Physiopathologie des granulomatoses systémiques

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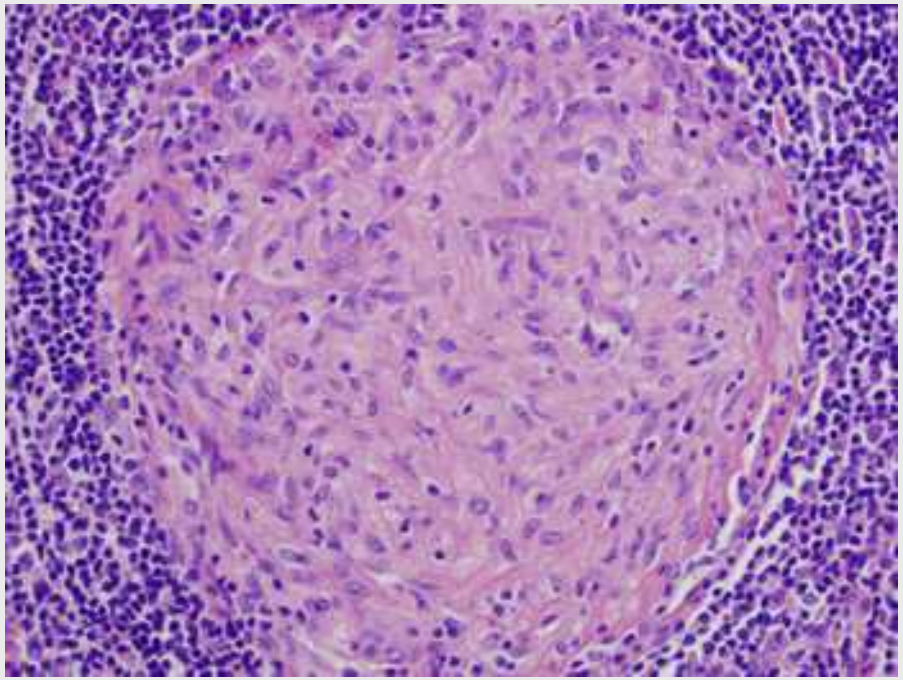
Granuloma

From Wikipedia, the free encyclopedia

- *Granuloma (plural granulomas or granulomata) is an inflammation found in many diseases. It is a collection of immune cells known as macrophages. Granulomas form when the immune system attempts to wall off substances that it perceives as foreign but is unable to eliminate. Such substances include infectious organisms such as bacteria and fungi as well as other materials such as keratin and suture fragments.The adjective granulomatous means characterized by granulomas.*

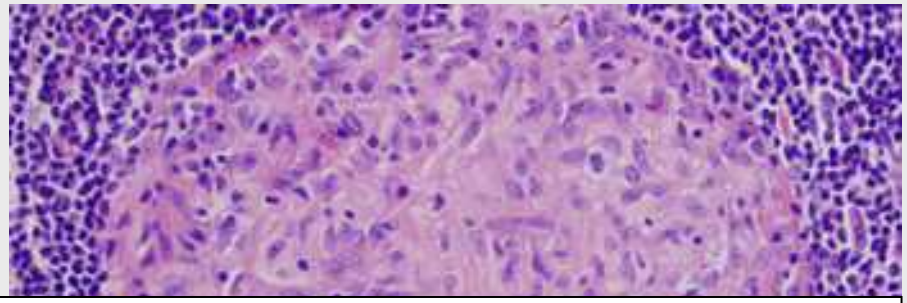


The granuloma in this picture was found in a lymph node of a patient with Mycobacterium avium infection

Granuloma

From Wikipedia, the free encyclopedia

- *Granuloma (plural granulomas or granulomata) is an inflammation found in many diseases. It is a collection of immune cells known as macrophages. Granulomas form when the immune system attempts to wall off substances that it perceives as foreign but is unable to eliminate. Such substances include infectious organisms such as bacteria and fungi as well as other materials such as keratin and suture fragments. The adjective granulomatous means characterized by granulomas.*



Attention à ce qui est compris sous la dénomination de granulome!

- granulomes à corps étranger
- granulomes à cellules épithélioïdes

Agression

Inflammation aiguë

(poly N → macrophages)

élimination de l'Agent agresseur → résolution

persistance de l'Agent agresseur

inflammation chronique

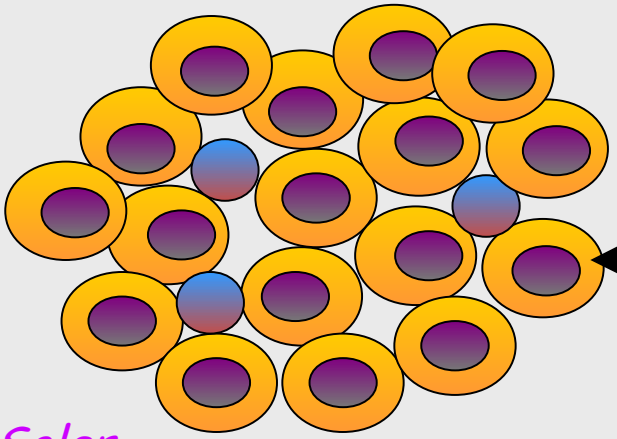
(macrophages)

Ag + *(+ Ly T)* → granulomes de type immun

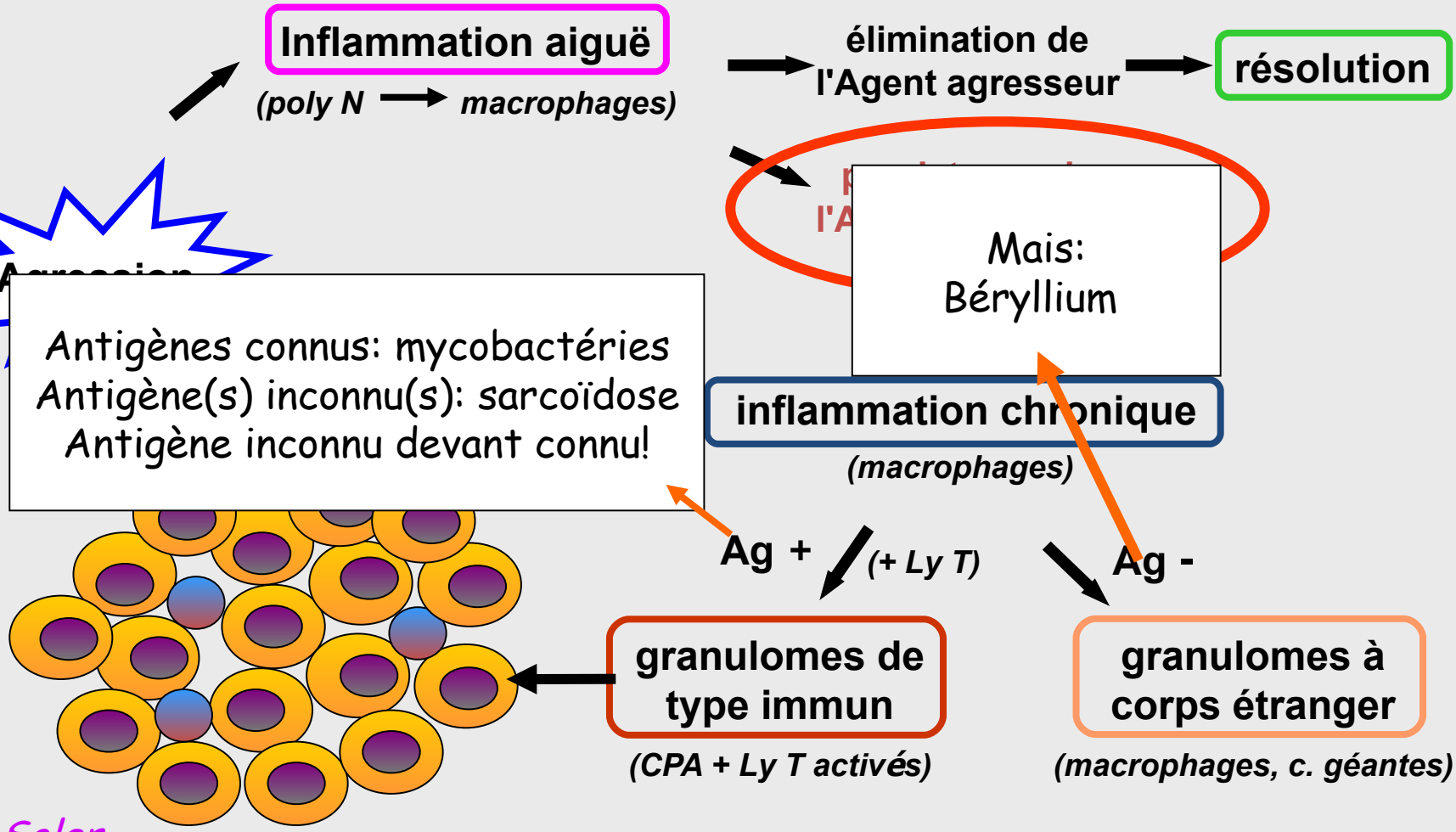
(CPA + Ly T activés)

Ag - → granulomes à corps étranger

(macrophages, c. géantes)



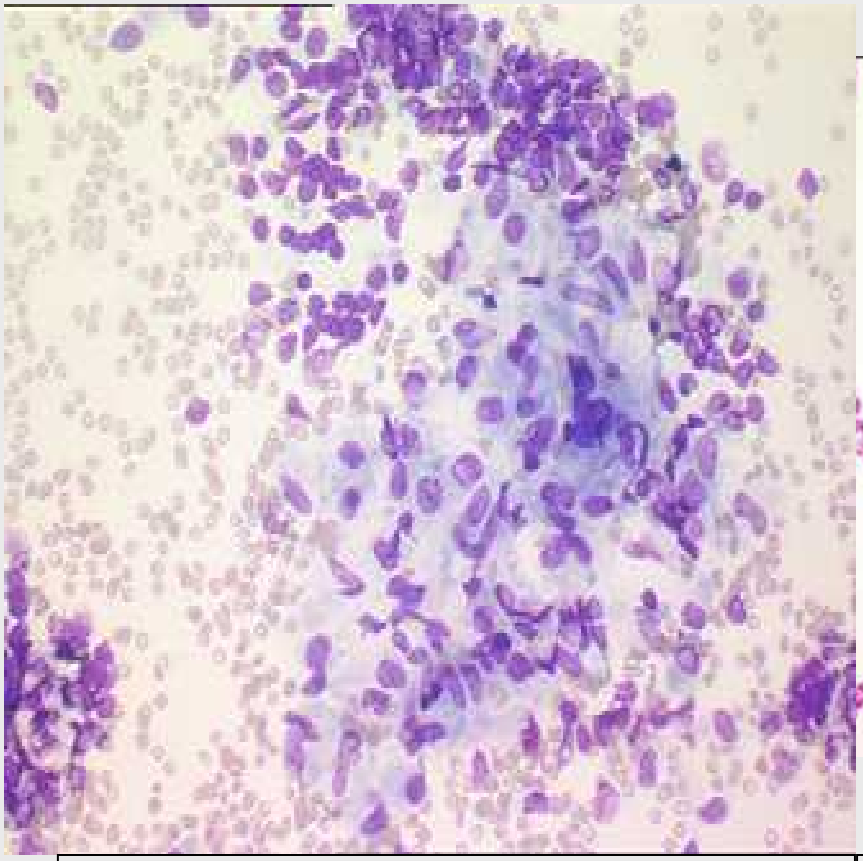
Paul Soler


Inflammation aiguë
(poly N → macrophages)
élimination de
l'Agent agresseur
résolution
Mais:
Béryllium
Antigènes connus: mycobactéries
Antigène(s) inconnu(s): sarcoïdose
Antigène inconnu devant connu!
inflammation chronique
(macrophages)
Ag +
(+ Ly T)
Ag -
granulomes de
type immun
(CPA + Ly T activés)
granulomes à
corps étranger
(macrophages, c. géantes)

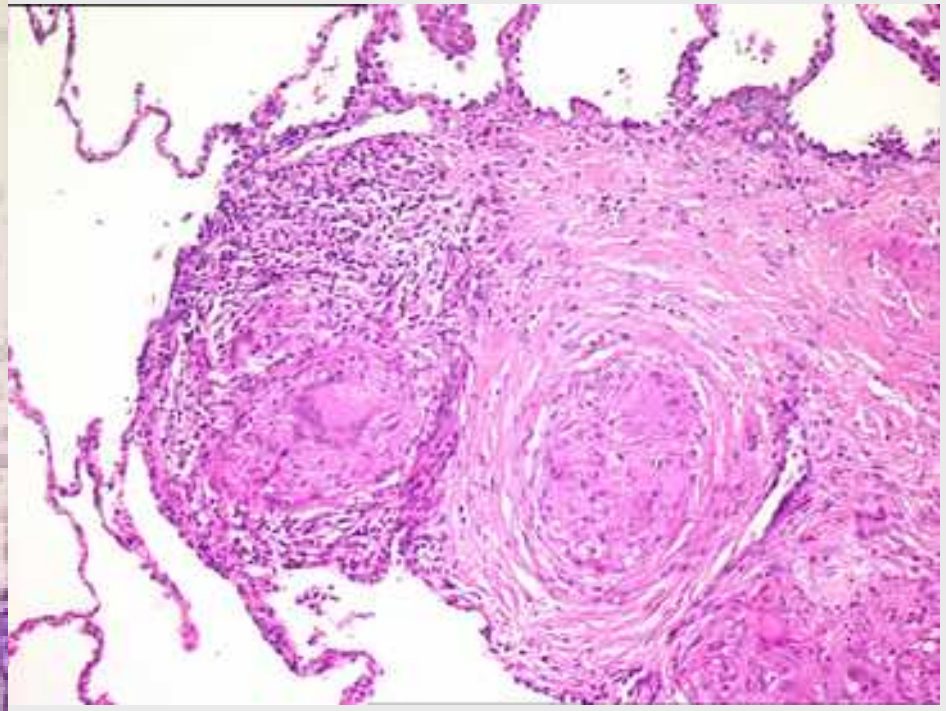
Paul Soler

- *1899 Caesar Boeck: skin nodules characterized by compact sharply defined foci of « epithelioid cells with pale nuclei and also a few giant cells »Thinking this resembled sarcoma he called the condition « multiple benign sarcoid of the skin »*

