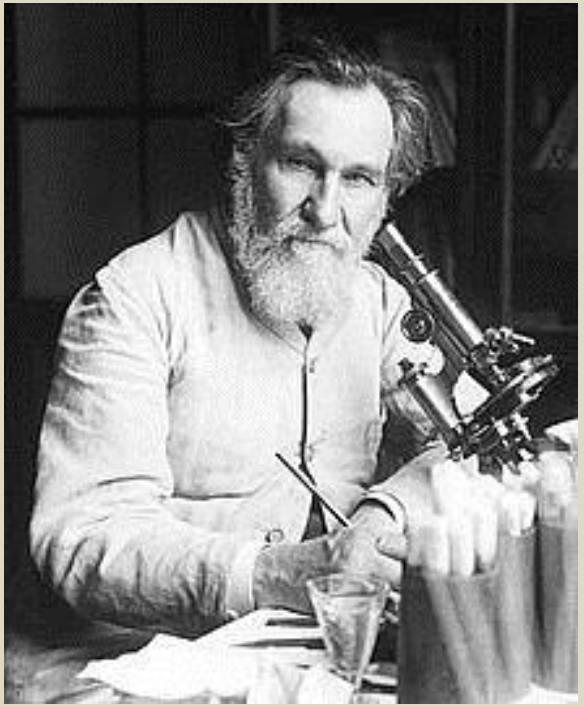
Le granulome revisité

JF Bernaudin. Janvier 2018

Sorbonne Université Médecine Paris 6
Pneumologie hôpital Avicenne Bobigny
EA2363 Université Paris 13

- *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

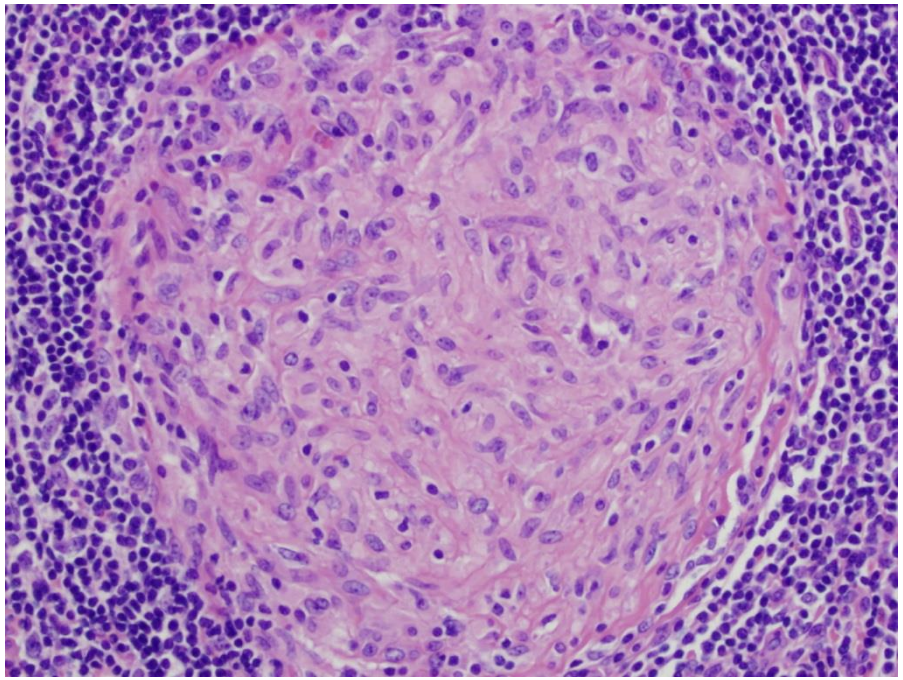


(Ilya Ilitch Metchnikov) Élie Metchnikoff, *(né le 15 mai 1845 à Ivanovka près de Kharkov, actuelle Ukraine et mort le 15 juillet 1916 à Paris). Avec Paul Ehrlich co-lauréat du Prix Nobel de physiologie ou médecine en 1908.*

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.*

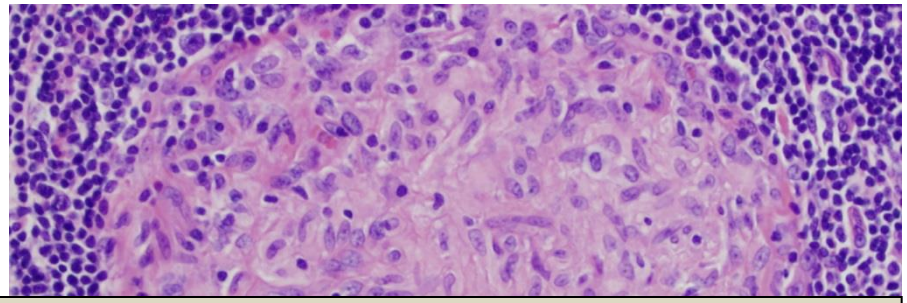


The granuloma in this picture was found in a lymph node of a patient with Mycobacterium avium infection

