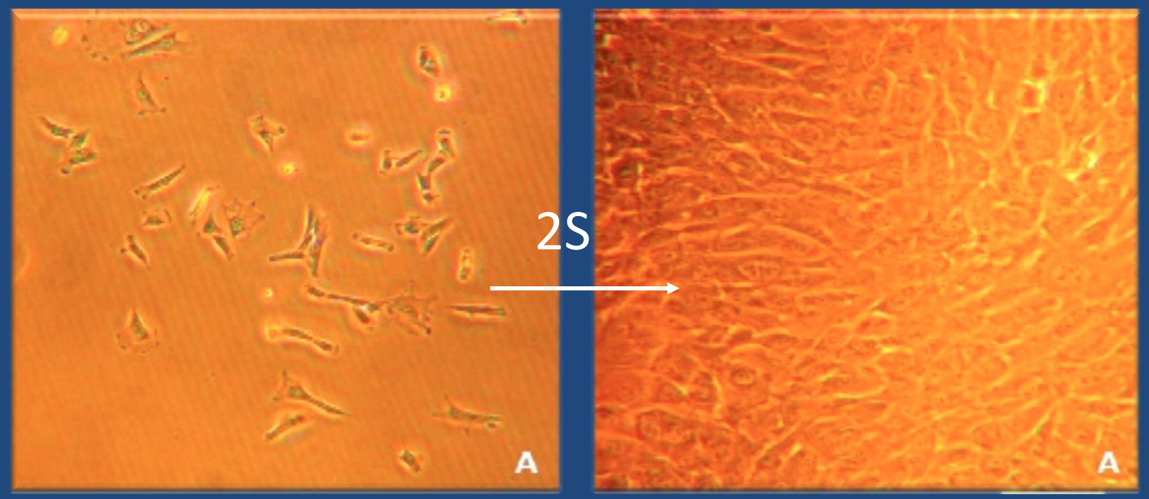
Autologue

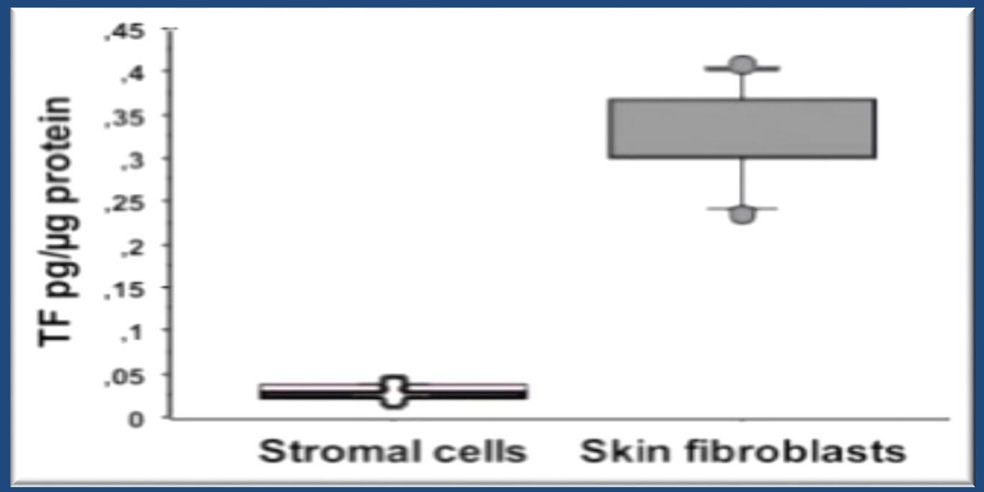


CELLULES STROMALES MESENCHYMATEUSES:

- Intégrin β 1, actin: +
- Activité procoagulante faible comparée aux fibroblastes et CML.

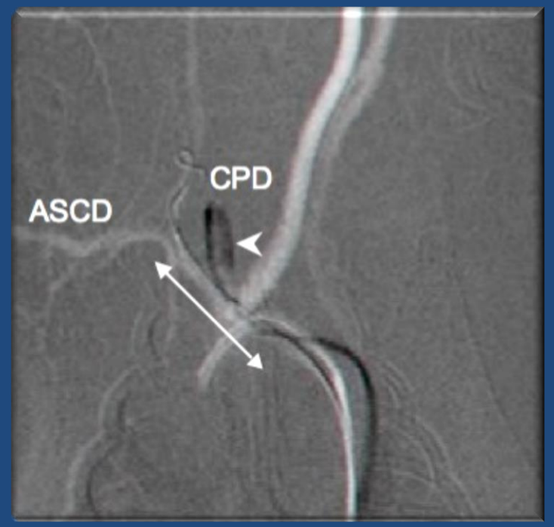


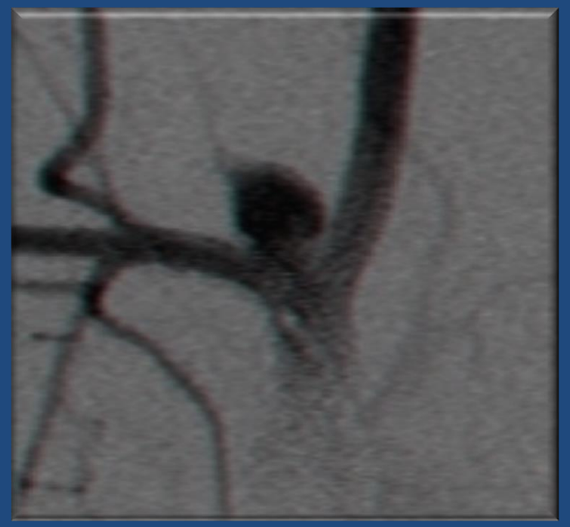




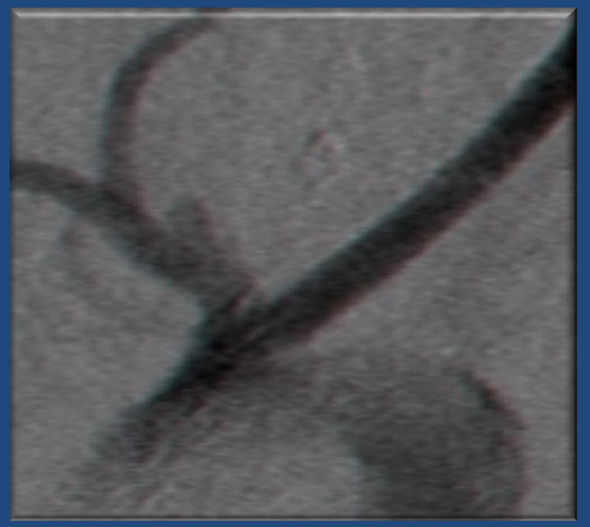
Rouchaud et al., Neuroradiology. 2013;55(6):741-9.