  Ianuzzi MC et al. NEJM 2007



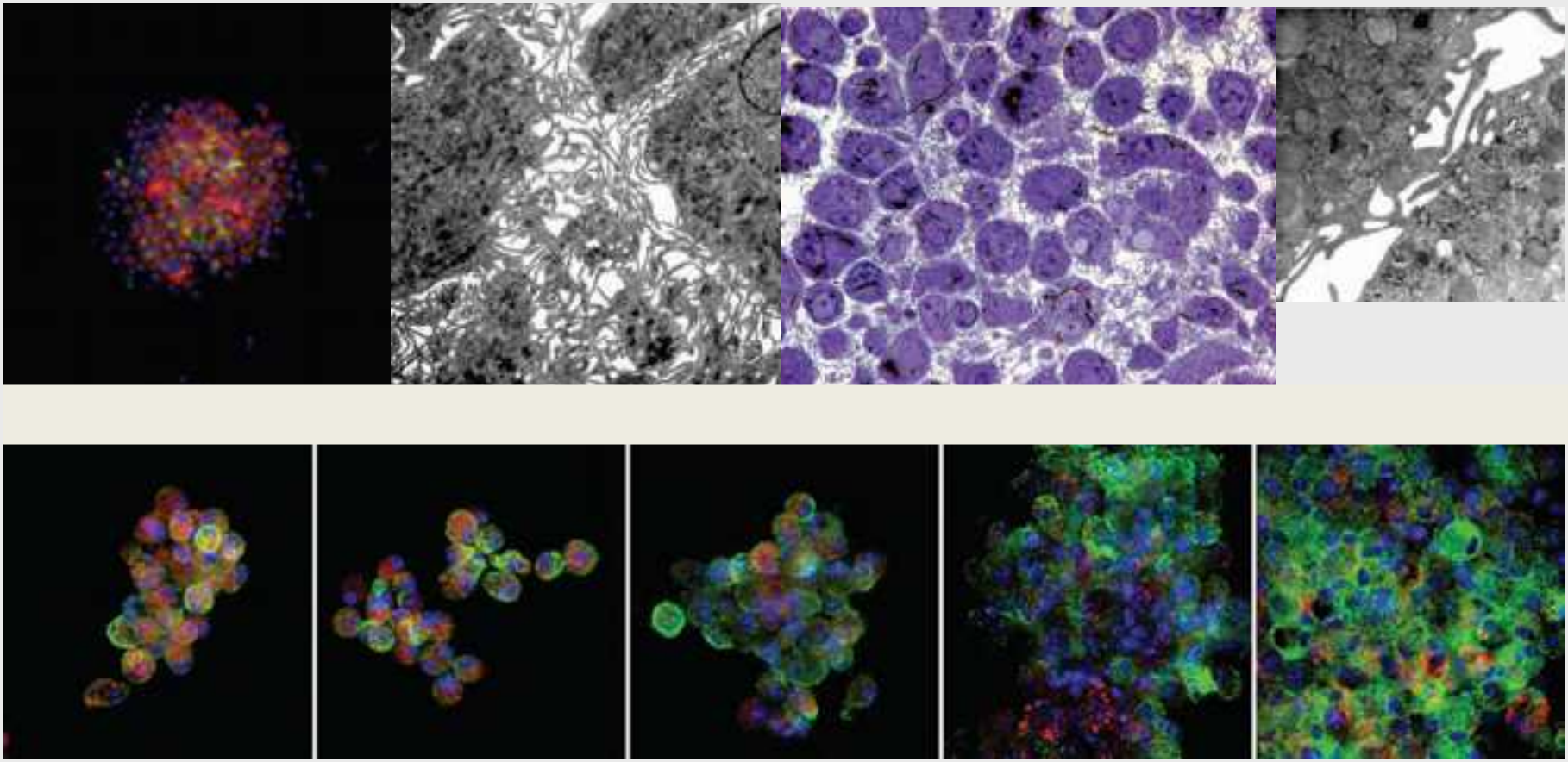
EBUS FNA Dr Jocelyne Fleury Tenon

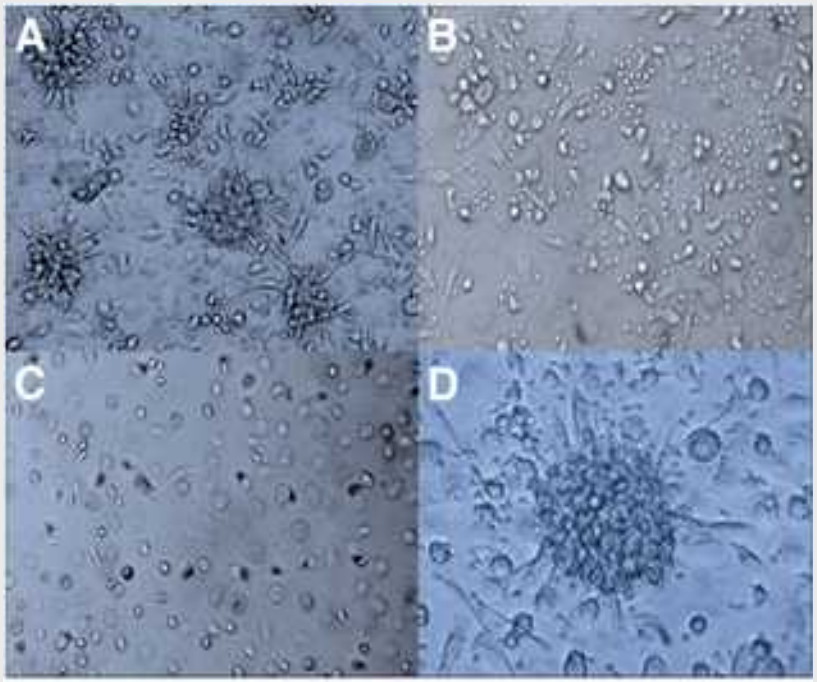


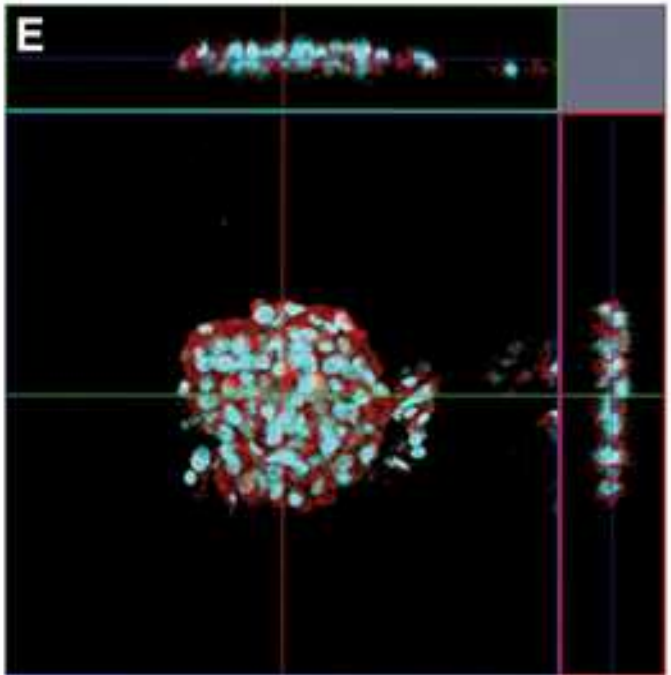
Biopsie pulmonaire Dr Marianne Kambouchner Avicenne

Granulomes épithélioïdes et sarcoidose

Sanchez et al. A 3-dimensional in vitro model of epithelioid granulomas induced by high aspect ratio nanomaterials
Particle and Fibre Toxicology 2011, 8:17



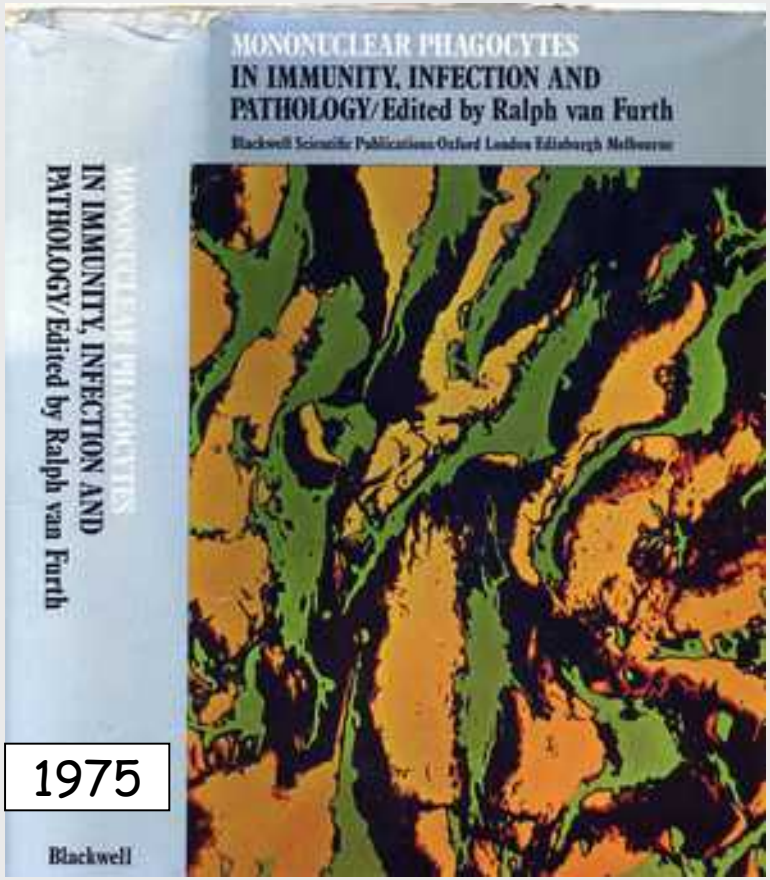




Wang et al.
Formation of granuloma-like cellular aggregates by co-culture of PBMCs and macrophages infected with M. leprae.
BMC Infectious Diseases 2013, 13:279

- *Granuloma is characterized by a core of monocyte-derived epithelioid histiocytes and multinucleate giant cells with interspersed CD4+T lymphocytes. A minority of cells near or by the granuloma are CD8+ T Ly, Treg, fibroblasts and B-Lymphocytes*

Baughman R, et al AJRCCM 2011



- *Adams DO*
  The granulomatous inflammatory response . A review. Am J Pathol 1976
- *Spector WG*
  The granulomatous inflammatory exudate Int Rev Exp Pathol 1969
- *Cohn ZA The structure and function of monocytes and macrophages Adv Immunol 1968*

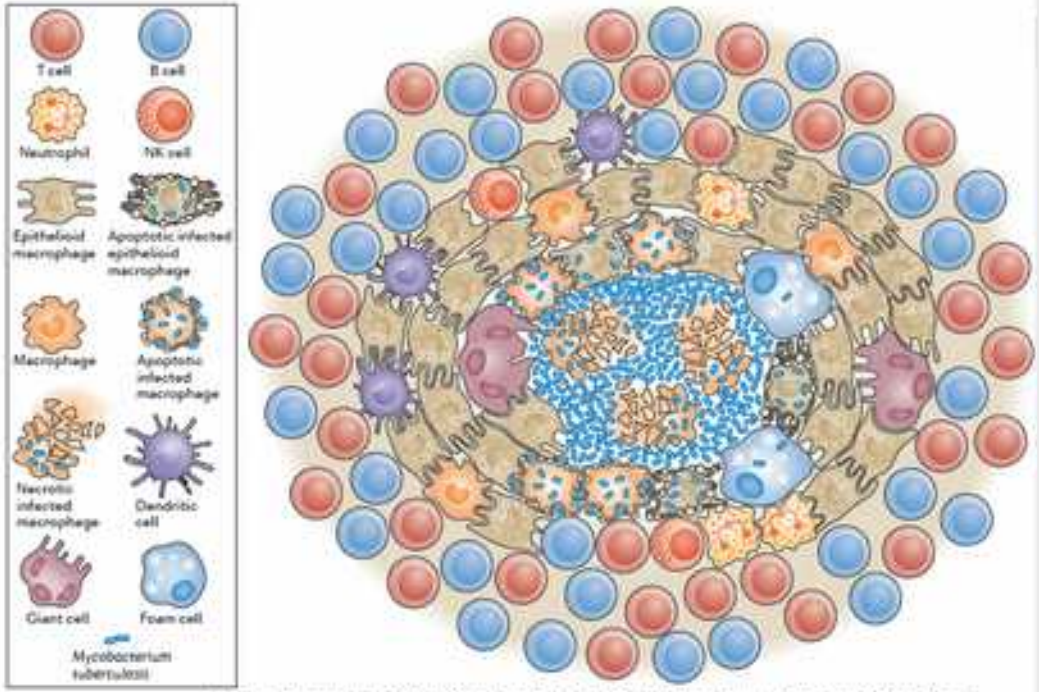
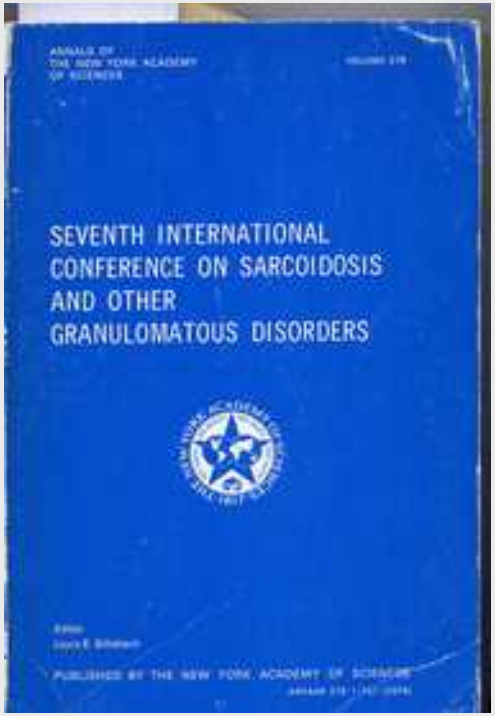


Figure 1 | **Structure and cellular constituents of the tuberculous granuloma.** The tuberculous granuloma at its most basic is a compact, organized aggregate of epithelioid cells — macrophages that have undergone a specialized transformation to have tightly interdigitated cell membranes that link adjacent cells. Epithelioid cells can be highly phagocytic but in some cases do not contain bacteria at all. Granuloma macrophages can also fuse into multinucleated giant cells or differentiate into foam cells, which are characterized by lipid accumulation. Foam cells have been noted to be most frequently located at the rim of the necrotic centre of a mature tuberculous granuloma. The consequences of these changes are not well understood, but in general foam cells and multinucleated giant cells have been reported to contain only a few bacteria, if any. Bacteria are most commonly present in the central necrotic areas in which dead and dying macrophages can be seen. Many other cell types also populate the granuloma, such as neutrophils, dendritic cells, B and T cells, natural killer (NK) cells, fibroblasts and cells that secrete extracellular matrix components. Finally, the epithelial cells surrounding the granuloma (not shown) are now thought to participate in its formation also.