Granuloma

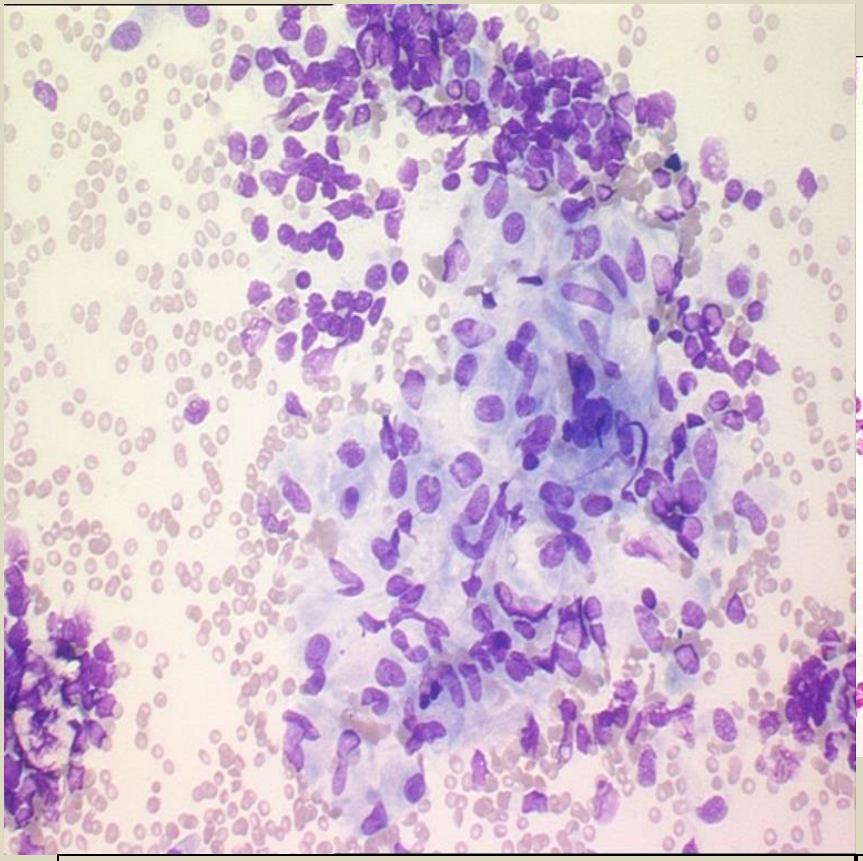
From Wikipedia, the free encyclopedia

- *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.*

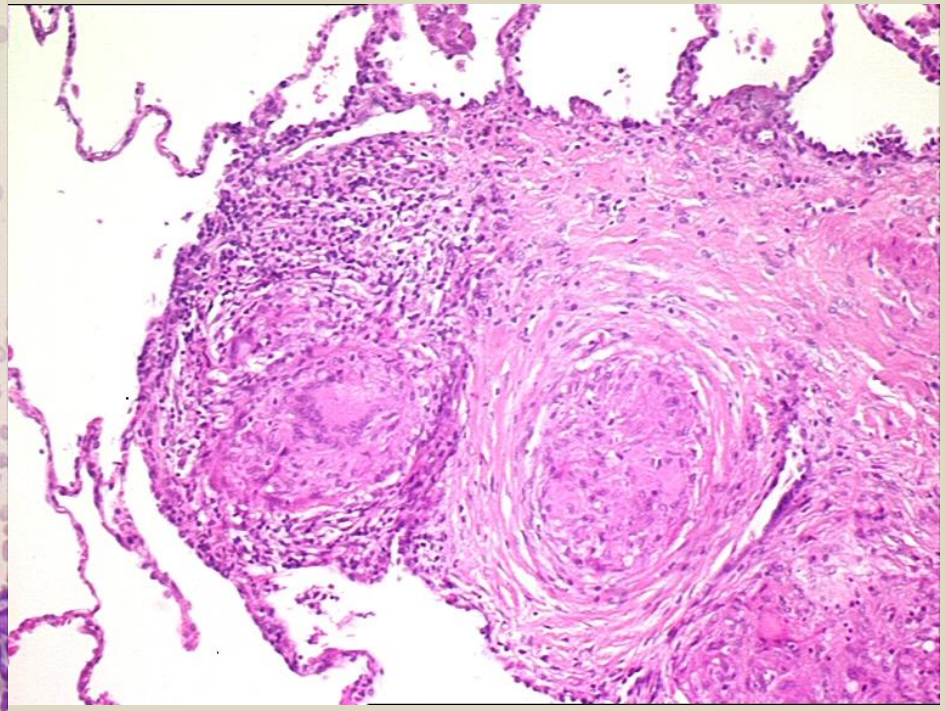


Attention à ce qui est compris sous la dénomination de granulome