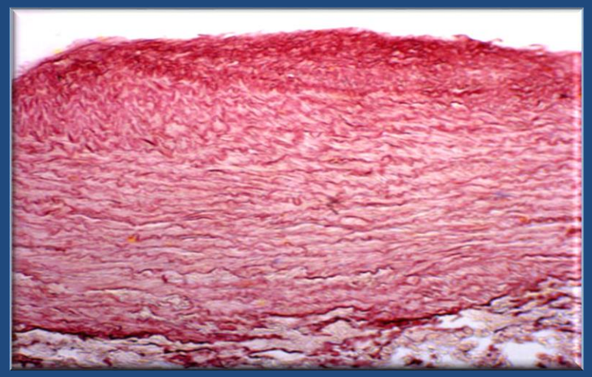
Cellules Stromales Mésenchymateuses

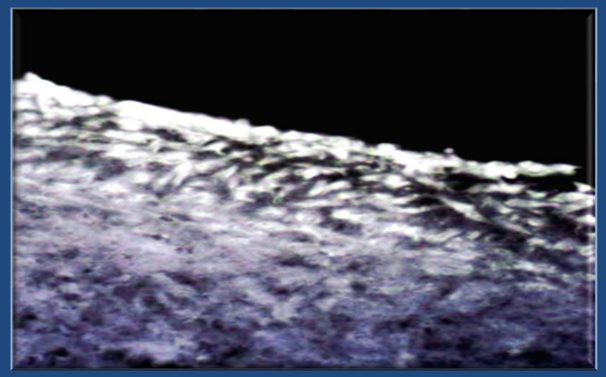


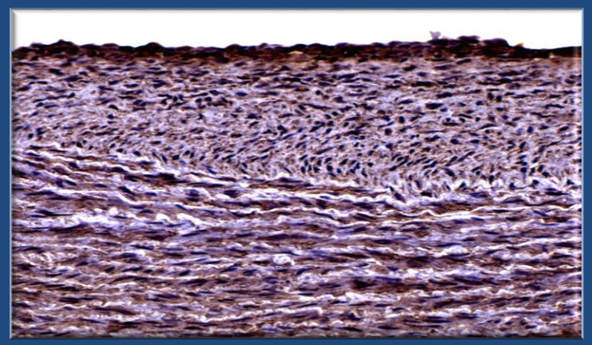


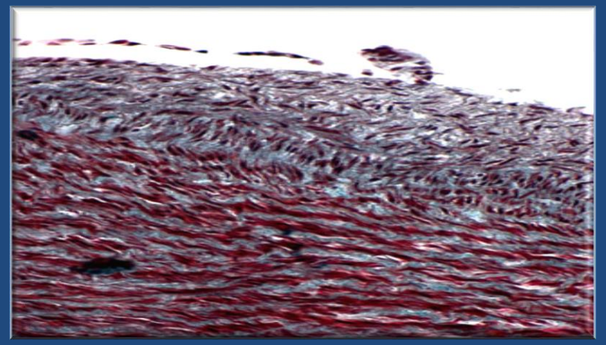
3S

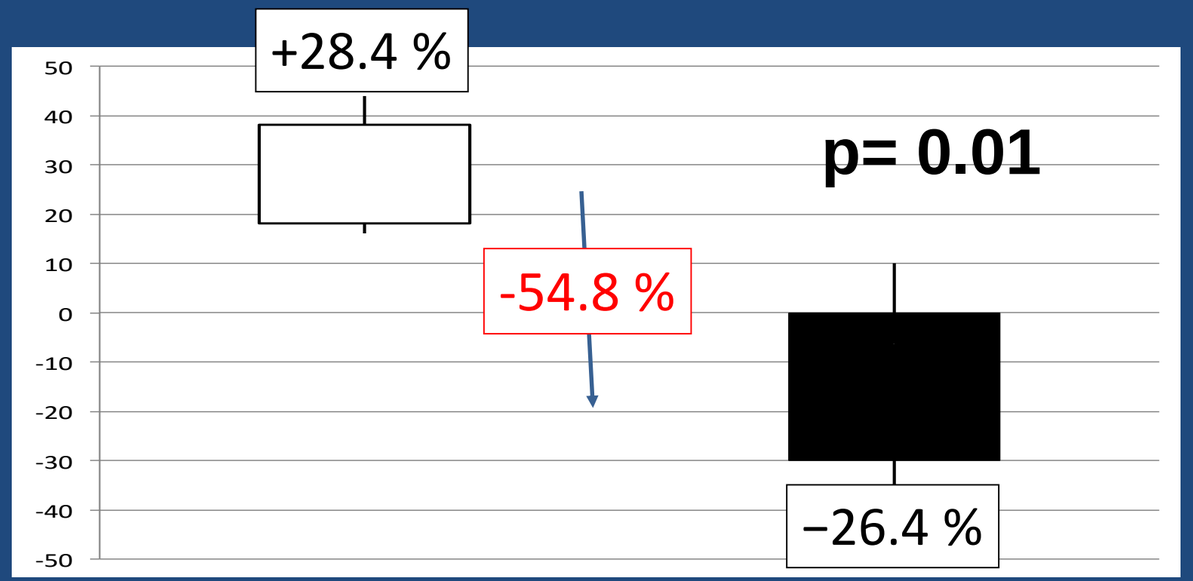










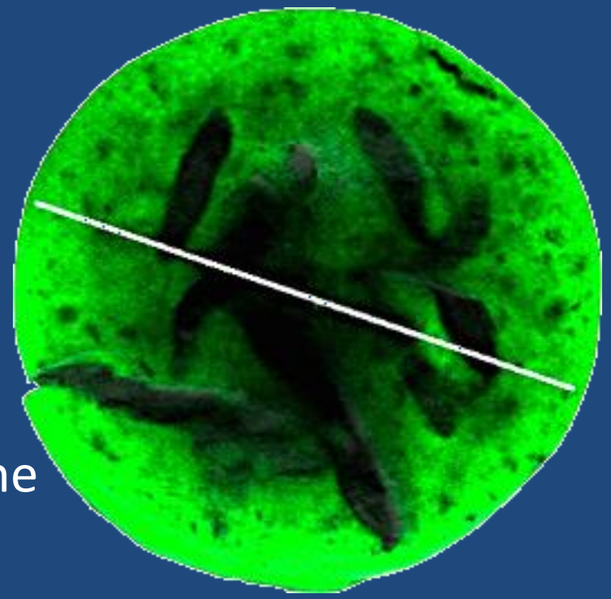


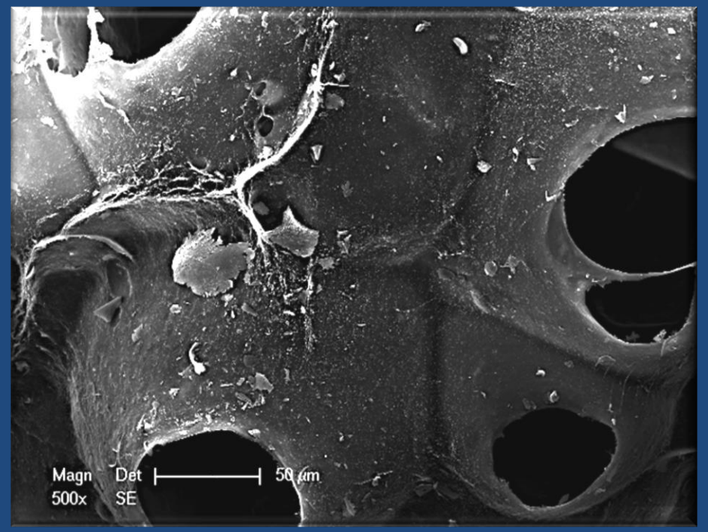
Rouchaud et al., Neuroradiology. 2013;55(6):741-9.