L Ramakrishnan Nature Rev Imunol 2012

1976



MORPHOLOGY AND DISTRIBUTION OF THE CELLS OF A SARCOID GRANULOMA: ULTRASTRUCTURAL STUDY OF SERIAL SECTIONS

P. Soler and F. Basset

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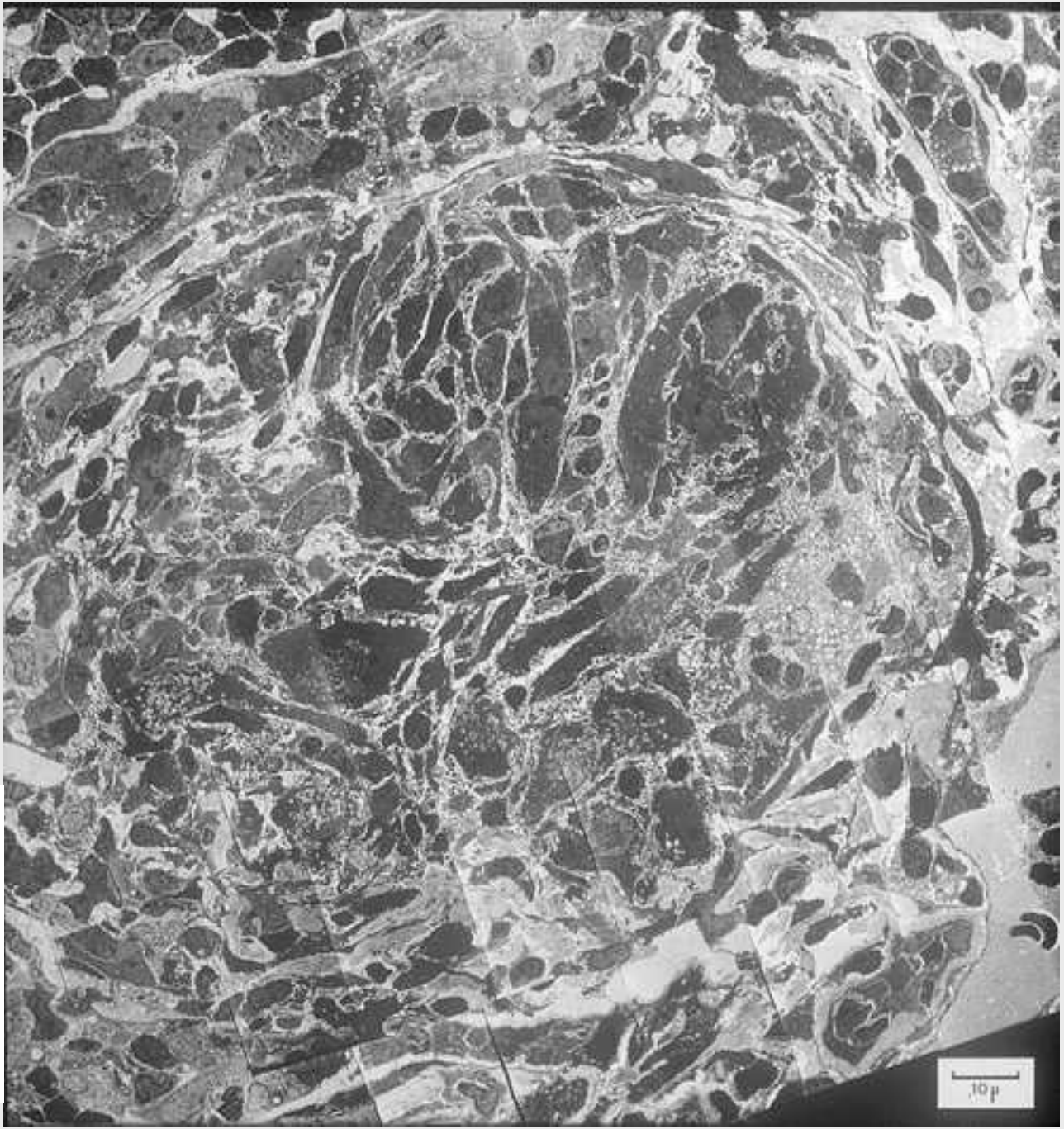
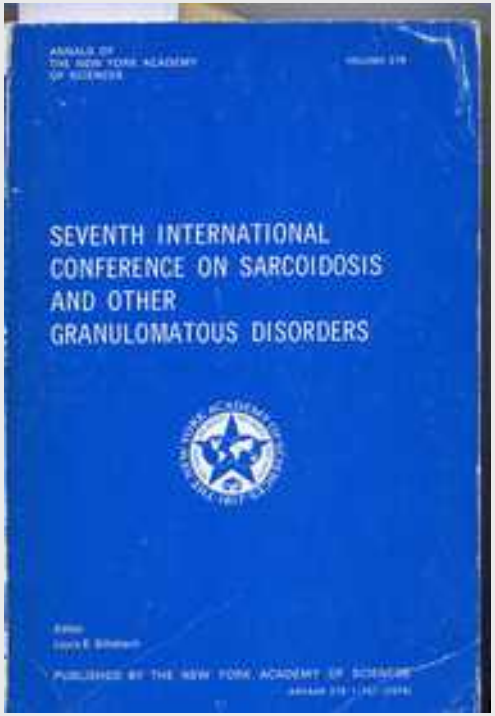
Hôpital Bichat
Paris, France

J. F. Bernaudin and J. Chretien

Laboratoire de Pathologie Pulmonaire
Université Créteil-Val de Marne
Créteil, France



1976



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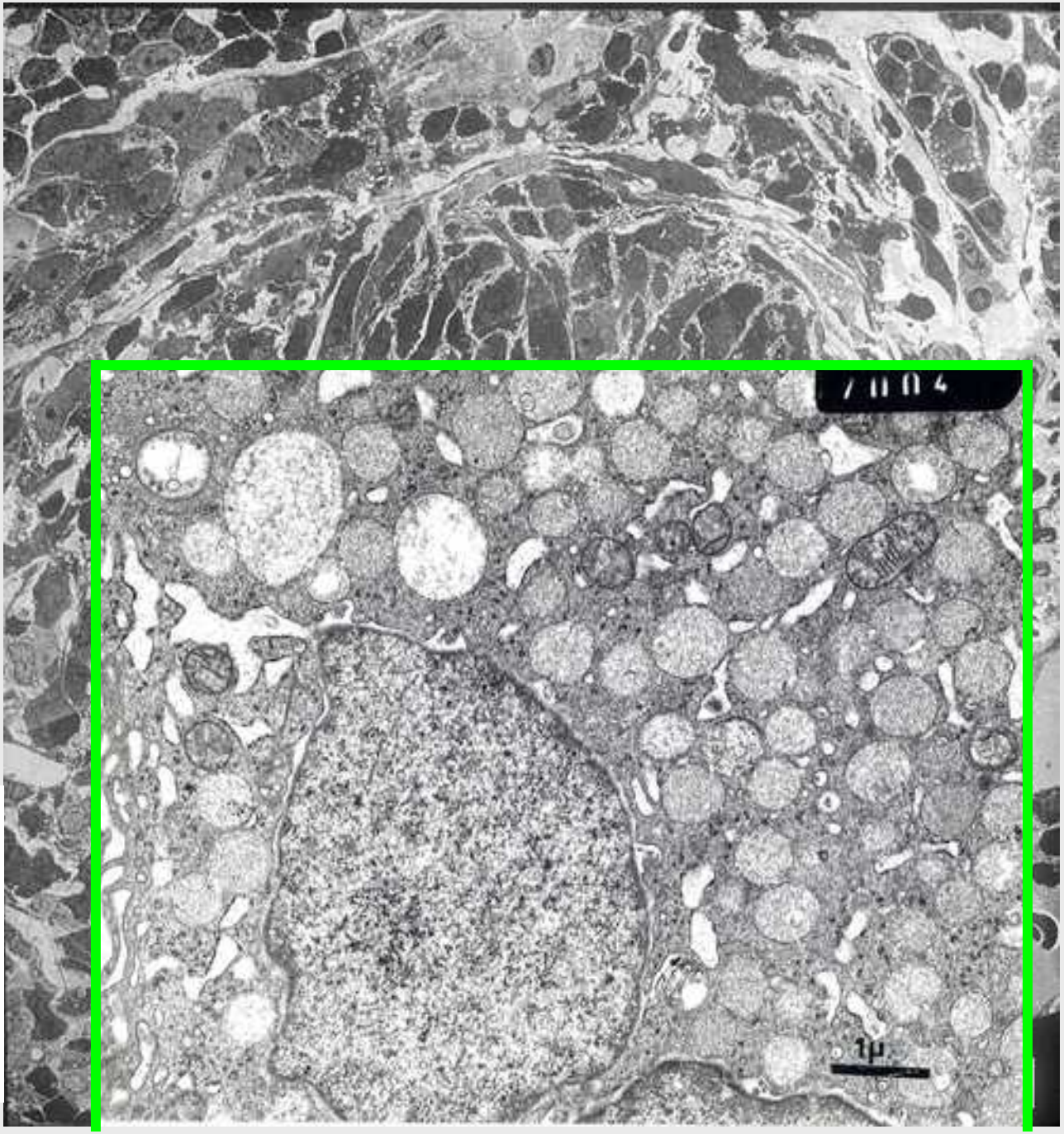
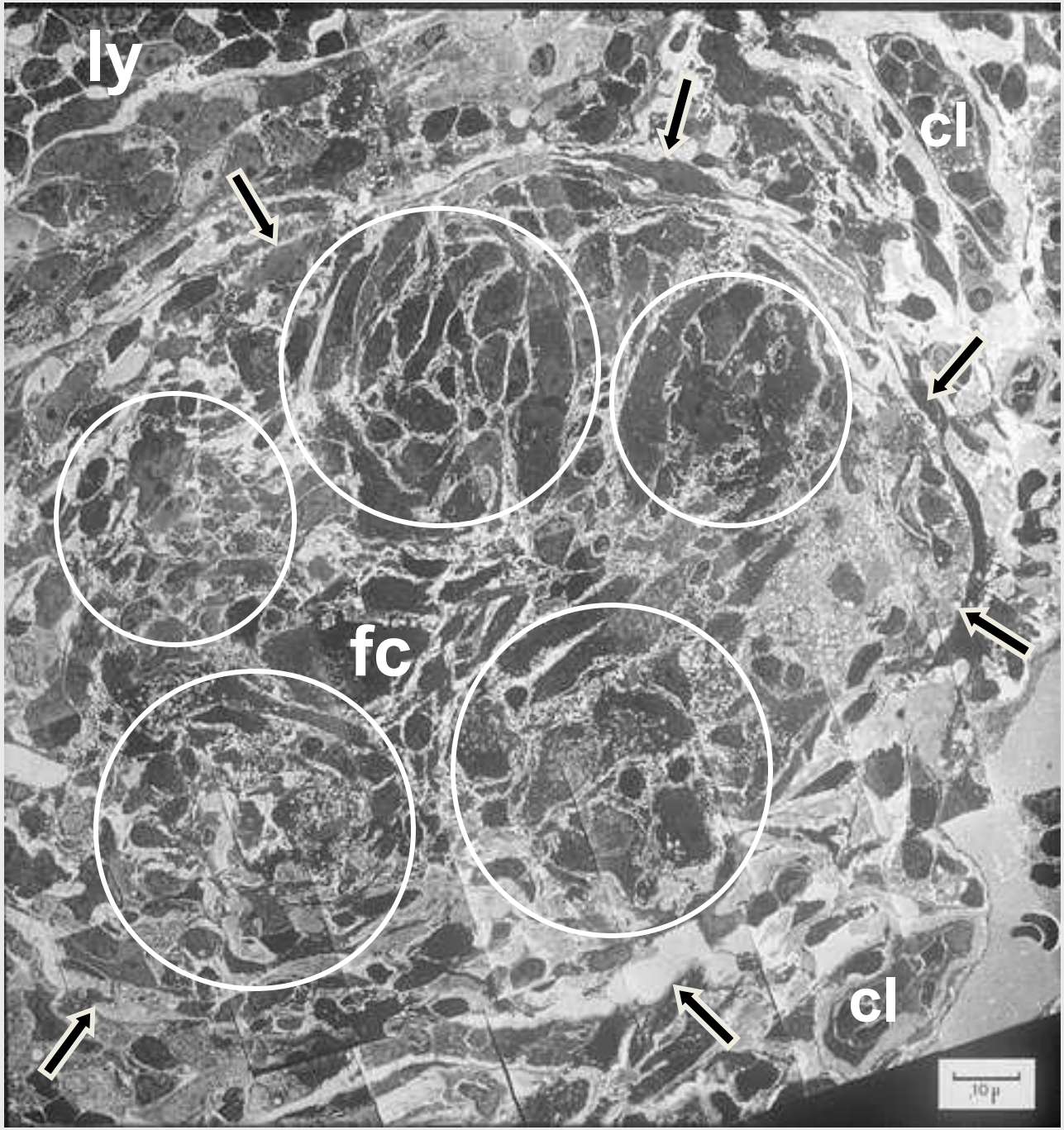
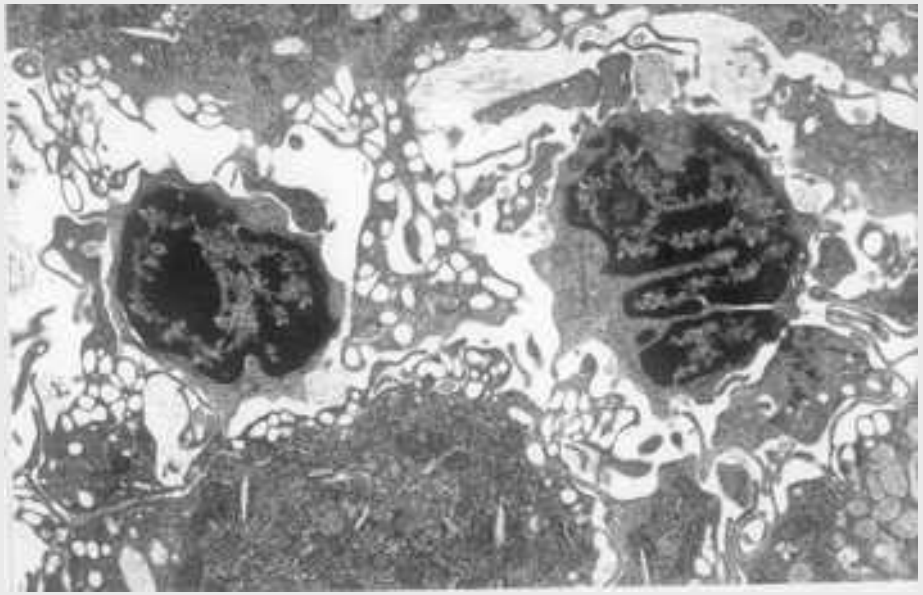
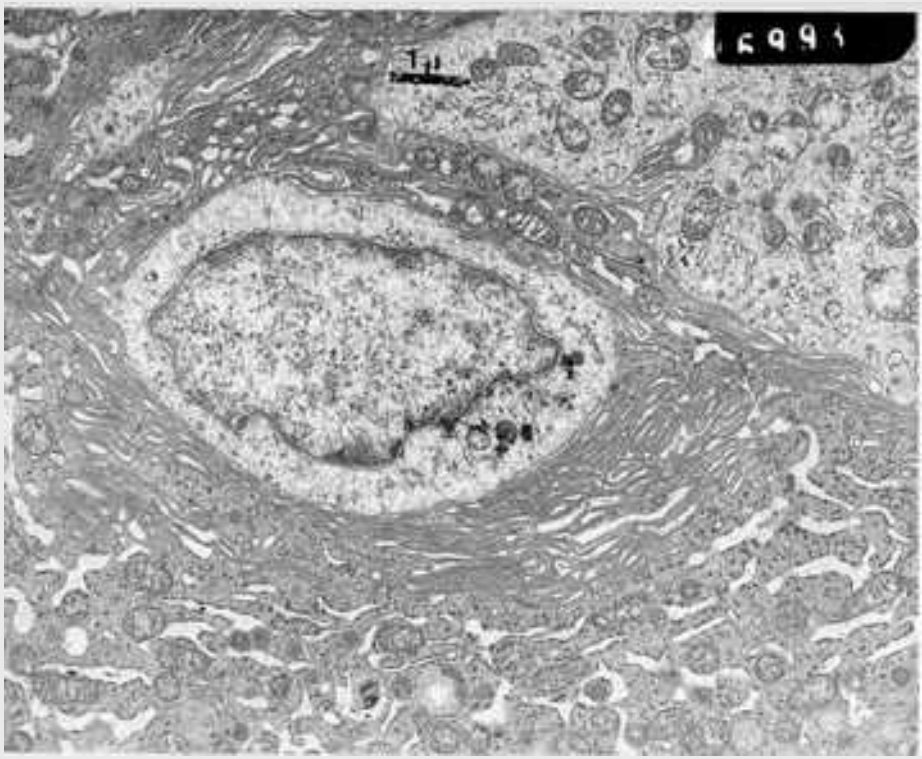
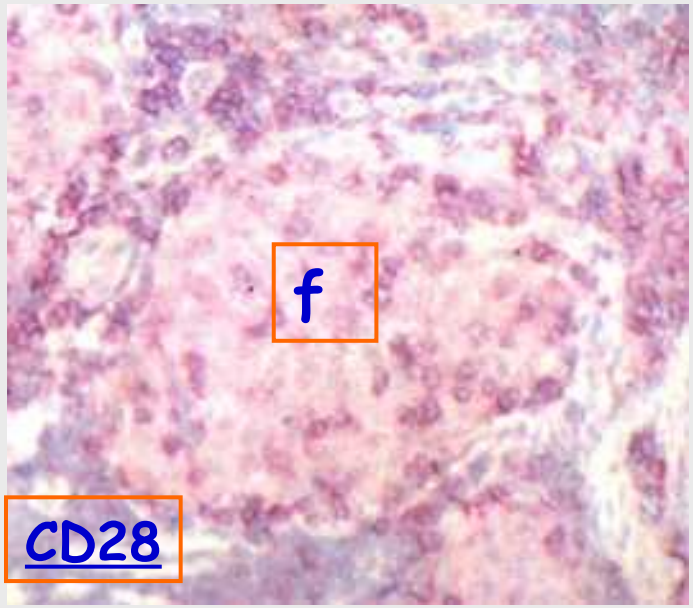