- granulomes à corps étranger
- granulomes à cellules épithélioïdes

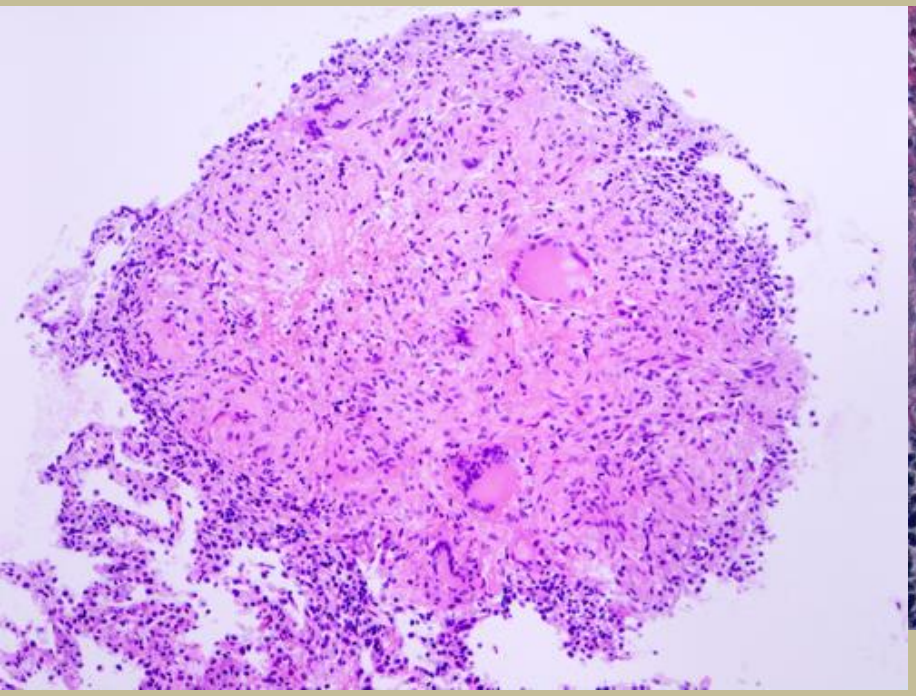


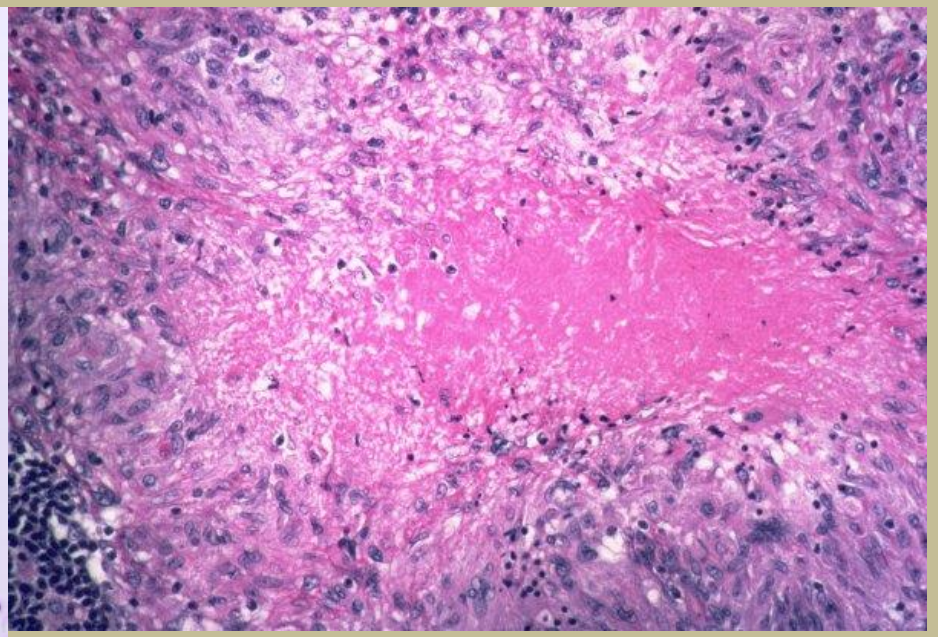
EBUS FNA Dr Jocelyne Fleury Tenon



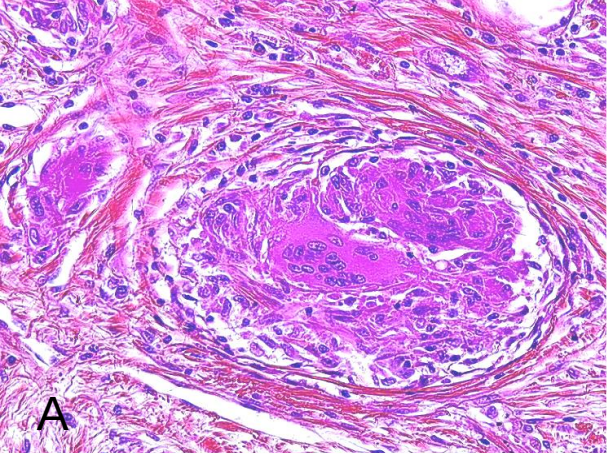
Biopsie pulmonaire Dr Marianne Kambouchner Avicenne