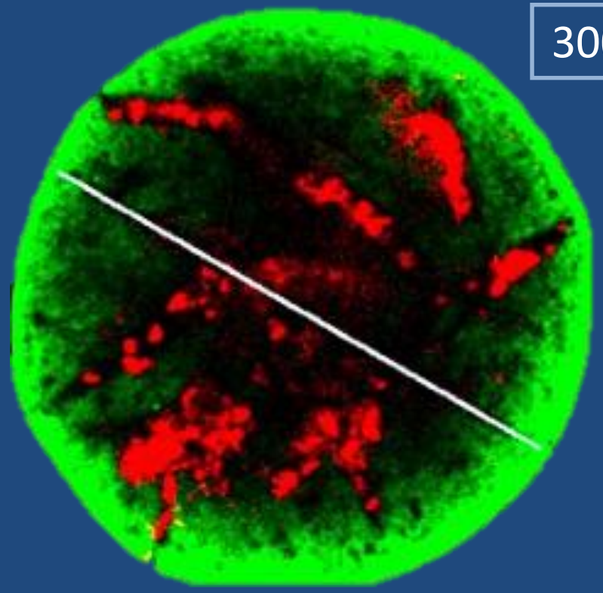
Optimisation par ingéniérie tissulaire

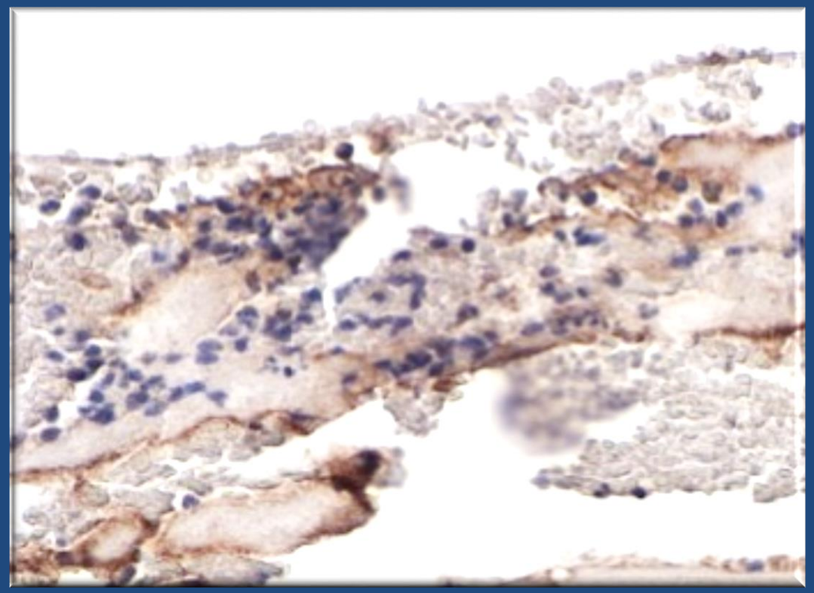
300-500 µm

Fucoïdane

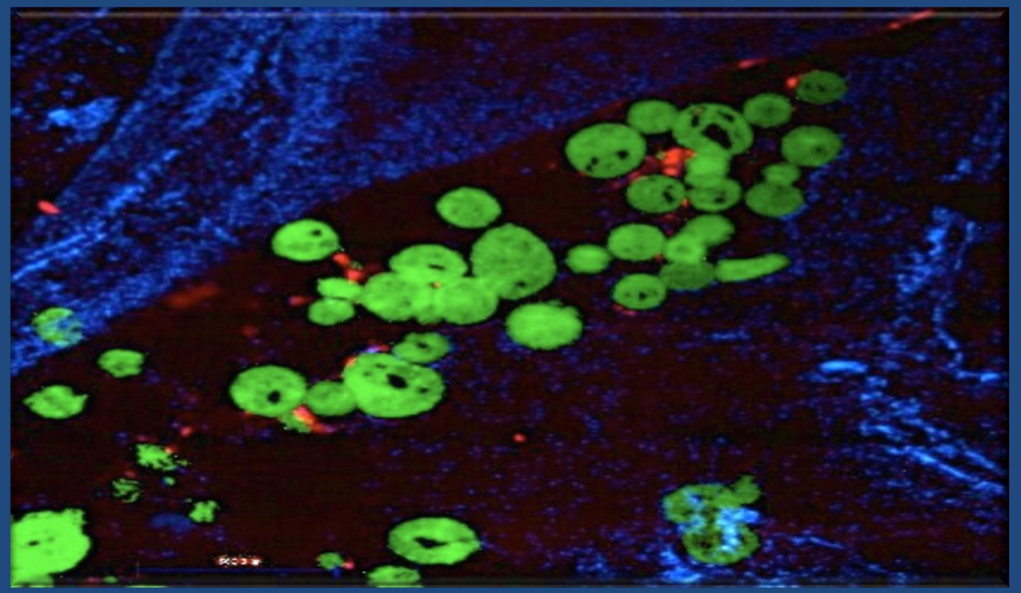








P-sélectine



Augmentation de la délivrance locale de cellules: **+ 60%.**

Rouchaud, Mazighi et al. *Non publié*

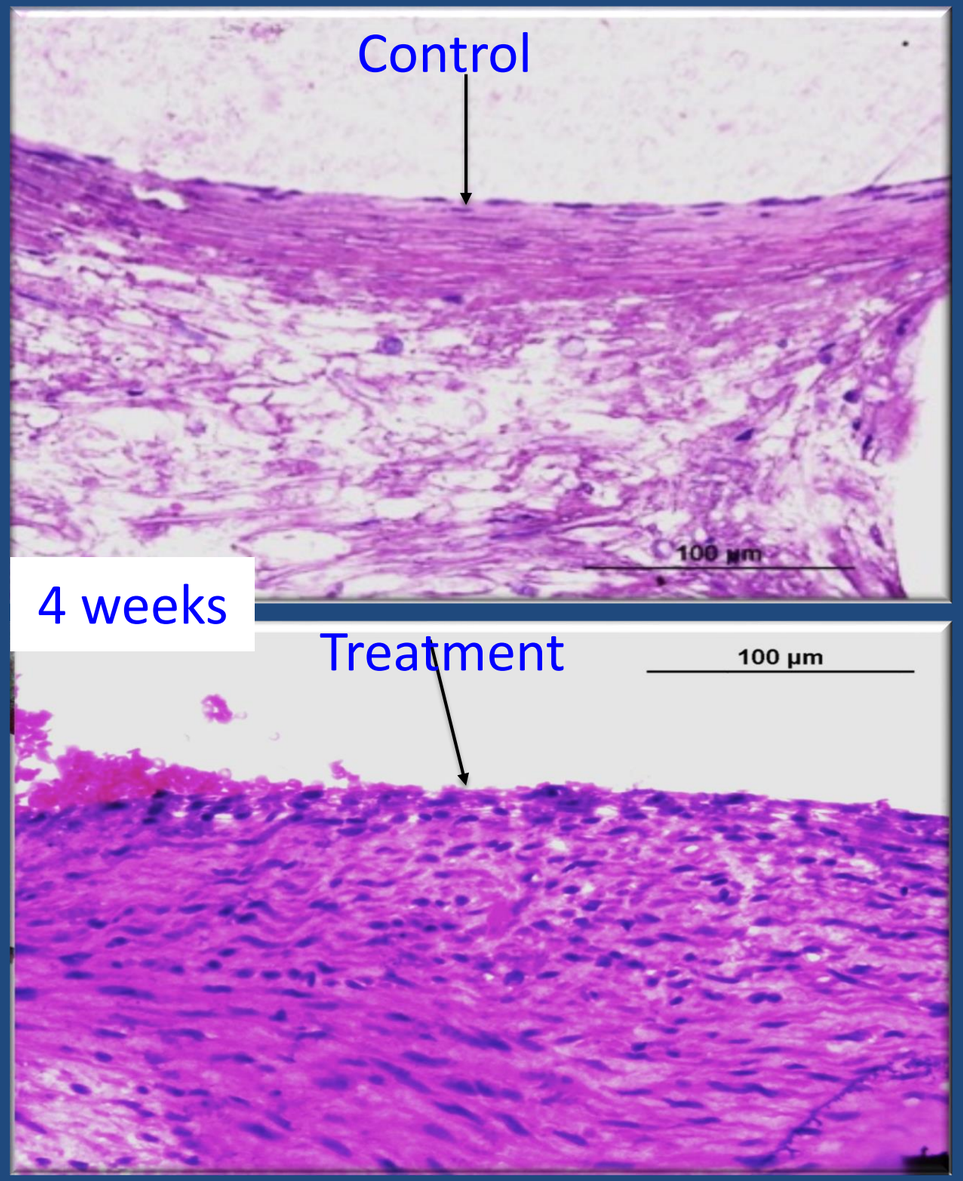
Cellules Stromales Mésenchymateuses

- CSM Homologues (pool venant de 3 lapins).
- 5.10^6 cellules dans l'anévrysme après le premier coil.