P Soler



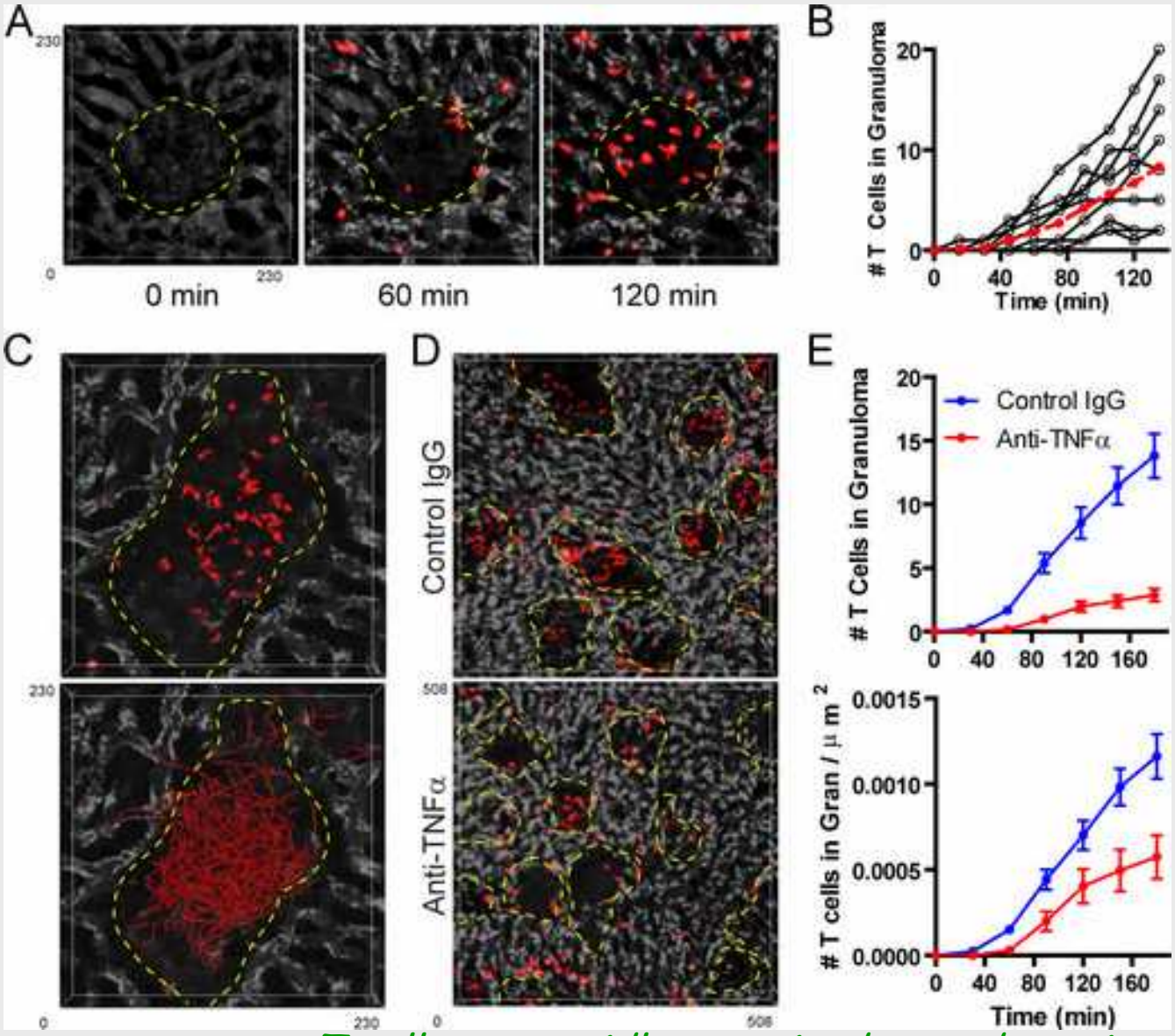




lymphocytes CD4+ / CD45RO+ / □ □
exprimant le CD28 ligand de CD80, CD86

P Soler

P Soler,



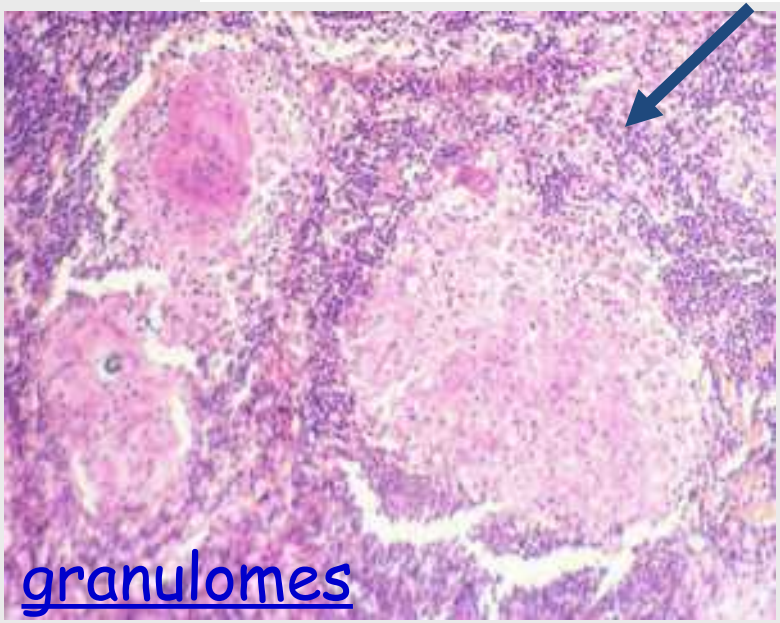
T cells are rapidly recruited to and retained within BCG induced liver granuloma structures
Egen JG et al. Immunity 2008

ALVEOLITIS AND GRANULOMAS: SEQUENTIAL COURSE IN PULMONARY SARCOIDOSIS

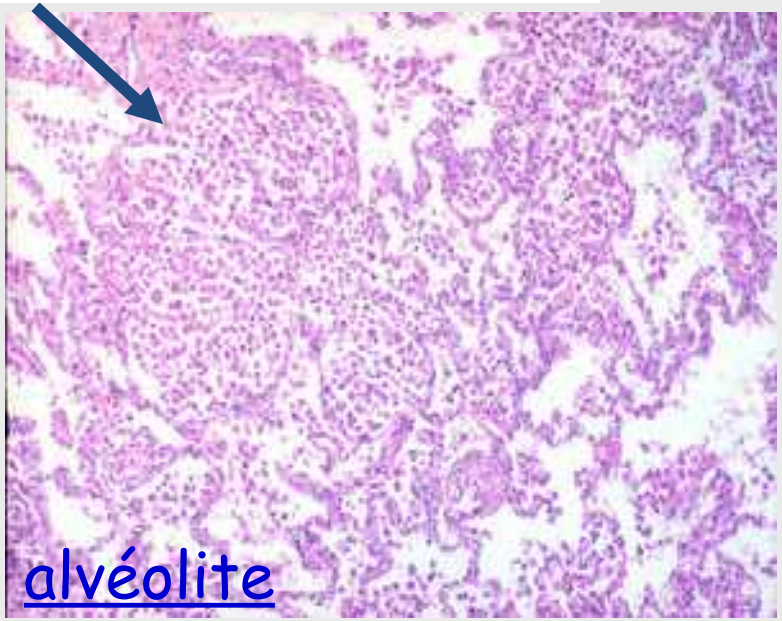
J. LACRONIQUE*, J.-F. BERNAUDIN**, P. SOLER***, F. LANGE**, O. KAWANAMI†, G. SAUMON***, R. GEORGES***, F. BASSET***

* INSERM U. 214, Hôpital Laennec, Paris, France. ** Service d'Histologie, Département de Pathologie, ERA-CNRS 845, Université Paris-Val de Marne, Hôpital Henri-Mondor, Créteil, France. *** INSERM U. 82, Hôpital Bichat, Paris, France. † Pulmonary Branch and Pathology Branch, NHLBI-NIH, Bethesda MD, USA.

Sarcoidosis (1987) Vp 36-42 Pergamon Press



granulomes



alvéolite

Hunninghake GW, Crystal RG. Pulmonary sarcoidosis: a disorder mediated by excess helper T-lymphocyte activity at sites of disease activity. N Engl J Med. 1981 Aug 20;305(8):429-34.

TABLE 3. T-CELL SUBSETS AND CCR5+ LYMPHOCYTES AND MACROPHAGES IN BAL IN THE STUDY POPULATION*

	Control Subjects ($n = 18$)	Sarcoidosis Stage I ($n = 12$)	Sarcoidosis Stage II ($n = 9$)	Sarcoidosis Stage III ($n = 9$)	Kruskal-Wallis p
CD4+, %	40.1 (26.0–48.0)	68.4 (54.2–87.8)†	54.6 (30.2–68.9)†	45.5 (20.2–64.0)	0.0004
CD8+, %	26.4 (13.1–30.3)	14.3 (6.1–45.0)	25.0 (12.0–31.1)	41.0 (29.4–48.6)‡	0.0001
CD4+/CD8+	1.6 (0.9–2.4)	4.9 (1.9–10.3)†	2.1 (1.2–5.3)	1.2 (0.5–1.7)	0.0001
ly CCR5 +, %	20.5 (2.0–40.0)	82.5 (75.0–97.2)†	80.0 (67.0–92.4)†	64.2 (55.0–82.4)†	0.0001
AM CCR5 +, %	2.75 (0–25.8)	53.8 (39.0–65.0)†	43.5 (29.8–62.4)†	31.4 (25.0–42.1)†	0.0001

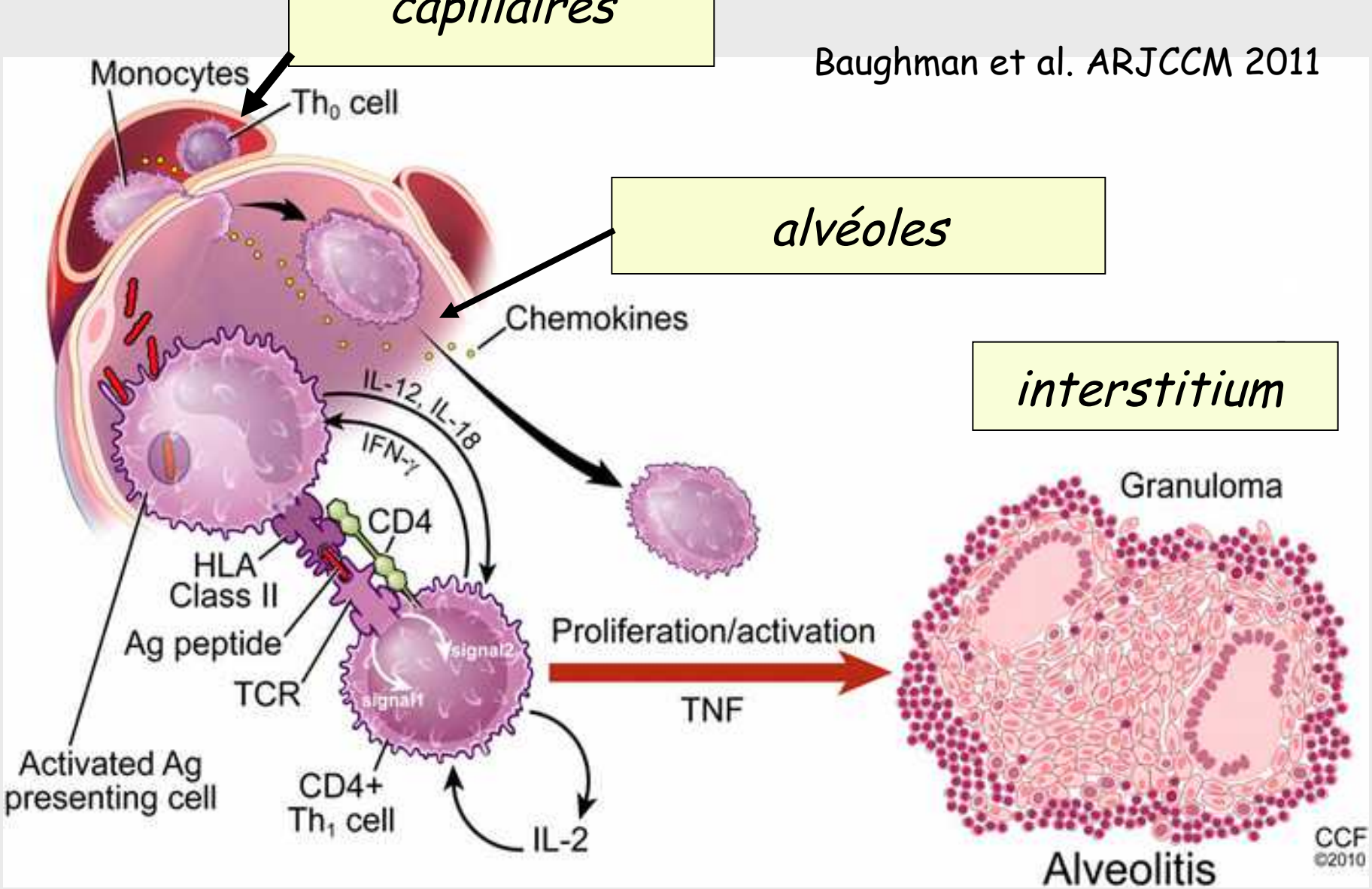
Definition of abbreviations: AM = alveolar macrophages; ly = lymphocytes.
* Values are medians (range).
Mann-Whitney U test analysis: †$p < 0.001$ versus controls; ‡$p < 0.01$ versus the other groups.