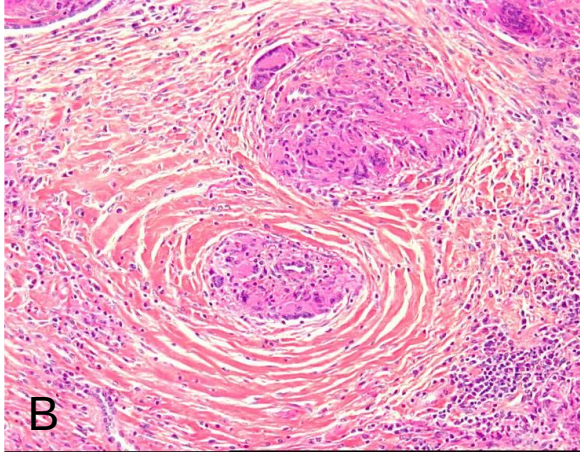
Granulomes épithélioïdes et sarcoidose

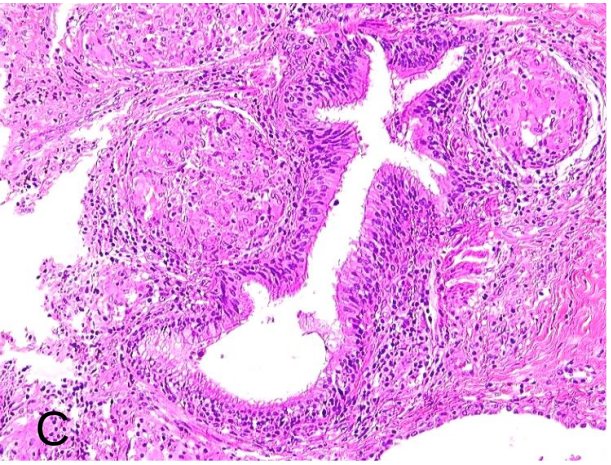


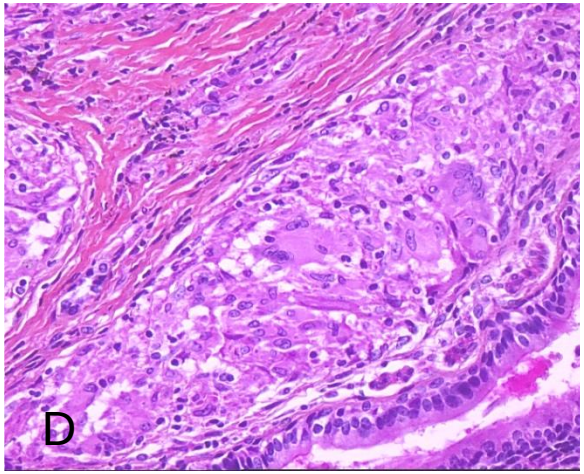


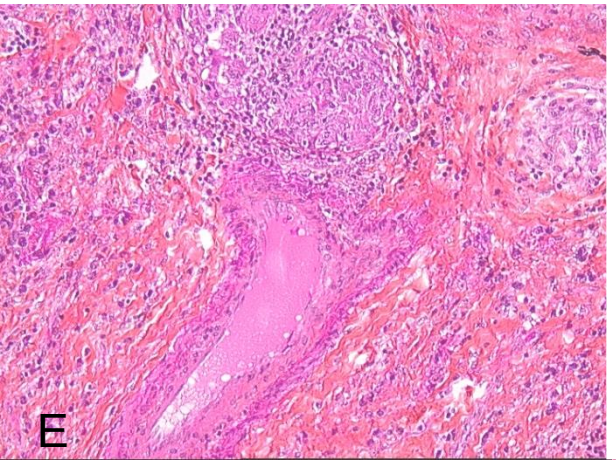
tuberculose

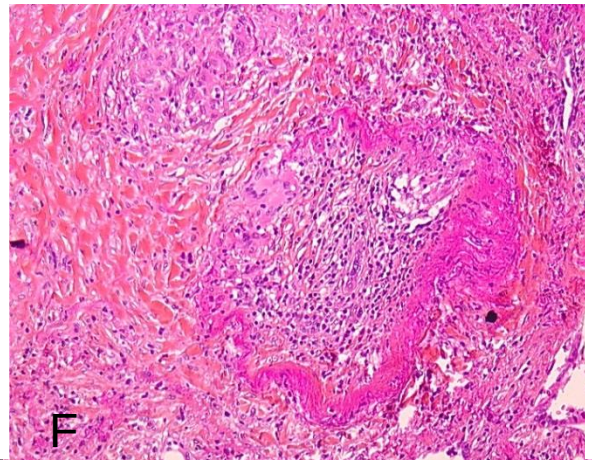












Sarcoidose pulmonaire: Granulomes associés aux lymphatiques:

Poumons:

-zones sous pleurales
-péribronchovasculaires
-cloisons interlobulaires

Atteintes
- parenchymateuses,
- des voies aériennes (bronches bronchioles)
- vasculaires (veines et artères)

Ganglions médiastinaux

Dr Marianne Kambouchner
Avicenne Bobigny

Histologic pattern of granulomatous interstitial pneumonias modified according to *Cheung 2003*;
(D Valeyre et al. Seminars in Critical and Respiratory Medicine 2014)

	Distribution	Granulomas	Associated features *
Sarcoidosis	Lymphangitic (associated to vessels, pleura, airways)	Well circumscribed coalescent +++ Perigranulomatous fibrosis Little inflammation	Unusual
Berylliosis	Lymphangitic as for sarcoidosis and/or scattered small granulomas with interstitial inflammation	*Similar to sarcoidosis* Well circumscribed coalescent +++ Perigranulomatous fibrosis	
Infections (mycobacterias fungi)	Randomly distributed or bronchiolocentricity	Frequently palissadic around geographic necrosis Perigranulomatous inflammation Few fibrosis or none	OP -/+ Int.Inf -/+
Hypersensitivity pneumonitis	Airway centered inflammation (bronchioles, alveolar ducts)	Small non-necrotizing loose granulomas without associated fibrosis	OP -/+ Int.Inf +
Hot tube lung	Bronchiolocentric and randomly distributed	Solitary with a cuff of lymphocytes	OP-/+ Int.Inf +
Sjogren's syndrome	Interstitial	Small non necrotizing interstitial granulomas	Peribronchial lymphoid hyperplasia