Table 5.4: Semi-quantitative histological scores, based on light microscopy

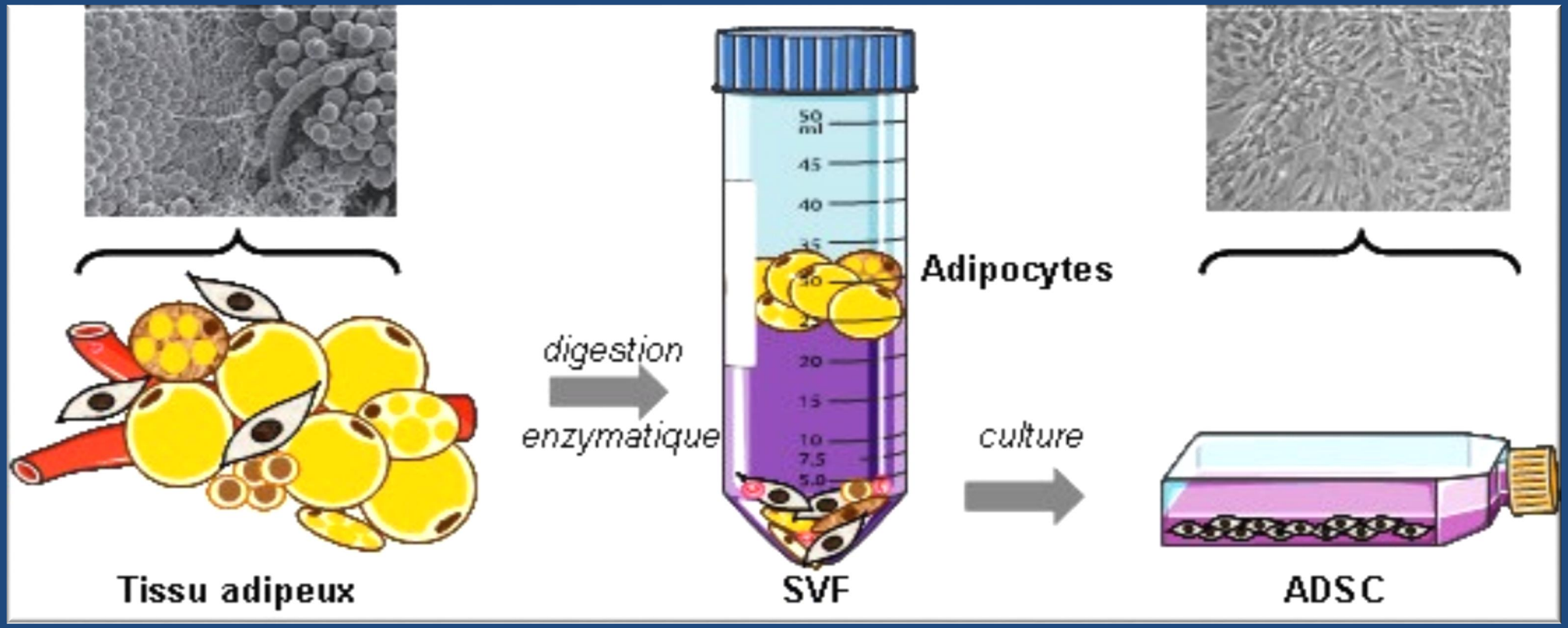
Group	Gross Neck	Micro Neck	Neck Comp.	Dome Histo.
Control	1	1	1	0
	3	2	1	0
Vehicle	3	4	2	3
	3	2	2	2
Treatment	3	4	2	3
	3	4	2	4
	N/A	N/A	N/A	4

- Kruskal-Wallis p-value = 0.02
- Mann-Whitney U treatment vs control p-value=0.01