TABLE 2. CHARACTERISTICS OF BAL FROM THE STUDY POPULATION*

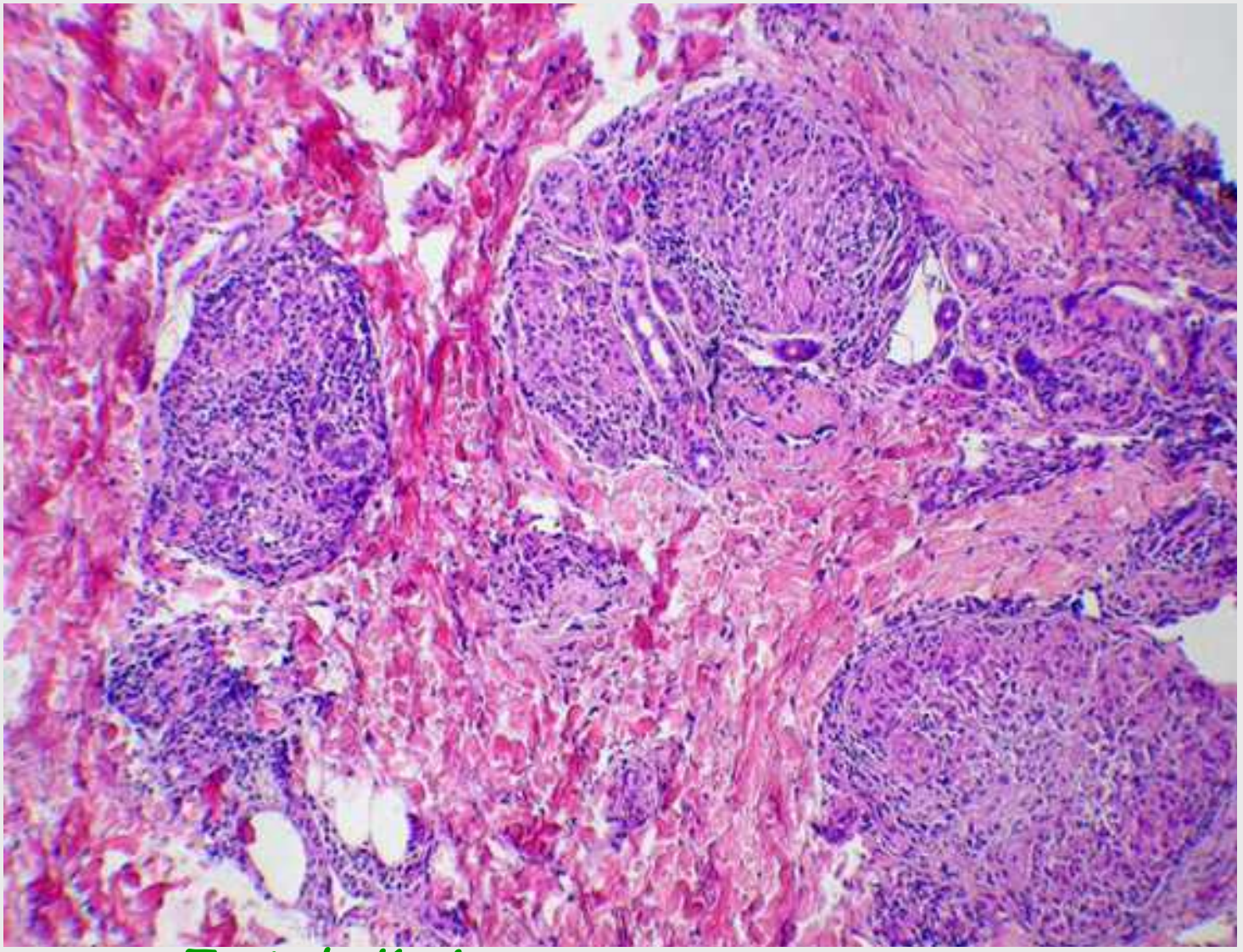
	Control Subjects ($n = 18$)	Sarcoidosis Stage I ($n = 12$)	Sarcoidosis Stage II ($n = 9$)	Sarcoidosis Stage III ($n = 9$)	Kruskal-Wallis p
Recovery, ml	84 (63–102)	89 (64–95)	83 (67–97)	84 (62–100)	0.021
Cell/ml × 10^3	125.1 (54.6–245.4)	290.9 (129.3–398.1)	173.2 (105.9–492.6)	233.2 (90.9–481.4)	0.0006
Macrophages, %	90.5 (74.3–95.6)	59.3 (35.7–85.6)	51.5 (22.0–85.2)	66.2 (29.3–81.3)	0.0001
Lymphocytes, %	8.5 (2.2–23.1)	39.3 (13.3–63.7)§	46.2 (11.7–73.5)§	18.3 (13.9–46.0)§	0.0001
Neutrophils, %	1.5 (0.2–2.8)	1.7 (0.2–5.8)	3.6 (1.7–10.2)†	6.8 (2.1–21.4)†	0.004
Eosinophils, %	0.3 (0–1.1)	0.3 (0–0.7)	0.6 (0–2.4)‡	2.1 (0.1–3.3)‡	NS
Basophils, %	0.1 (0–0.9)	0.1 (0–0.4)	0.1 (0–0.9)	0.1 (0–1.3)	NS
Macrophages/ml × 10^3	105.6 (46.4–234.1)	172.5 (69.7–325.6)	103.9 (39.9–265.9)	151.7 (54.3–292.5)	0.0035
Lymphocytes/ml × 10^3	8.0 (2.2–37.1)	69.7 (23.9–233.7)§	78.5 (15.9–362.0)§	53.9 (33.7–221.5)§	0.0001
Neutrophils/ml × 10^3	1.7 (0.2–5.4)	2.6 (0.7–12.7)	7.1 (2.9–28.5)†	11.6 (1.9–103.0)†	0.0004
Eosinophils/ml × 10^3	0.5 (0–1.4)	0.9 (0–2.8)	1.4 (0–11.8)‡	5.5 (0.4–15.6)‡	0.035
Basophils/ml × 10^3	0.1 (0–1.5)	0.1 (0–1.4)	0.3 (0–2.5)	0.4 (0–2.5)	NS

* Values are medians (range).
Mann-Whitney U test analysis: †$p < 0.005$, ‡$p < 0.01$ versus controls and sarcoidosis Stage I; §$p < 0.001$ versus controls.

Capelli A et al. AJRCCM 2002


capillaires
Baughman et al. ARJCCM 2011
Monocytes
Th0 cell
alvéoles
Chemokines
interstitium
IL-12, IL-18
IFN-γ
CD4
HLA
Class II
Ag peptide
TCR
signal2
signal1
Activated Ag
presenting cell
CD4+
Th1 cell
IL-2
Proliferation/activation
TNF
Granuloma
Alveolitis
CCF
©2010

- Sarcoidosis: antigen-induced disease? *(CE Broos et al 2013)*
  - *Epidemiology: environnemental and occupational risk factors (musty odors, insecticides) (Newman RS et al. ARJCCM 2004)*
  - *Kveim –Siltzbach test*
  - *Propionibacterium acnes and Mycobacterium tuberculosis genome detected in sarcoid tissues (Eishy y et al. 2002mais Bocart D et al 1992)*
  - *T Ly in BAL responsive to Kat-G ou ESAT-6 (Chen et al 2008)*
  - *Limited clonality CD4+Tcell with AV2S3 TCR(Grunewald J et al 2010)*



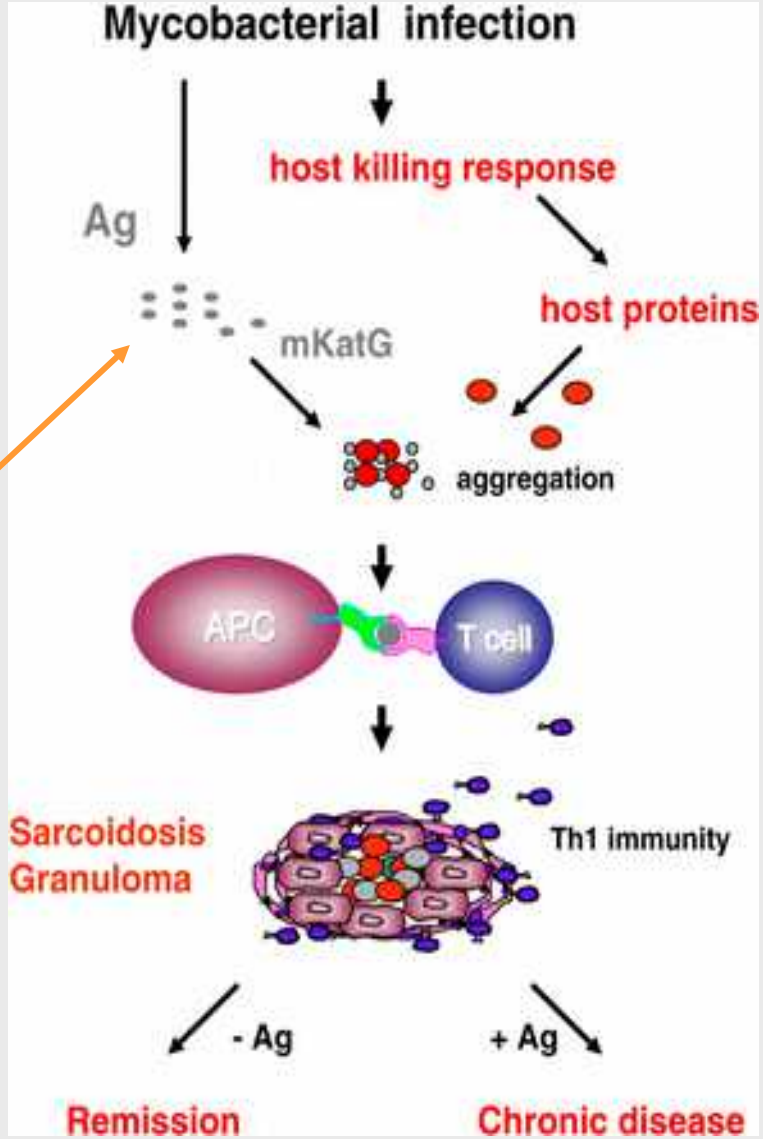
Test de Kveim

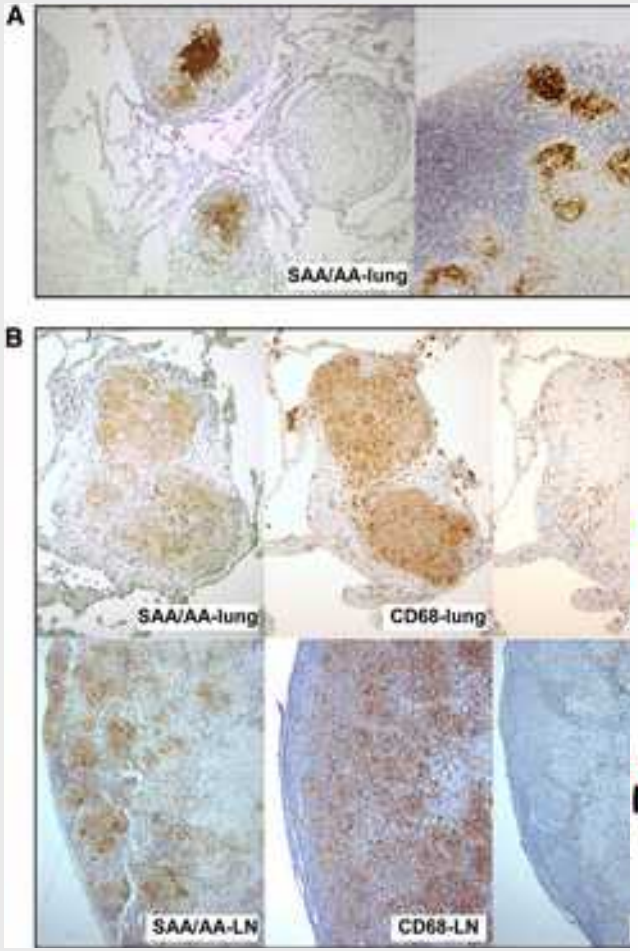
Morgenthau AS & Padilla ML 2009

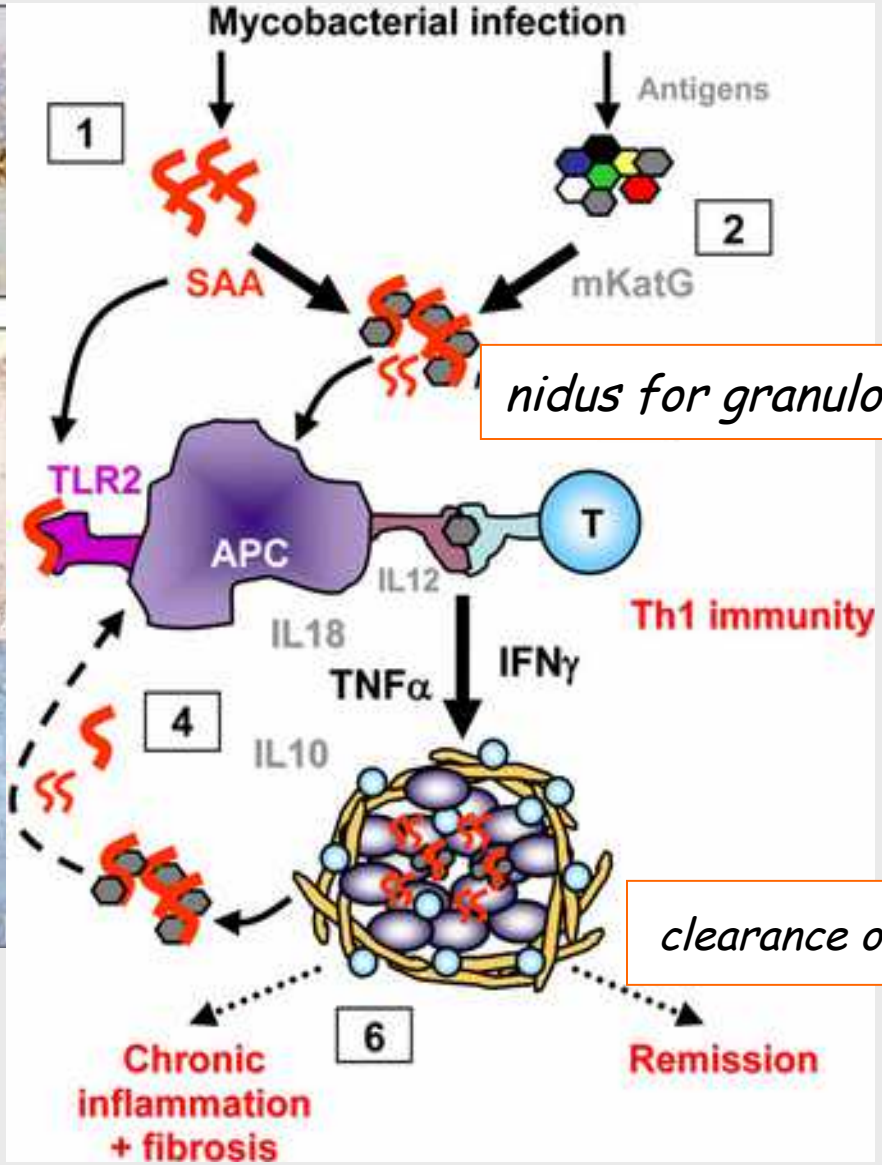
David R. Moller Potential etiologic agents in sarcoidosis

Proc Am Thorac Soc Vol 4. pp 465-468, 2007

mKatG protéine: catalase-peroxydase de mycobactérie







Serum Amyloid A regulates granulomatous inflammation in sarcoidosis through Toll-like Receptor 2
Chen ES …….Moller DR AJRCCM 2010