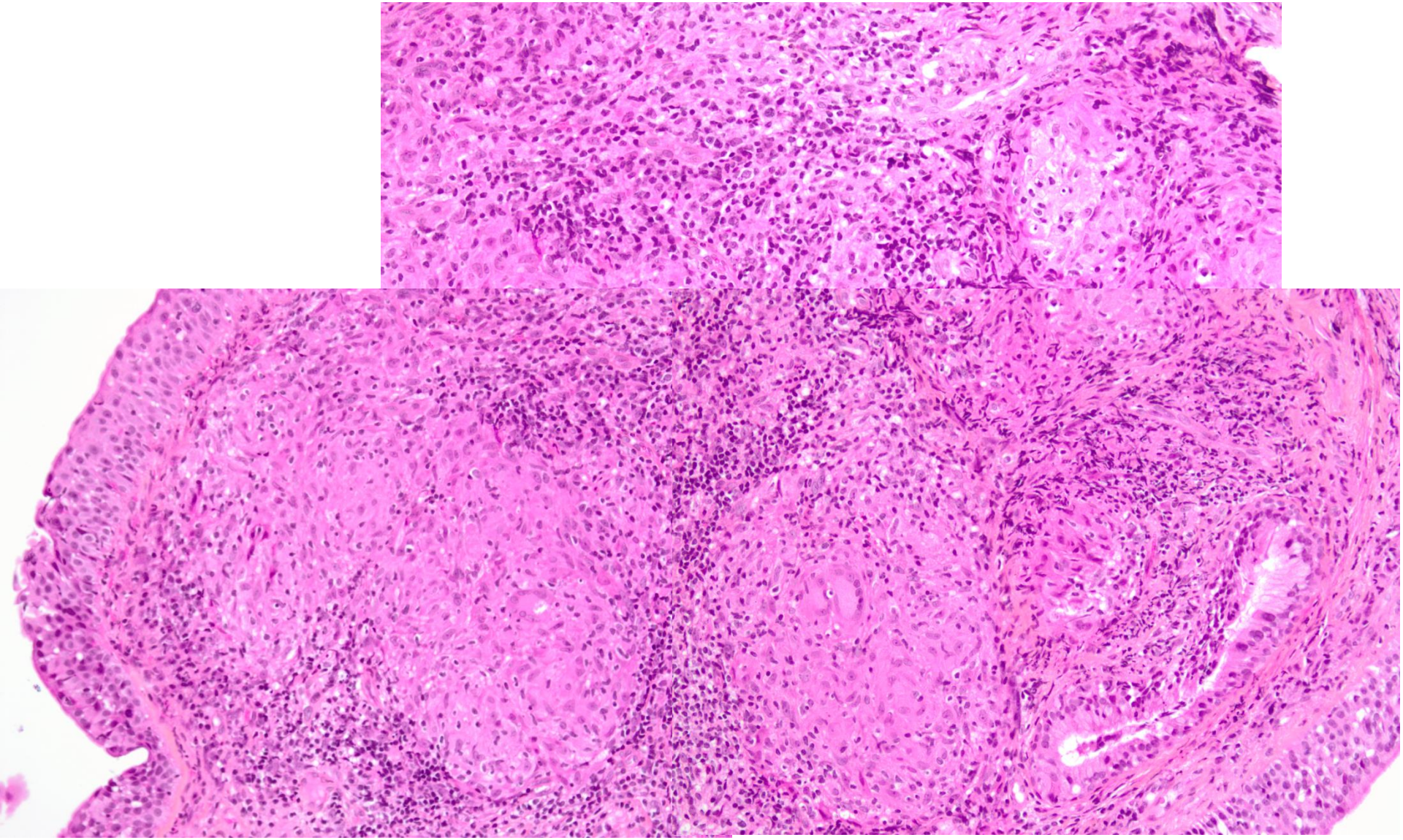
*Associated features: OP organizing pneumonia; IntInf. Interstitial Inflammation