Adibi A, Mitha AP, et al. *Non publié*

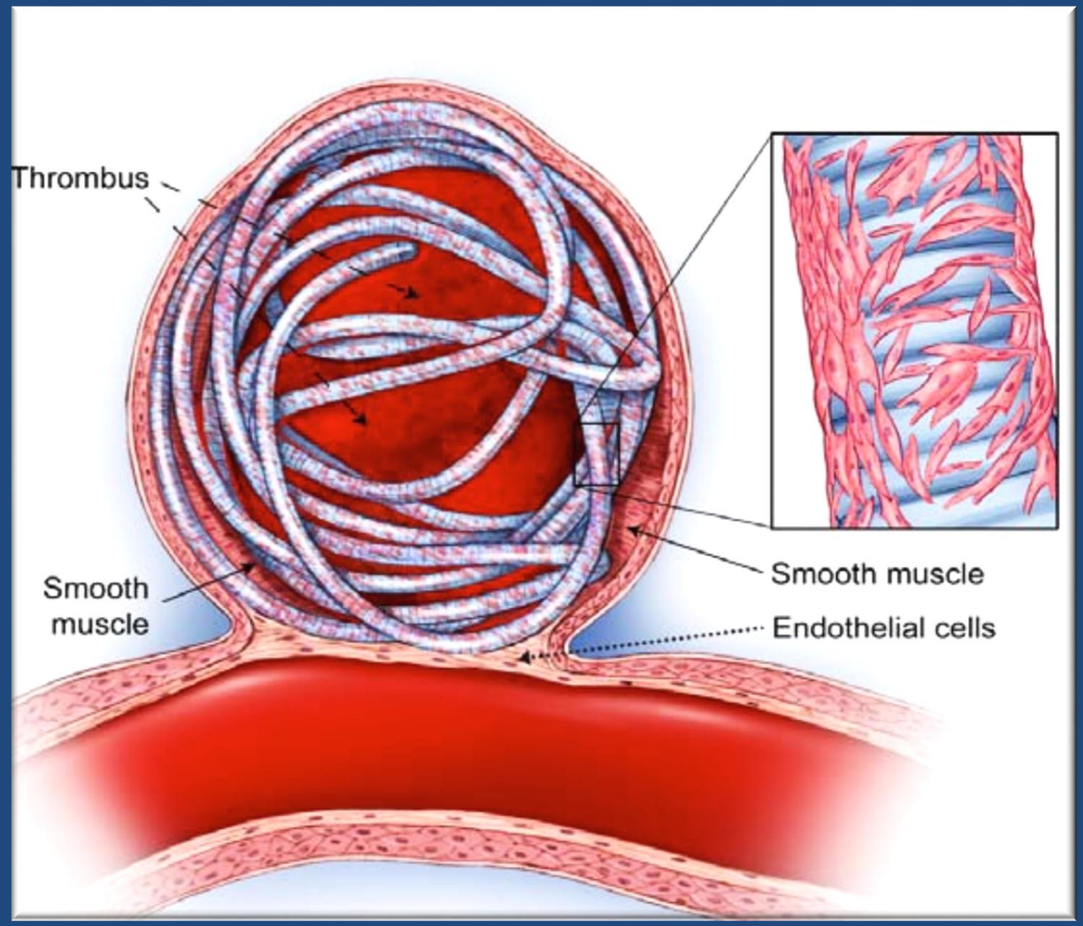
Cellules Stromales Adipocytaires



Leobon et al. Cardiovasc Res. 2009;83(4):757-67

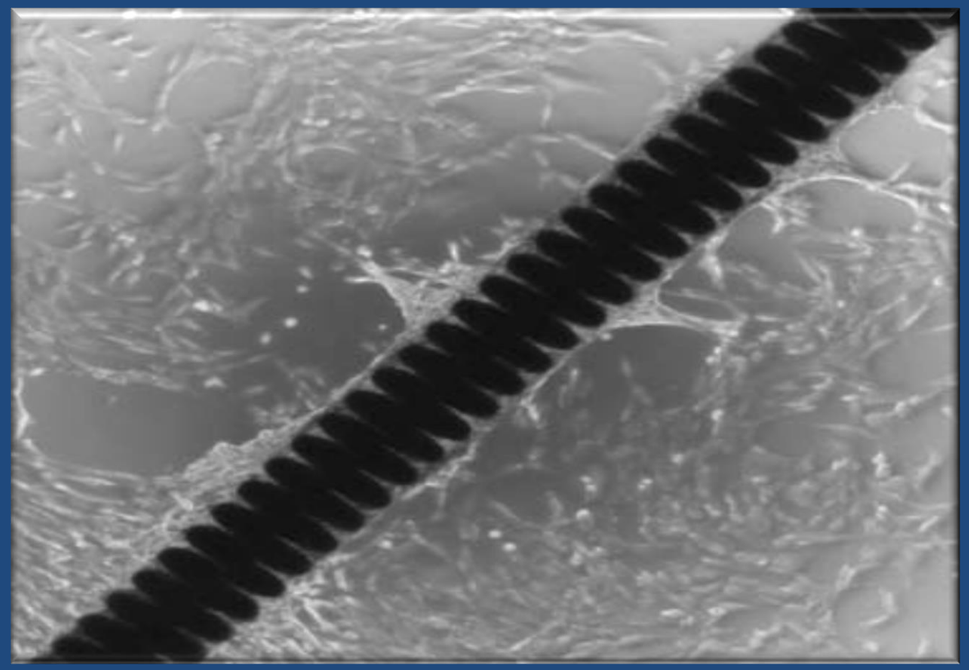
Cellules Stromales Adipocytaires

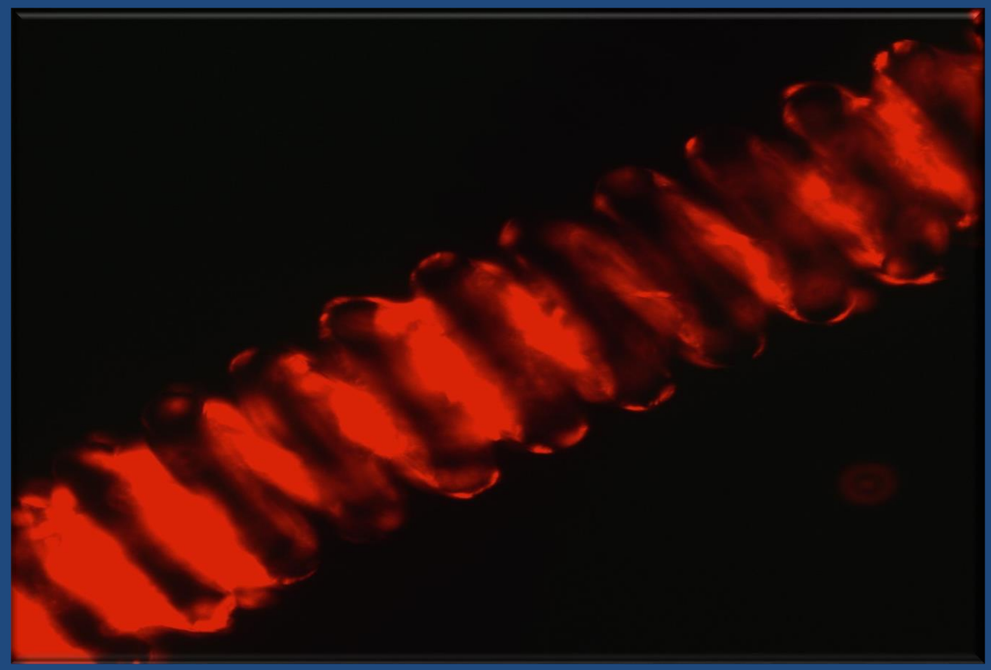
- 18 anévrysmes chez le lapin.
- Coils Axium.
- Expansion des cellules (environ 3 semaines)
- Coating des coils avec FNC (Fibrinogène + Collagène + Albumine).
- Culture des cellules sur les coils pendant 36 h.
- Traitement avec cellules stromales adipocytaires autologues (12.10^6).