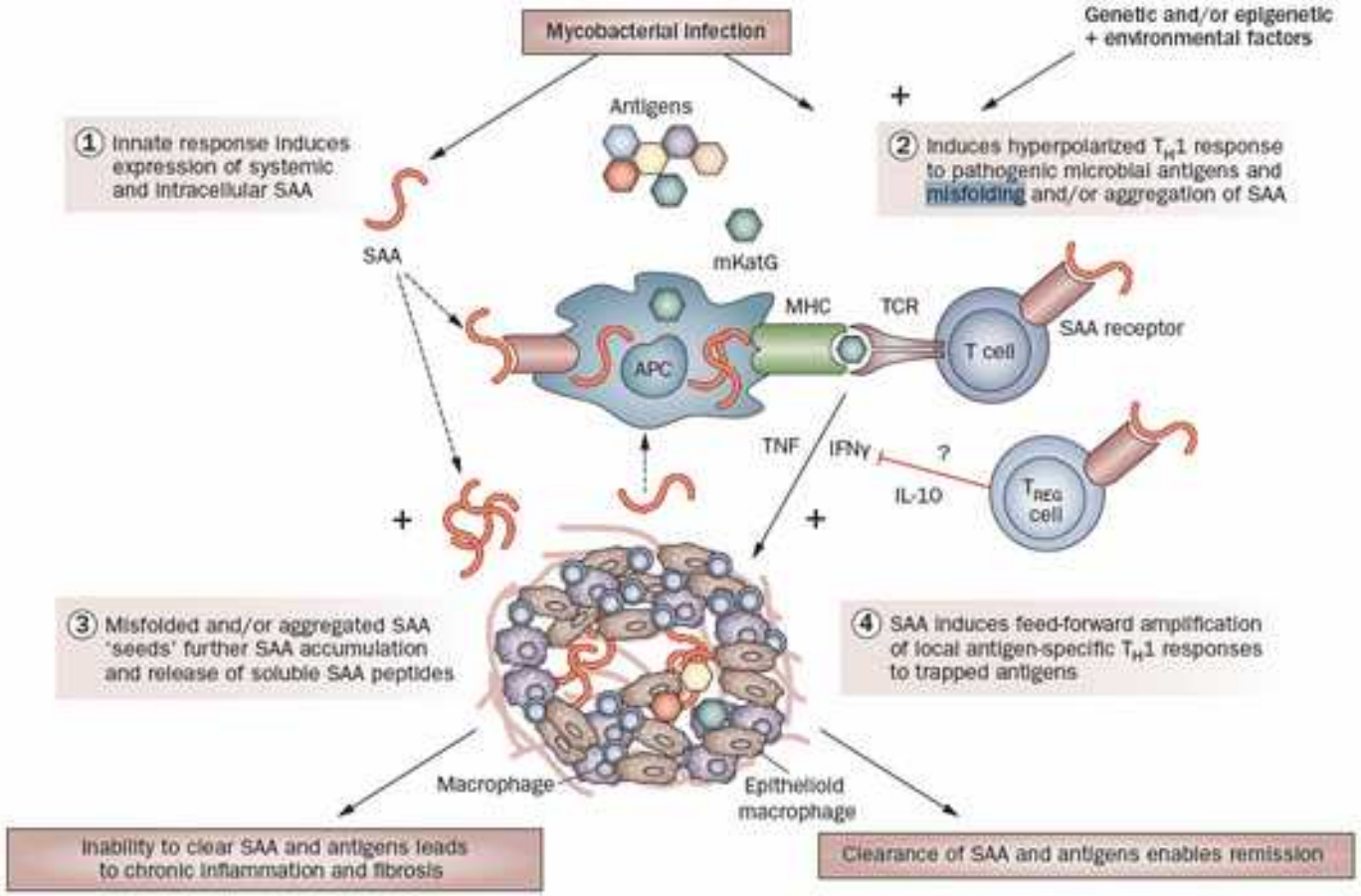


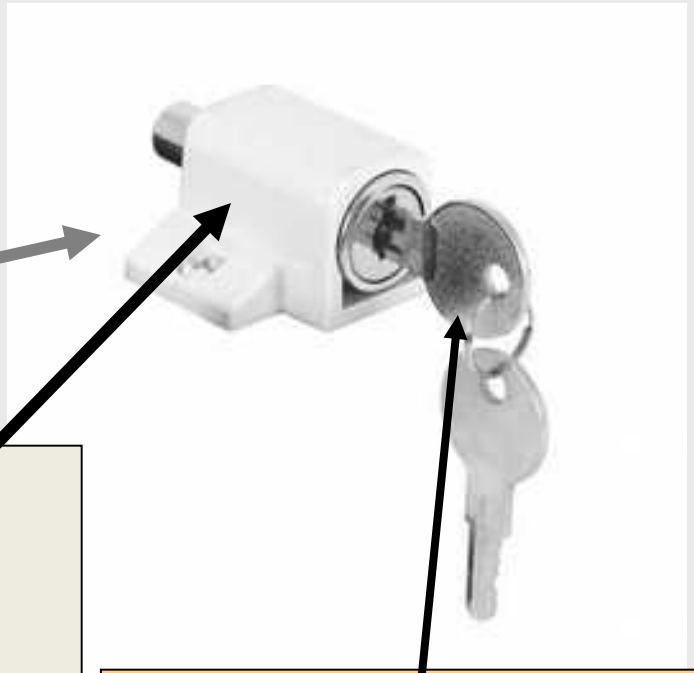
Figure 1 | Serum amyloid A misfolding hypothesis of the pathobiology of sarcoidosis. In this scenario, misfolded SAA aggregates serve as 'seeds', providing a poorly soluble nidus and a template for further SAA aggregation within sarcoidosis

Chen, E. S. & Moller, D. R. *Nat. Rev. Rheumatol.* 7, 457–467 (2011);

Antigène(s)

Ly T CD4+
Th1

Monocytes /
Macrophages



HLA-TCR

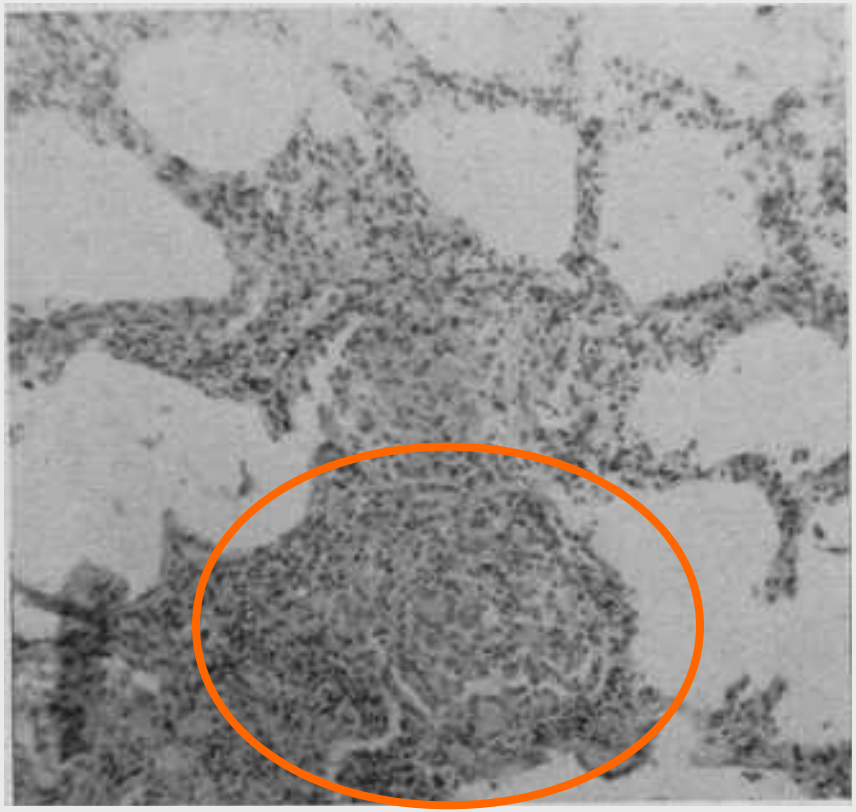
HLA-DRB1*1101 &HLA-DPB1*0101 risque x
HLA-DQB1
- HLA-DQB1*03 Lofgren/Suède
- HLA-DQB1*0201 bon pg (UK; Hollande)

Antigènes

Propionibacterium acnes
Mycobacterium tuberculosis
- mKatG protéine:
- catalase-peroxydase
- de mycobactérie (M. tuber.)

Song..Moller D 2005 JExp Med

*Kyra Oswald-Richter et al. Mycobacterial ESAT-6 and katG are recognized by sarcoidosis CD4+ T Cells when presented by the American Sarcoidosis Susceptibility Allele,DRB1*1101*
J Clin Immunol (2010) 30:157–166



PULMONARY GRANULOMATOSIS OF BERYLLIUM WORKERS

J. W. STURTRIDGE

Canad. M. A. J. Aug. 15, 1956, vol. 75

SUMMARY

Seven cases of spontaneous rupture of the oesophagus are reported and the salient points in diagnosis and treatment are outlined.

The results of experimental rupture of the human cadaveric oesophagus are given and a discussion of the mechanism of rupture suggests that it is due to a sudden rise of intra-abdominal pressure transmitted to a relaxed oesophagus, the outlet of which is obstructed.

Addendum.—Since this paper was submitted for publication a further case of spontaneous rupture of the oesophagus has been seen by one of us (M. K. T.) at St. George's Hospital, London. This was a female of 52 years with a spontaneous rupture of the oesophagus on the right side just below the arch of the azygos vein, who recovered after surgical repair. We would like to thank Mr. Siddons for permission to mention this patient.

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SKIN GRANULOMATA DUE TO BERYLLIUM OXIDE*

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We would like to emphasize the serious results that may follow the accidental introduction of beryllium into the skin. Two main varieties of beryllium skin disease are described by Tepper, Haedy, and Chamberlin (1961): (1) acute types including contact dermatitis and beryllium ulcer, which show non-specific histology and are due to soluble acid salts of beryllium; (2) subcutaneous granulomata which show a sarcoid-like lesion typical of chronic beryllium disease, and are usually caused by beryllium phosphors following injuries caused by broken fluorescent lamps. The majority of such skin granuloma cases have been reported from the United States (Tepper and others, 1961, p. 77) and a few similar cases from Great Britain by Lederer and Savage (1954) and Jordan and Darke (1958). One case has been reported following contamination with the pure metal (Dutra, 1949) and 2 cases following beryllium copper alloys (Sneddon, 1955, 1958).

We describe here the clinical and pathological features of what is thought to be the first case of beryllium skin granulomata due to beryllium oxide. This was in a man of 48 years who cut his right index finger on a grinding wheel contaminated with beryllium oxide. This eventually led to amputation of the finger and was then followed by lymphatic spread of beryllium to produce granulomata in the forearm.

CASE REPORT

Clinical Features.—The patient was first seen in a casualty department on 3 Sept., 1963, with what appeared to be a simple cut on the dorsal aspect of the proximal phalanx of the right index finger. This was caused by contact with a grinding wheel later found to have been contaminated with beryllium oxide (*vide infra*). The wound was cleaned and sutured, and after 1 week was apparently healed when the sutures were removed. One week later the lesion broke down, the wound edges became red and swollen, and it discharged pus. On culture of the pus there was a moderate growth of coagulase-positive *Staphylococcus aureus*, sensitive to penicillin and erythromycin. He was treated with an initial course of erythromycin followed by oral penicillin and dry dressing to the finger. A biopsy at this time (17 Oct.) from the base of the now ulcerated wound showed non-specific chronic inflammation.

* Accepted for publication March, 1966.

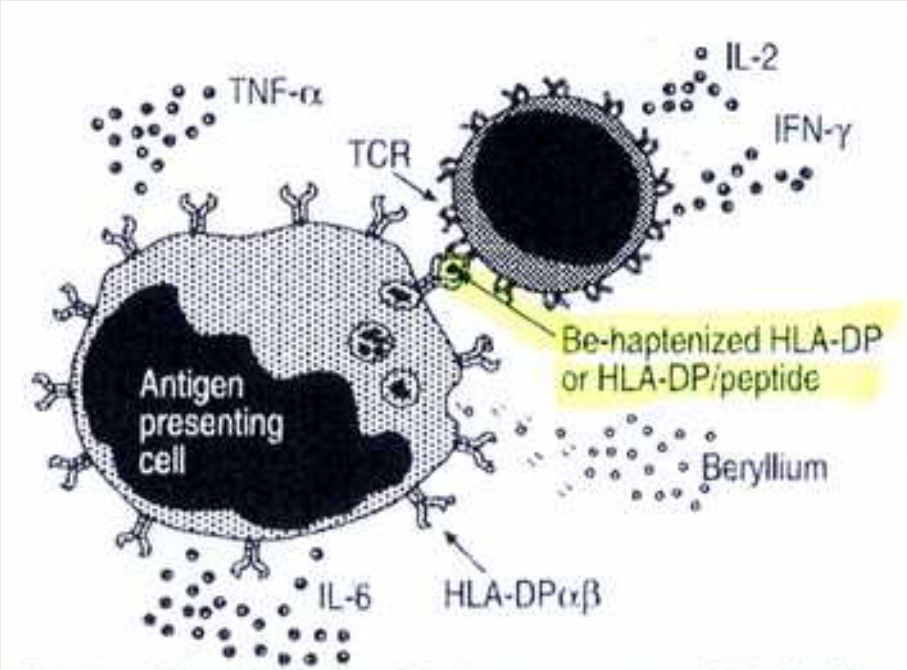
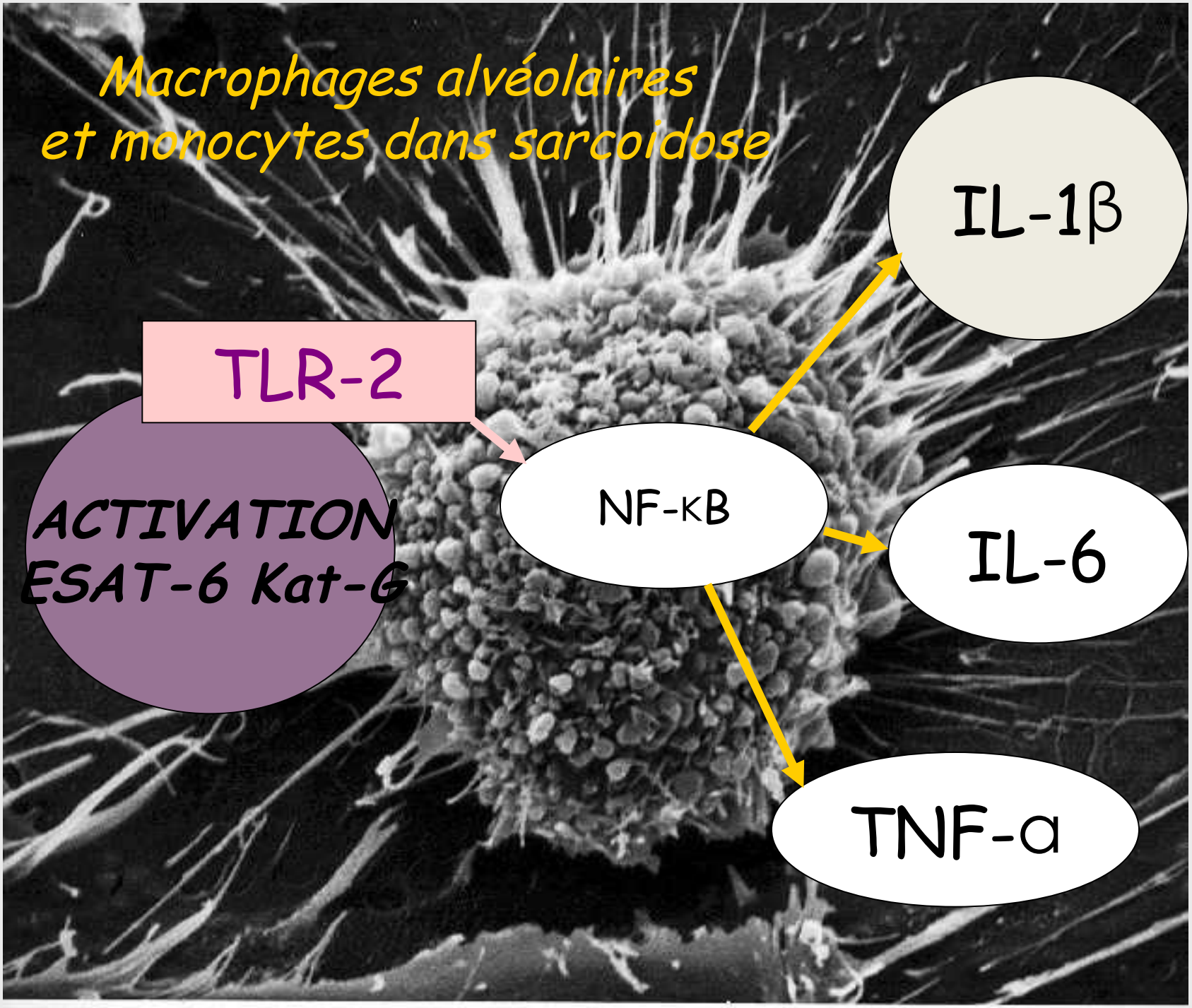