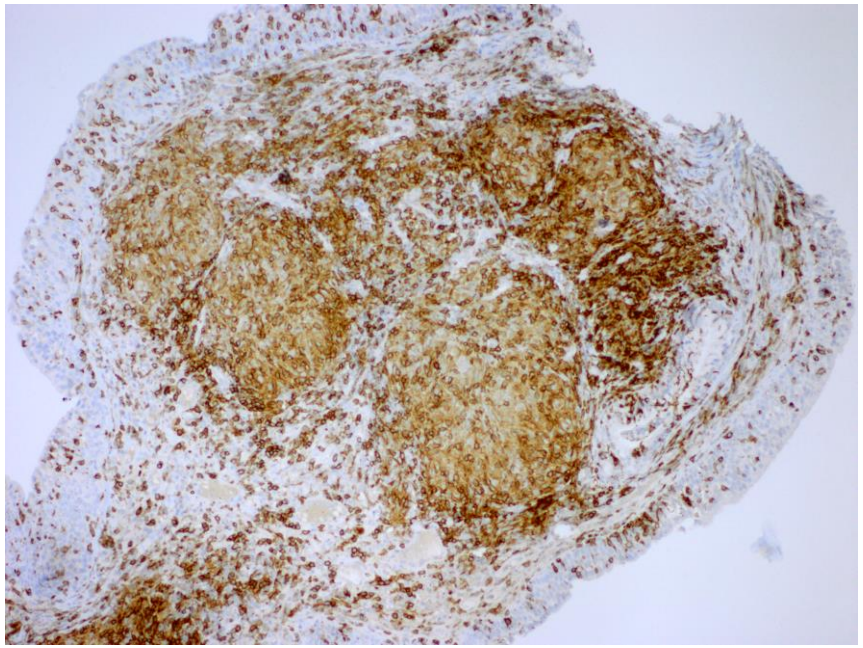

Les populations cellulaires
du granulome

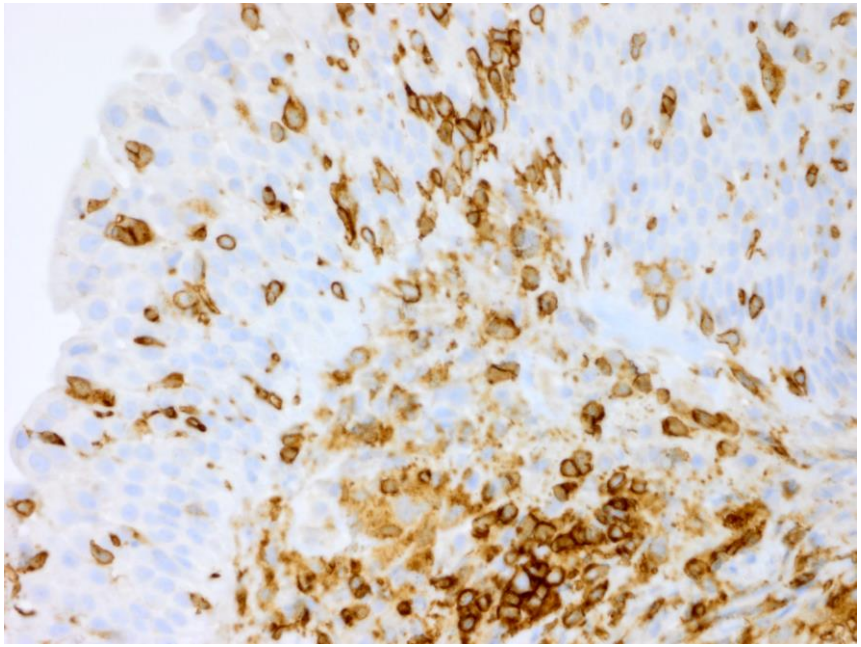
- *Granuloma is characterized by a core of monocyte-derived epithelioid histiocytes and multinucleate giant cells with interspersed CD4+T lymphocytes. A minority of cells near or by the granuloma are CD8+ T Ly, Treg, fibroblasts and B-Lymphocytes*