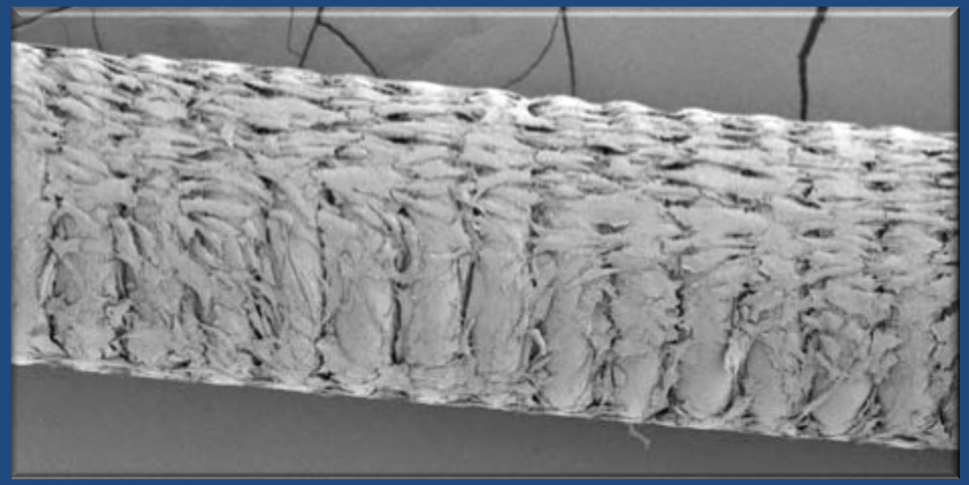


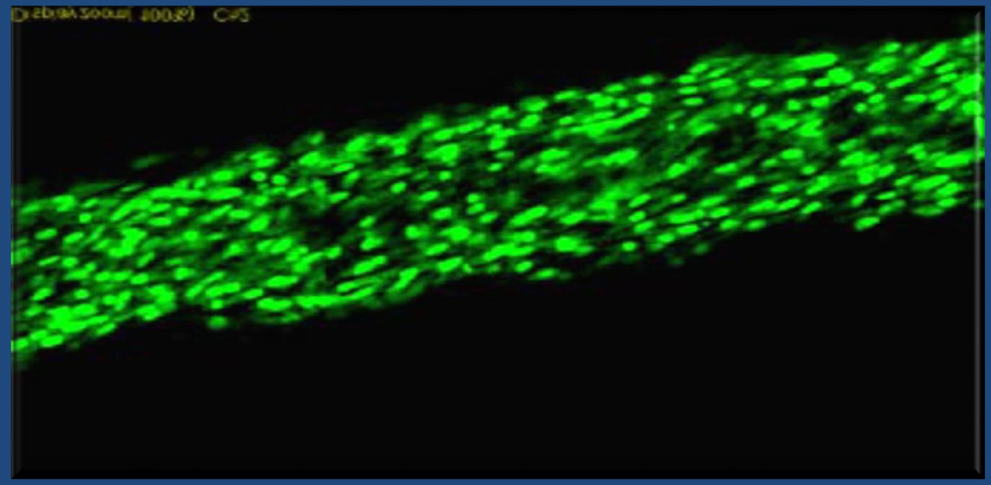
Rouchaud, Kallmes et al. *Non publié*

Cellules Stromales Adipocytaires



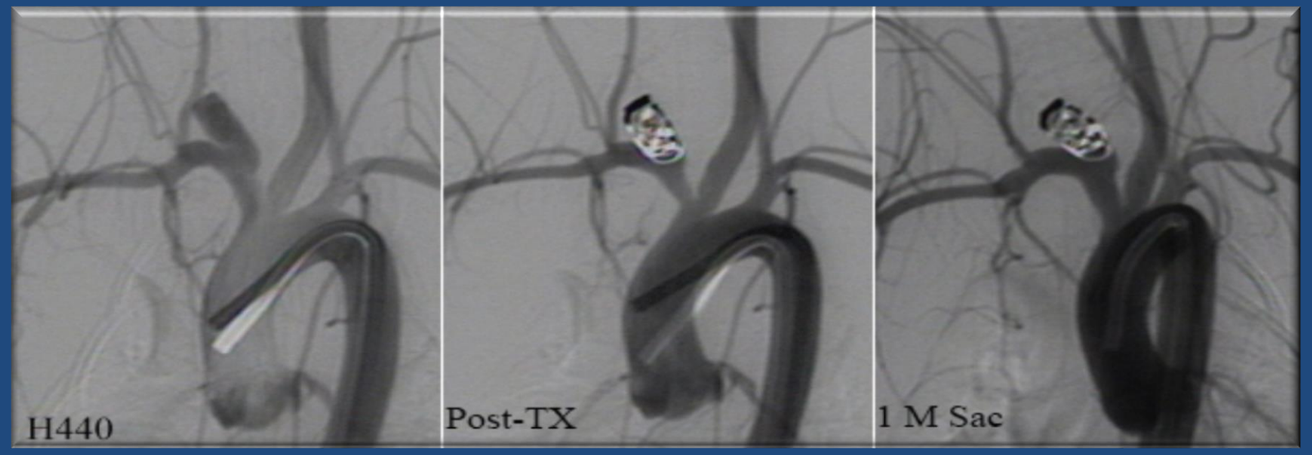




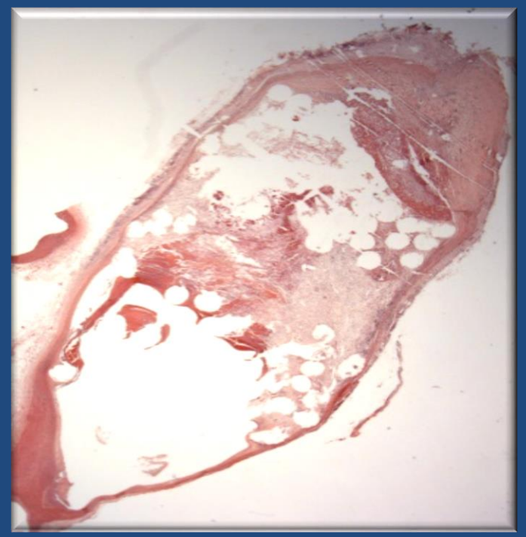


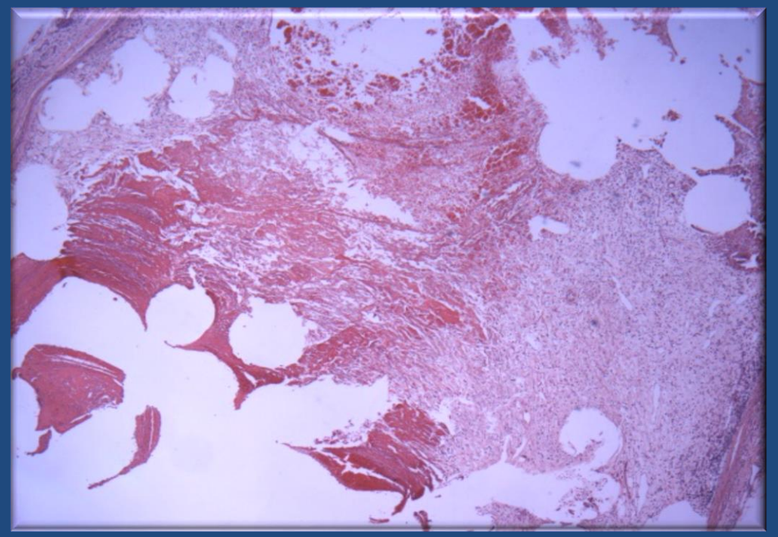
Rouchaud, Kallmes et al. *Non publié*

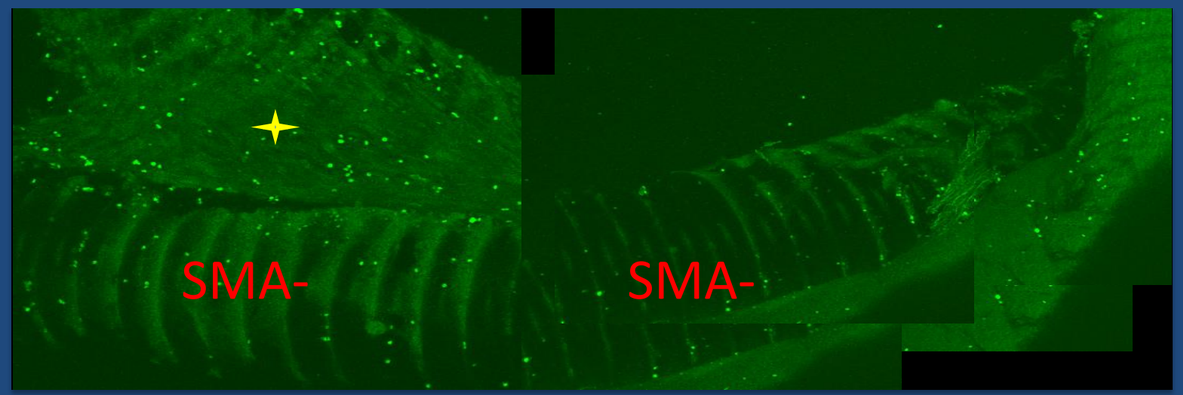
Cellules Stromales Adipocytaires



Contrôle



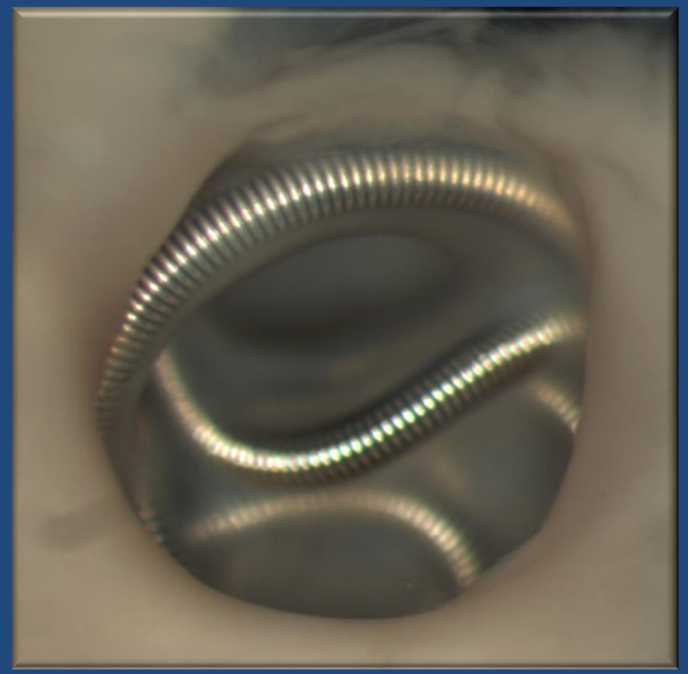


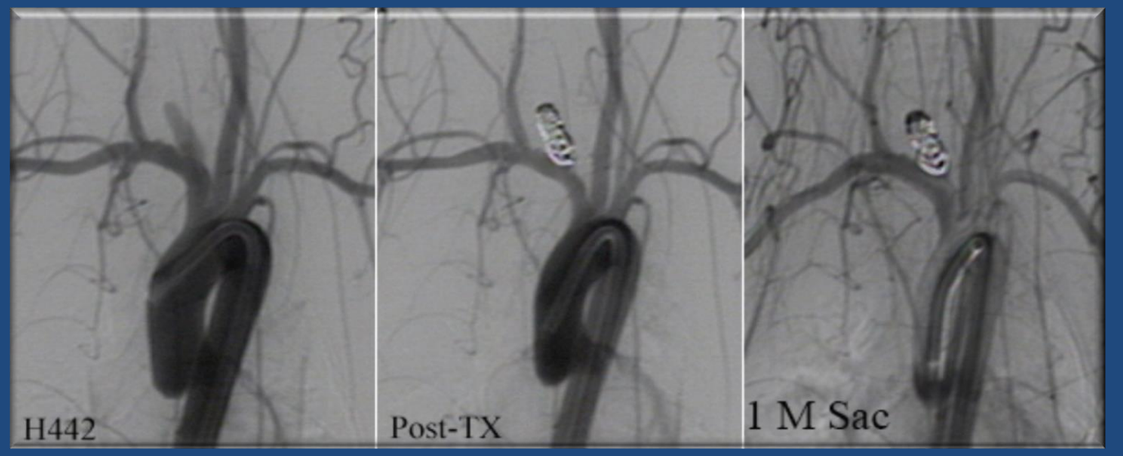


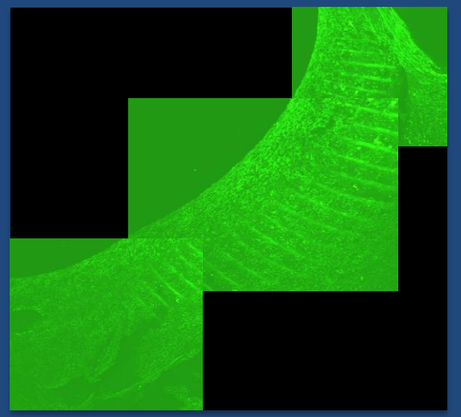
Rouchaud, Kallmes et al. *Non publié*

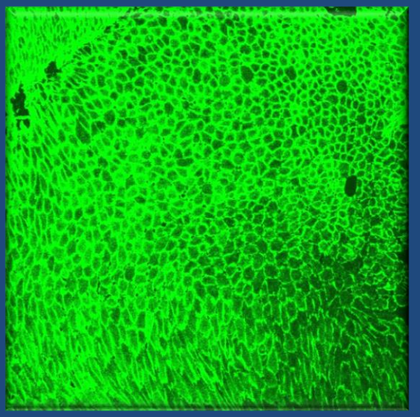