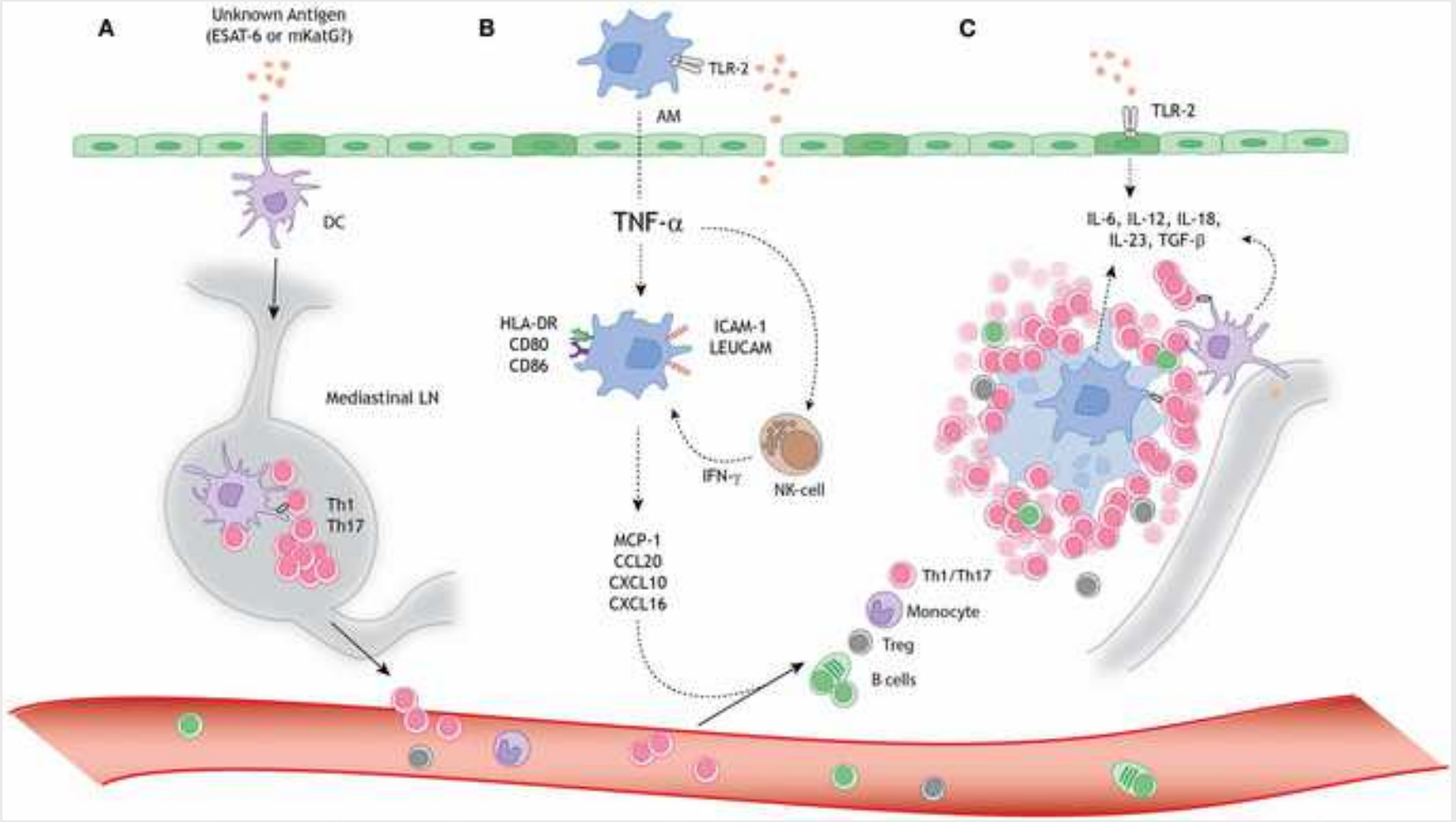
Fig. 4. – Schematic diagram of the immune response to Be in beryllio-sis. TNF-α: tumour necrosis factor-alpha; TCR: T-cell receptor; IL: interleukin; IFN-γ: interferon-gamma; HLA: human leukocyte antigen.

Saltini C et al ERJ 1988

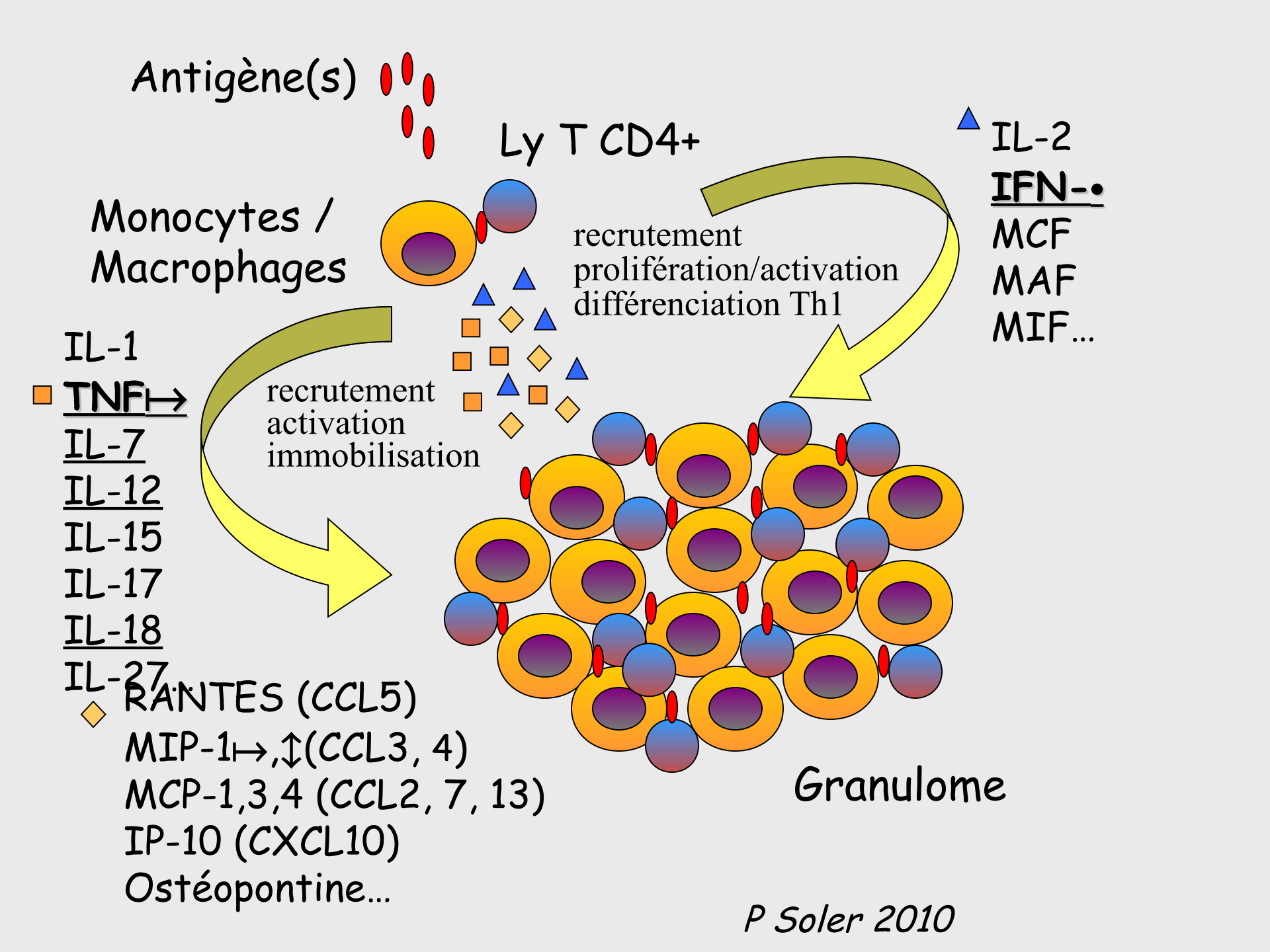
- *Beryllium specific MHC restricted antigen/hapten*
- *HLADPB1*0201 (HLADPGlu69 Chaine β)*

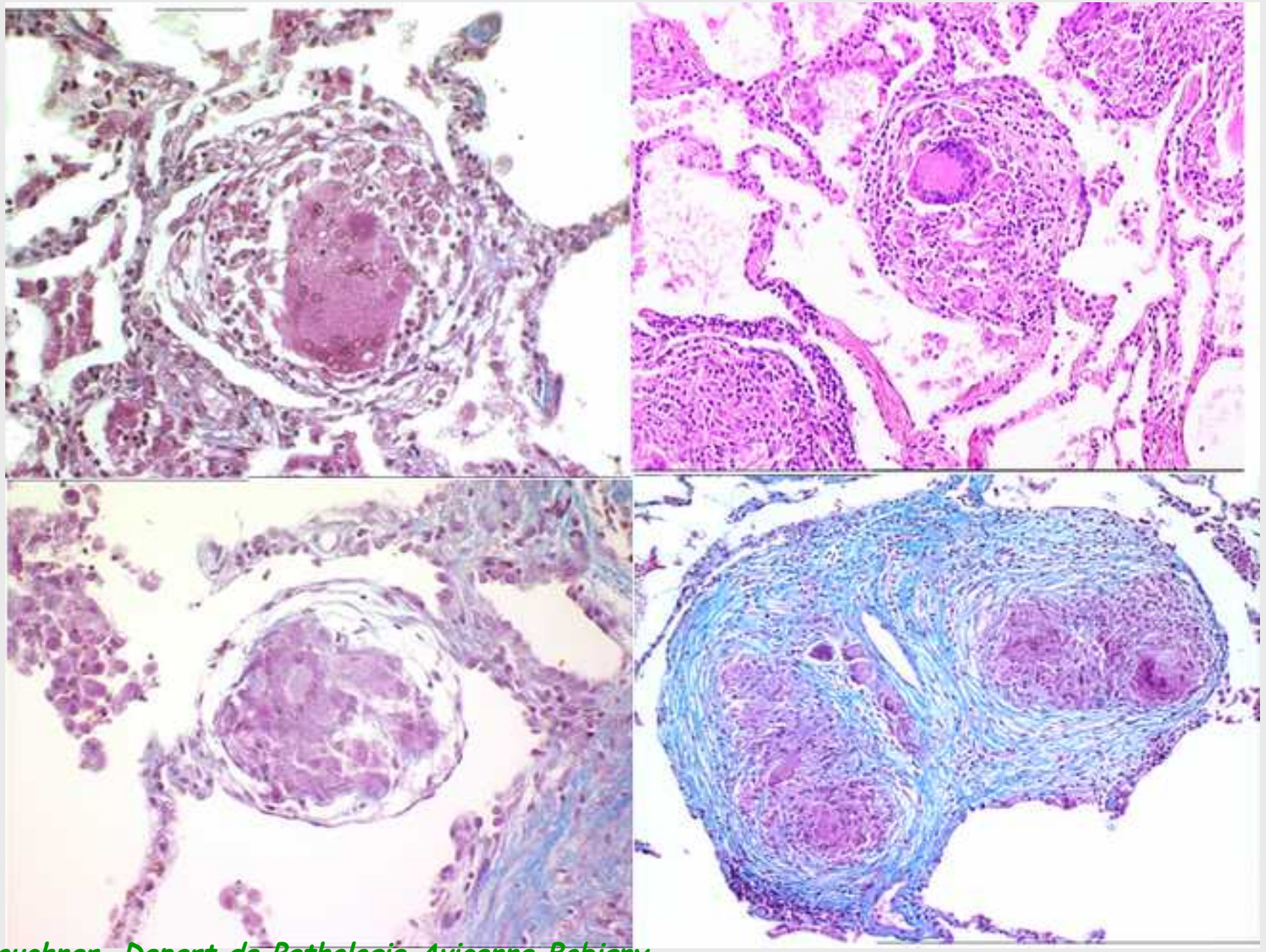
Richeldi l, Sorrentino P, Saltini C . Science 1993


Macrophages alvéolaires
et monocytes dans sarcoidose
IL-1β
TLR-2
ACTIVATION
ESAT-6 Kat-G
NF-κB
IL-6
TNF-α



Caroline E Broos et al. Frontiers Immunology 2013

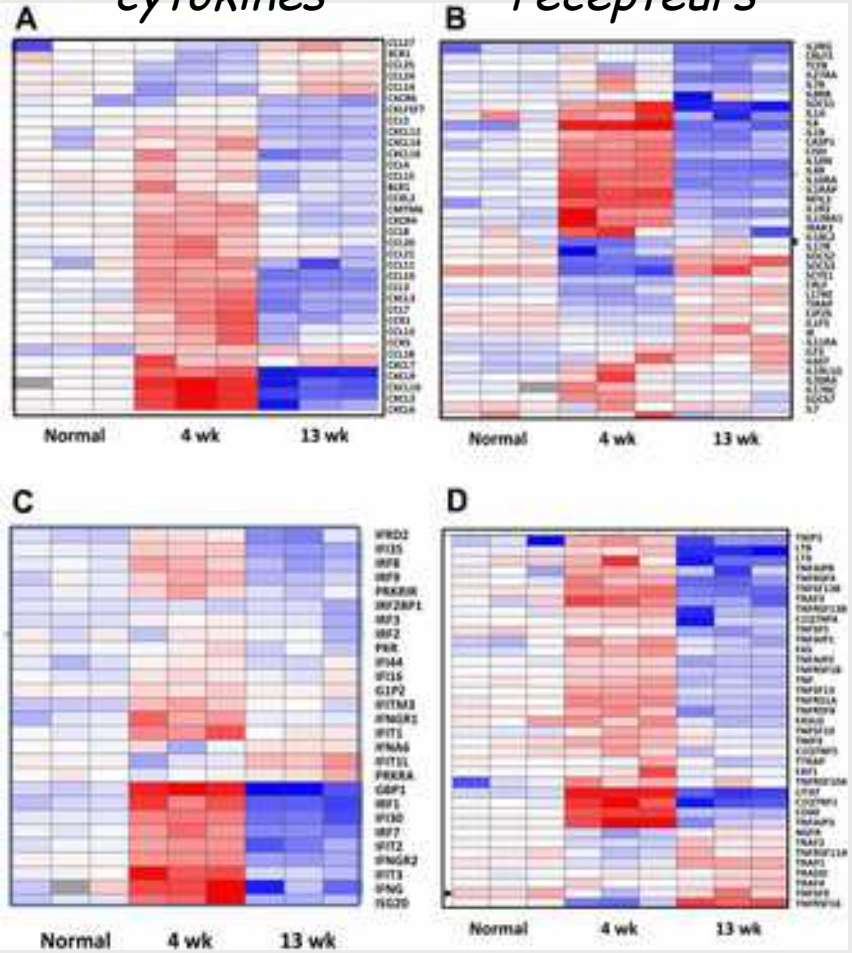

Antigène(s)
Ly T CD4+
IL-2
IFN-•
MCF
MAF
MIF…
Monocytes /
Macrophages
recrutement
prolifération/activation
différenciation Th1
IL-1
TNF↦
IL-7
IL-12
IL-15
IL-17
IL-18
IL-27
recrutement
activation
immobilisation
RANTES (CCL5)
MIP-1↦,↕(CCL3, 4)
MCP-1,3,4 (CCL2, 7, 13)
IP-10 (CXCL10)
Ostéopontine…
Granulome
P Soler 2010



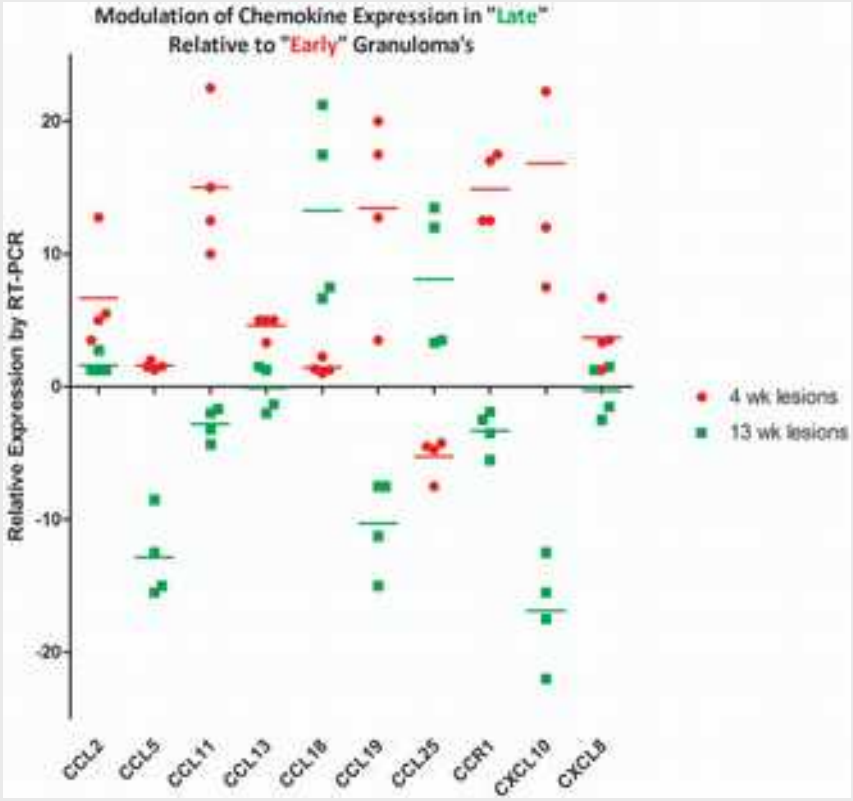
M Kambouchner, Depart de Pathologie Avicenne Bobigny