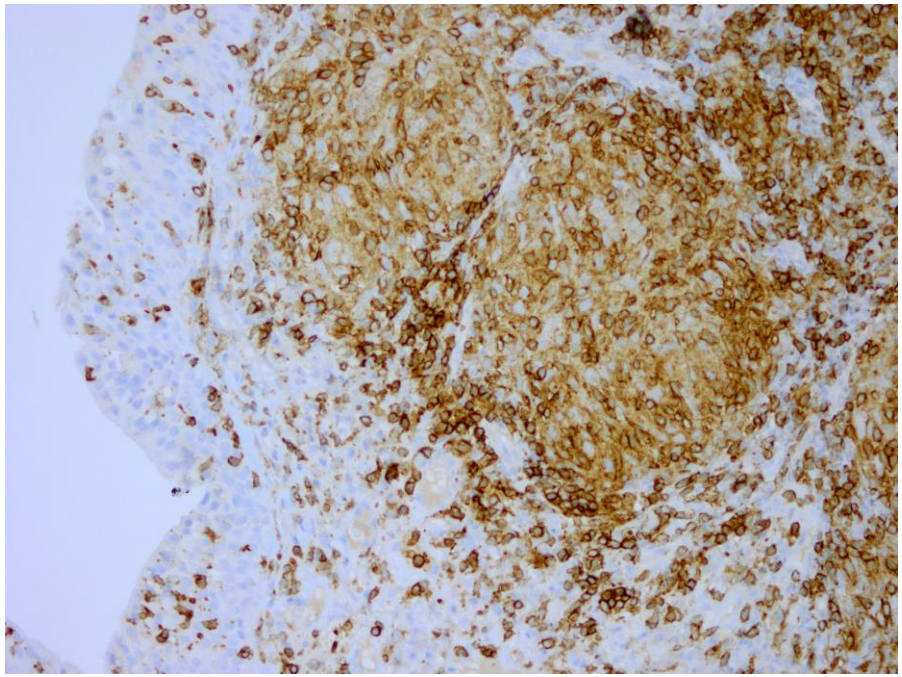
Baughman R, et al AJRCCM 2011

Exemple: biopsie bronchique , sarcoïdose

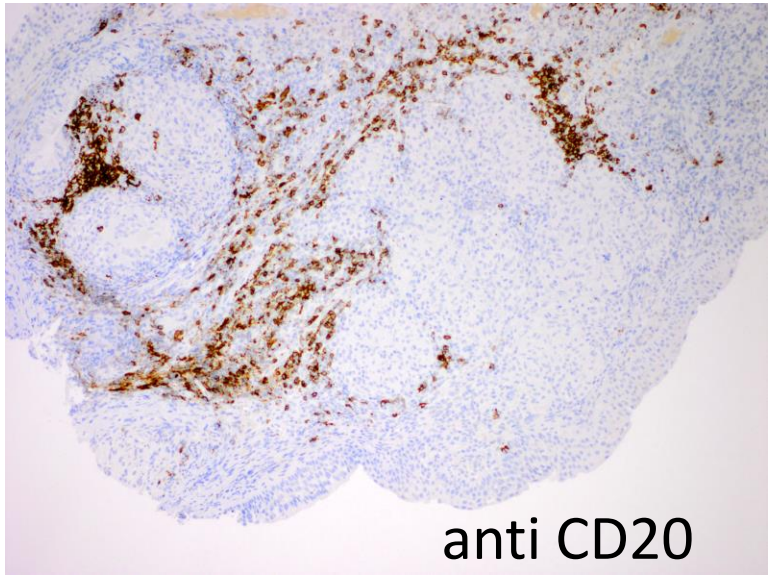