Cellules Stromales Adipocytaires

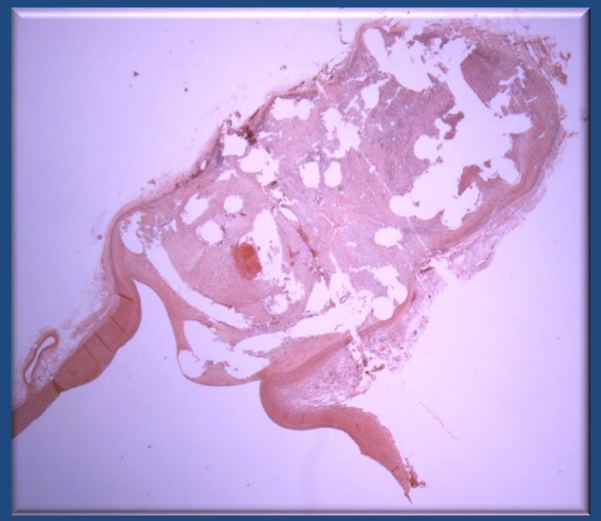
ADSC

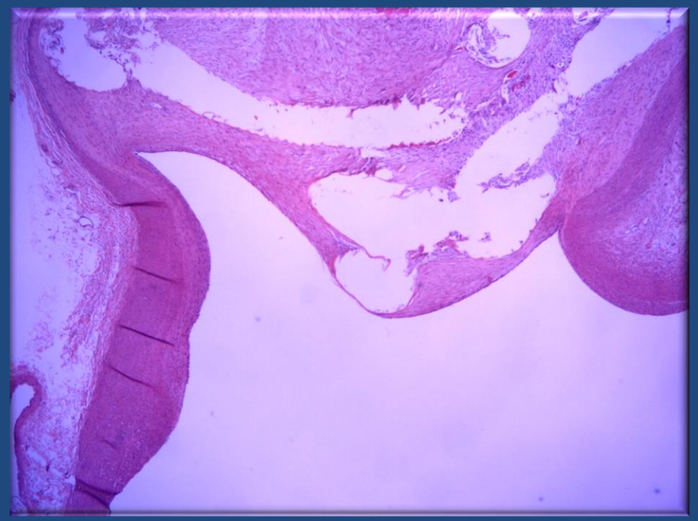










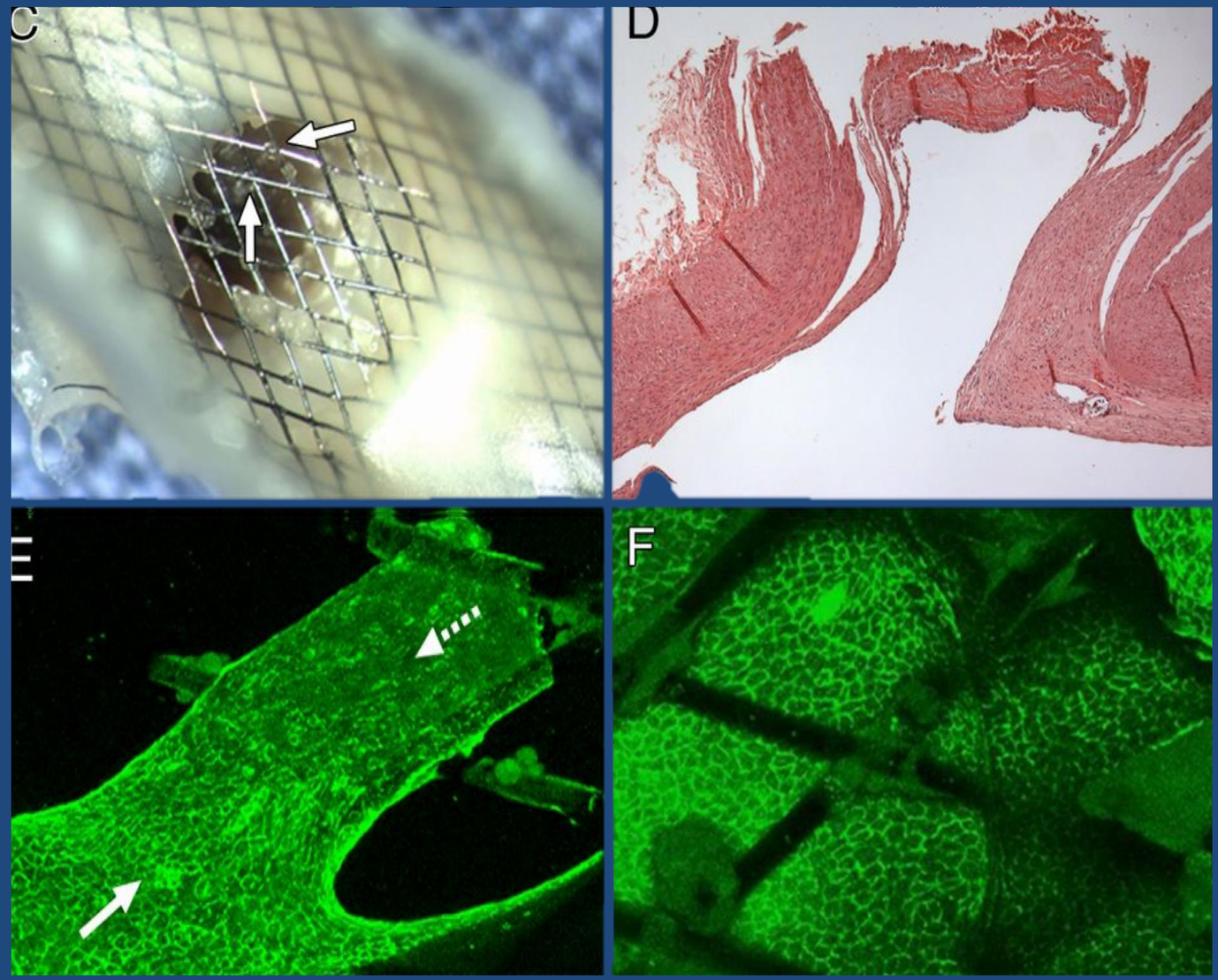


	Control (N=9)	MSC (N=9)	p-value
Median	31 810	902 262	**0.04113**
Q1, Q3	14 106 – 39 7315	608 991 – 1 799 849	**28.36**

Rouchaud, Kallmes et al. *Non publié*

Perspectives

- Association aux flow-diverters:
  - Augmentation de la couverture endothéliale.
  - Prévention du risque de rupture retardée par effet paracrine (diminution des MMP2-9)
- Association aux dispositifs intra-sacculaires (WEB).
- Autres supports.