Transcriptional Reprogramming in Nonhuman Primate (Rhesus Macaque) Tuberculosis Granulomas. S Mehra et al PLoSONE 2010

cytokines *récepteurs*

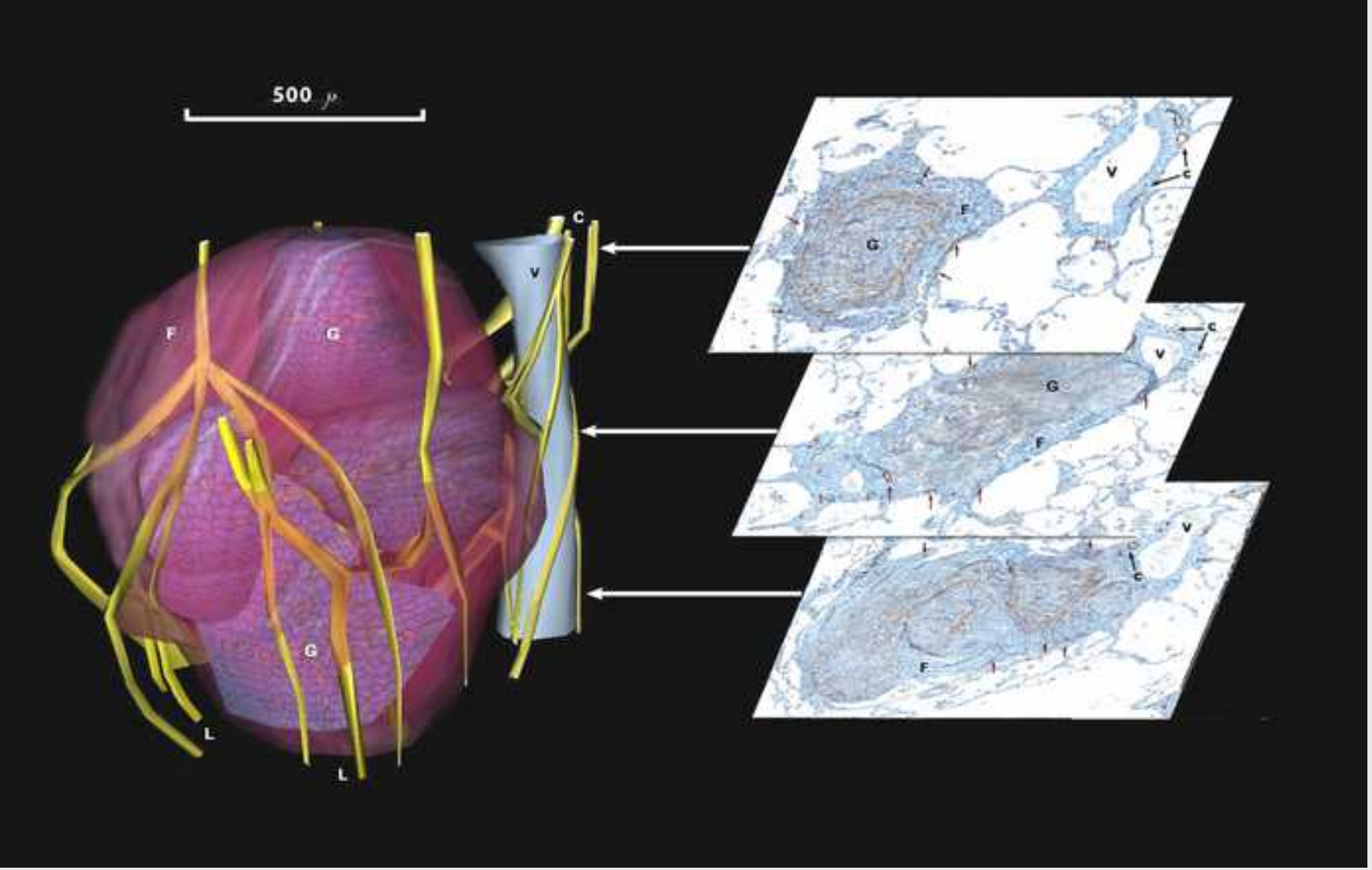


INFγ network *TNFα network*



Aspects histo identiques à 4 et 13 semaines!

En périphérie des granulomes:
lymphatiques



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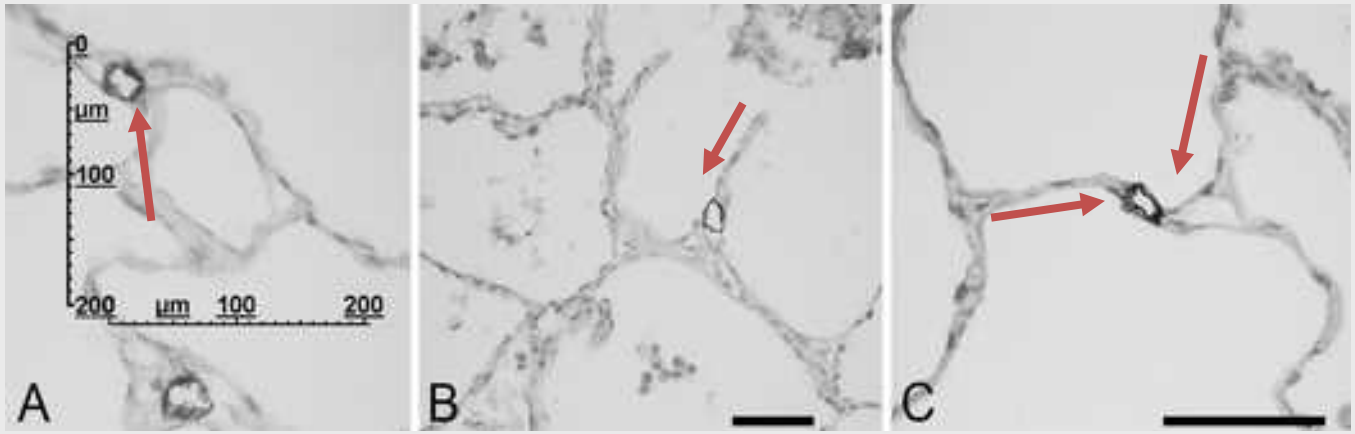


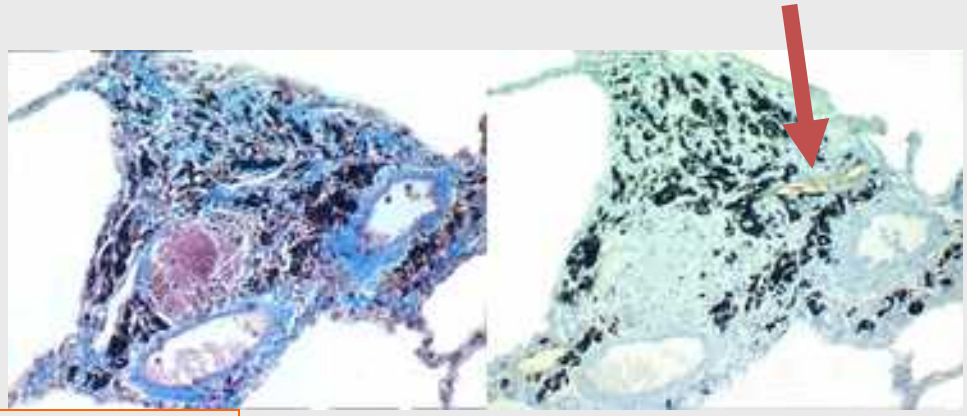
M Kambouchner & JFBernaudin
J Histochem Cytochem 2009

664 MACKLIN: LUNG FLUID

Canad M.A.J 1955

LUNG FLUID, ALVEOLAR DUST DRIFT, AND INITIAL LESIONS OF DISEASE IN THE LUNGS*

CHARLES C. MACKLIN, M.B., M.D., M.A., Ph.D., D.Sc., F.R.S.C., *Toronto*



« sumps » puisards, zones de vidange
« initial foci of a wide variety of disease condition » (mycobac, poussières)

Rev Mal Respir 2002, 19, 103-104.

LETTRE À LA RÉDACTION

Sarcoïdose et empoussièrement pulmonaire, une hypothèse pathogénique qui prend du crédit

Sarcoidosis and pulmonary dust exposure, a plausible pathogenic link

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(2) Département de pharmacologie clinique, Faculté de médecine Laennec, Lyon.

microparticules

- *Izbicki G, et al. World Trade Center "sarcoid-like" exposure to crystalline silica and risk of sarcoidosis . Occup Environ Med 1998*
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Annals of Diagnostic Pathology 11 (2007) 142–152

Annals of DIAGNOSTIC PATHOLOGY

nanoparticules

Review Article

The cause of sarcoidosis: the Centurial enigma solved

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Review

Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles

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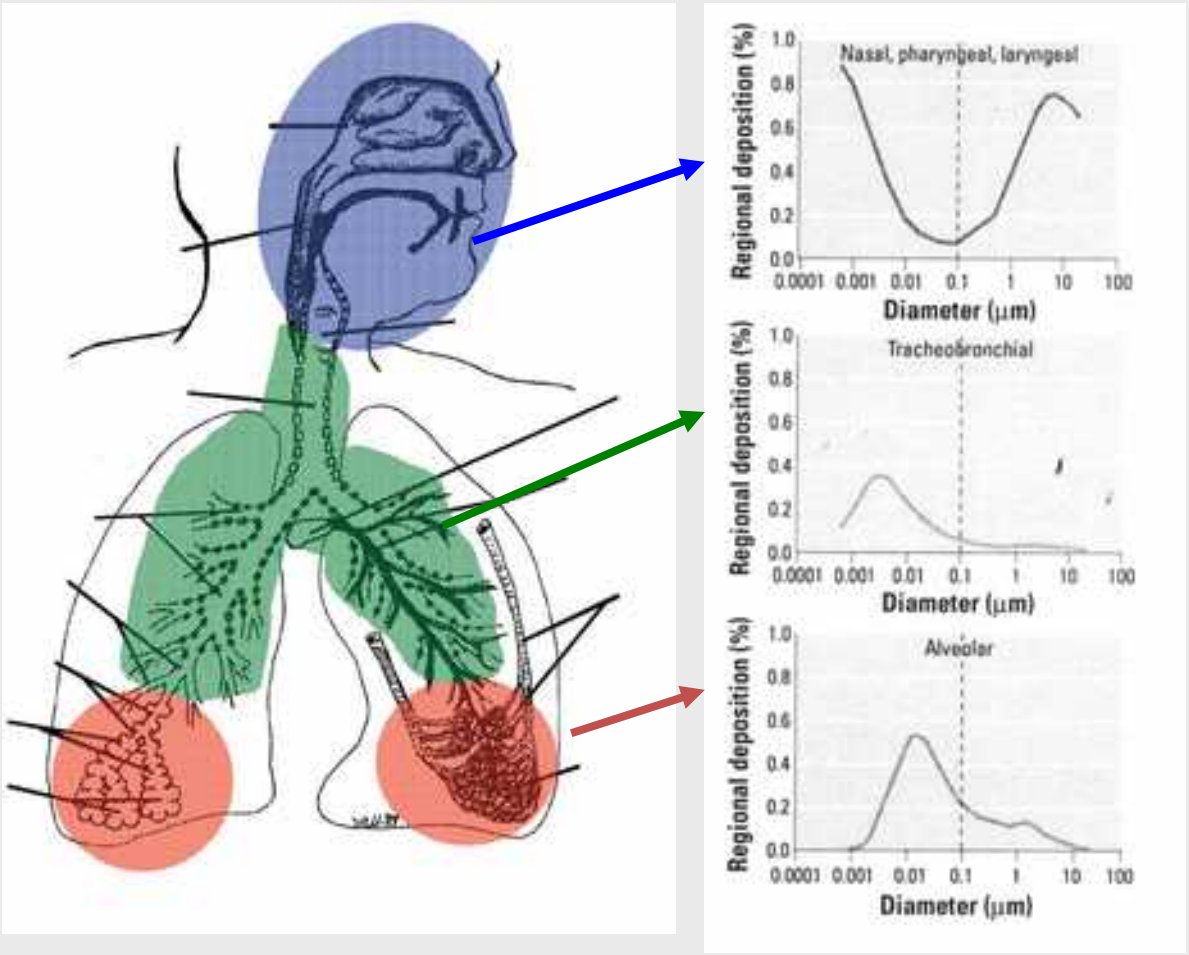
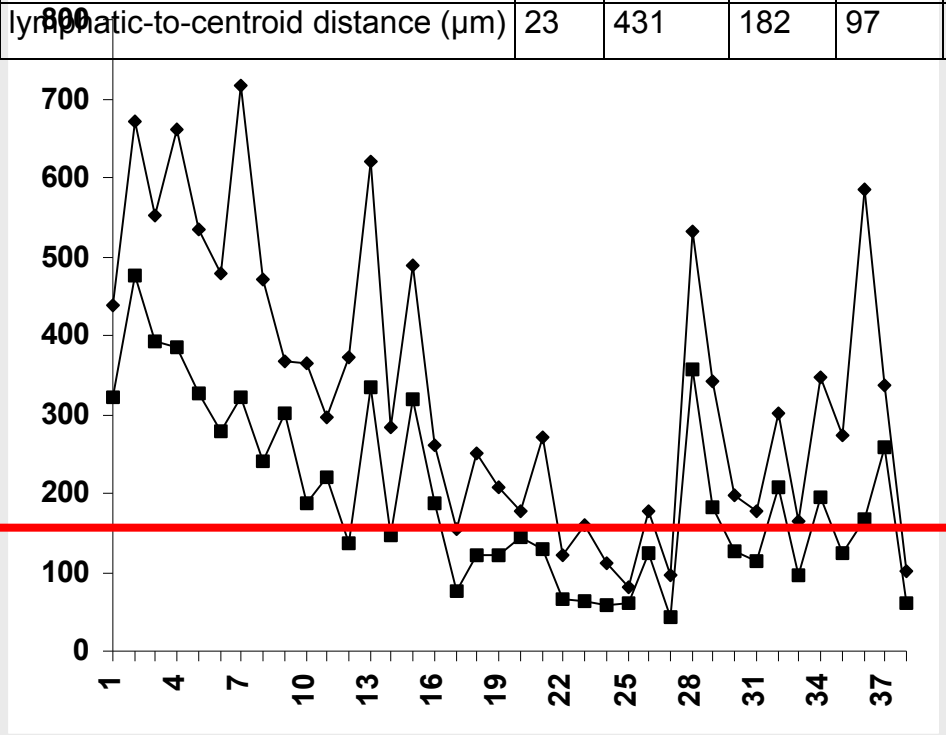


Table 1: Results of morphometric analysis of 38 selected intralobular granulomas chosen as being representative of this site.

	Min	Max	mean	SD±	median
minimum diameter (µm)	42	477	197	113	174
maximum diameter: (µm)	80	671	335	181	299
surface area (μm^2)	3677	249402	71748	70167	47742
perimeter (µm)	227	2215	991	573	873
sphericity index (SI)	0.58	0.97	0.86	0.07	0.88
lymphatics-to-edge distance (µm)	0	256	33	51	16.5
lymphatic-to-centroid distance (µm)	23	431	182	97	164



M Kambouchner et al. ERJ2011

- *« While there has been progress in sarcoidosis over the past few years, much is still unknown »*

  Baughman R, et al AJRCCM 2011

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