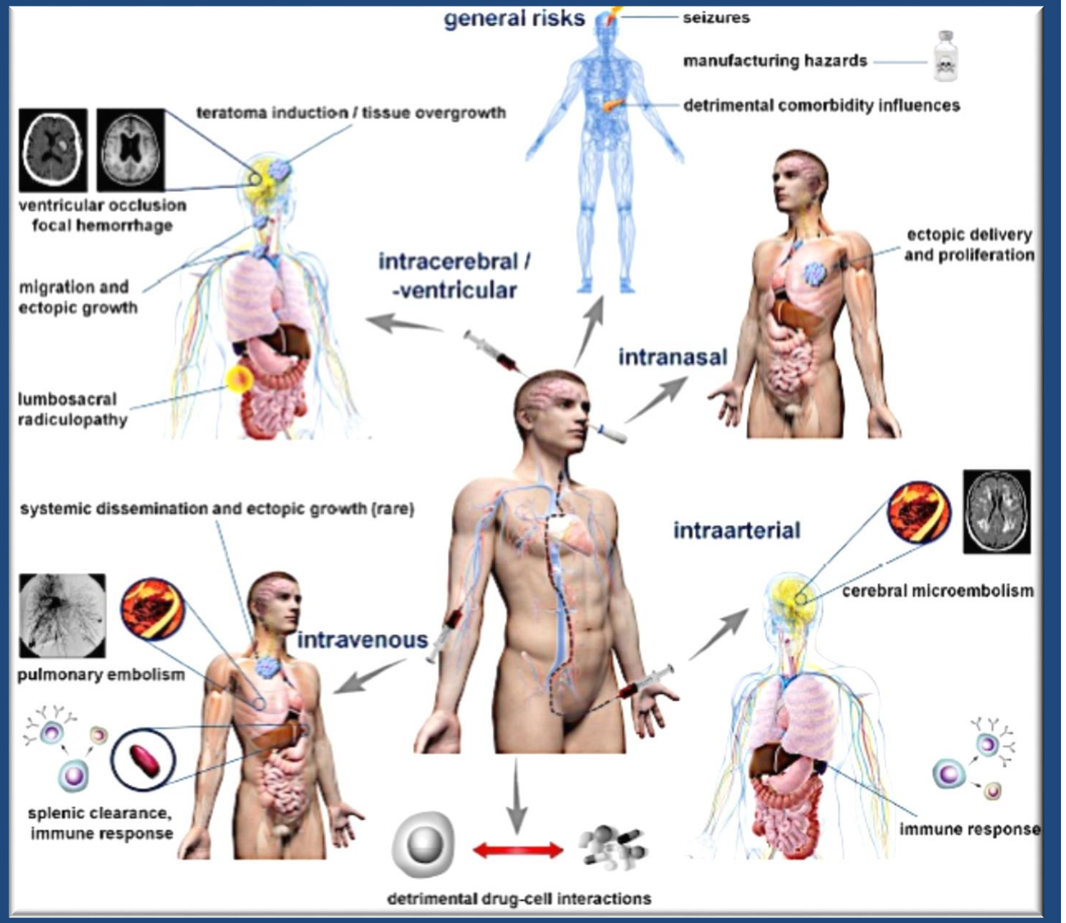


Kadirvel et al. Radiology 2014;270:394-399

Limites

- Risques de rejet en cas d’utilisation de cellules hétérologues.
- Cellules autologues impossibles en cas de traitement en urgence.
- Nécessité de planifier le traitement (quantité de cellules, fixation sur le support).
- Risque prolifératif ?

Essais cliniques dans le Stroke



Boltze et al. Front Neurol. 2015;6:155.

Study	Design	Patients	Cell type	Cell source	Transplantation procedure			
		Treated/ controls			Time window	Route	*n*	Cell number/dose and further details
ONGOING CLINICAL TRIALS								
NCT01678534	Randomized, controlled, double blind, phase II	20	MSC	Allogenic adipose tissue	2 weeks	Intravenous	1×	1×10^6/kg
NCT01151124	Open-label, phase I	12	Neural stem/progenitor cells (CTX)	Allogeneic (human cortical neuroepithelium)	0.5–5 years	Intraparenchymal	1×	Dose escalation: 2×, 5×, 10×, 20 × 10^6
NCT02117635	Open-label, phase II	up to 62 (two-stage)	Neural stem/progenitor cells (CTX)	Allogeneic (human cortical neuroepithelium)	4 weeks	Intraparenchymal	1×	2×10^7
NCT00875654	Randomized, open-label, phase II	30	MSC	Autologous bone marrow	6 weeks	Intravenous	2×	No further details provided
NCT01714167	Non-randomized, open-label, phase I	30	MSC	Autologous bone marrow	3–6 months	Intraparenchymal	1×	2–4 × 10^6
NCT01716481	Randomized, open-label, phase III	60	MSC	Autologous bone marrow	90 days	Intravenous	1×	No further details provided
NCT01962233	Open-label, phase I	10	MSC	Allogeneic cord blood	N/A	Intravenous	1×	1–8 × 10^8, no further details provided
NCT01297413	Non-randomized, open-label, phase I/II	35	MSC	Allogeneic bone marrow	6 months	Intravenous	1×	0.5–1.5 × 10^6
NCT02290483	Open-label, controlled, randomized, phase II	76	MNC	Autologous bone marrow	1–7 days	Intraarterial	1×	2 × 10^6, 5 × 10^6
NCT01468064	Double-blinded, randomized, controlled, phase II	90	Endothelial progenitor cells	Autologous bone marrow	5 weeks	Intravenous	2×	2.5 × 10^6 per injection, 1 week interval
NCT01832428	Open-label, phase I/II	50	MNC	Autologous bone marrow	N/A	Intrathecal	3×	1 × 10^8 per injection, 1 week interval
NCT01673932	Open-label, randomized, phase I	12	MNC	Allogeneic umbilical cord blood	6–60 months	Intraparenchymal	1×	10–40 × 10^6
NCT01461720	Single-blinded, non-randomized, phase II	50	MSC	Autologous bone marrow	0.5–2 months	Intravenous	1×	N/A
NCT02378947	Double-blinded, randomized, phase I/II	18	MSC	Umbilical cord blood (allogeneic?)	0 day, 0 and 7 days	Intravenous	1× 2×	2 × 10^8 per injection, 1 week interval for the second injection
NCT01501773	Open-label, randomized, phase II	120	MNC	Autologous bone marrow	7–30 days	Intravenous	1×	30–500 × 10^6
NCT00950521	Open-label, randomized, phase II	30	$CD34^+$	Autologous peripheral blood	6–60 months	Intraparenchymal	1×	2–8 × 10^6

George et al. Neuron. 2015;87(2):297-309.

Conclusion

- Thérapeutique innovante et efficace pour le traitement des anévrysmes intracrâniens.
- Effet direct sur la recellularisation du segment pathologique.
- Intérêt +++ des cellules stromales.
- Thérapeutique unique ou adjuvante aux traitements mécaniques.
- Circuits pour cellules souches existent en clinique.
- **Transfert à l'Homme ? ? ?**

MAYO CLINIC

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