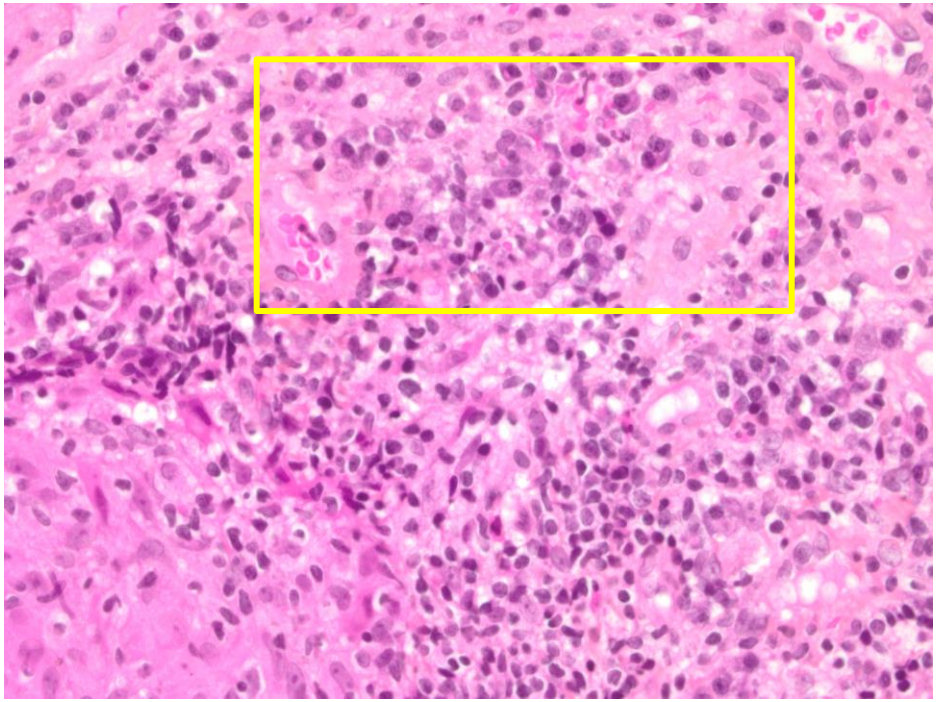






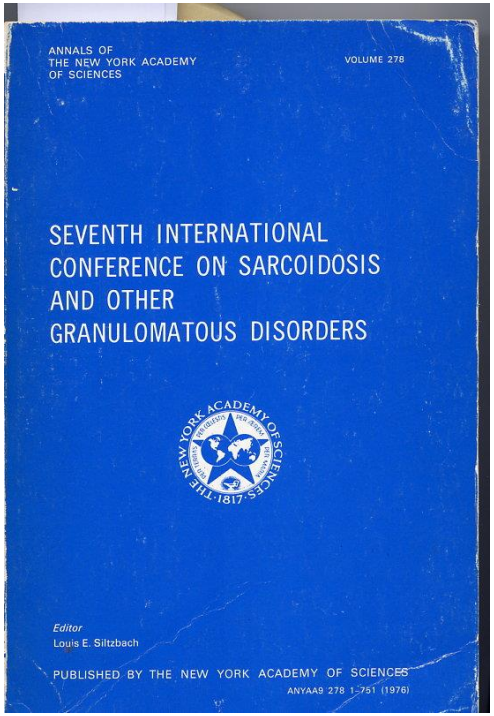
antiCD4





plasmocytes

1976



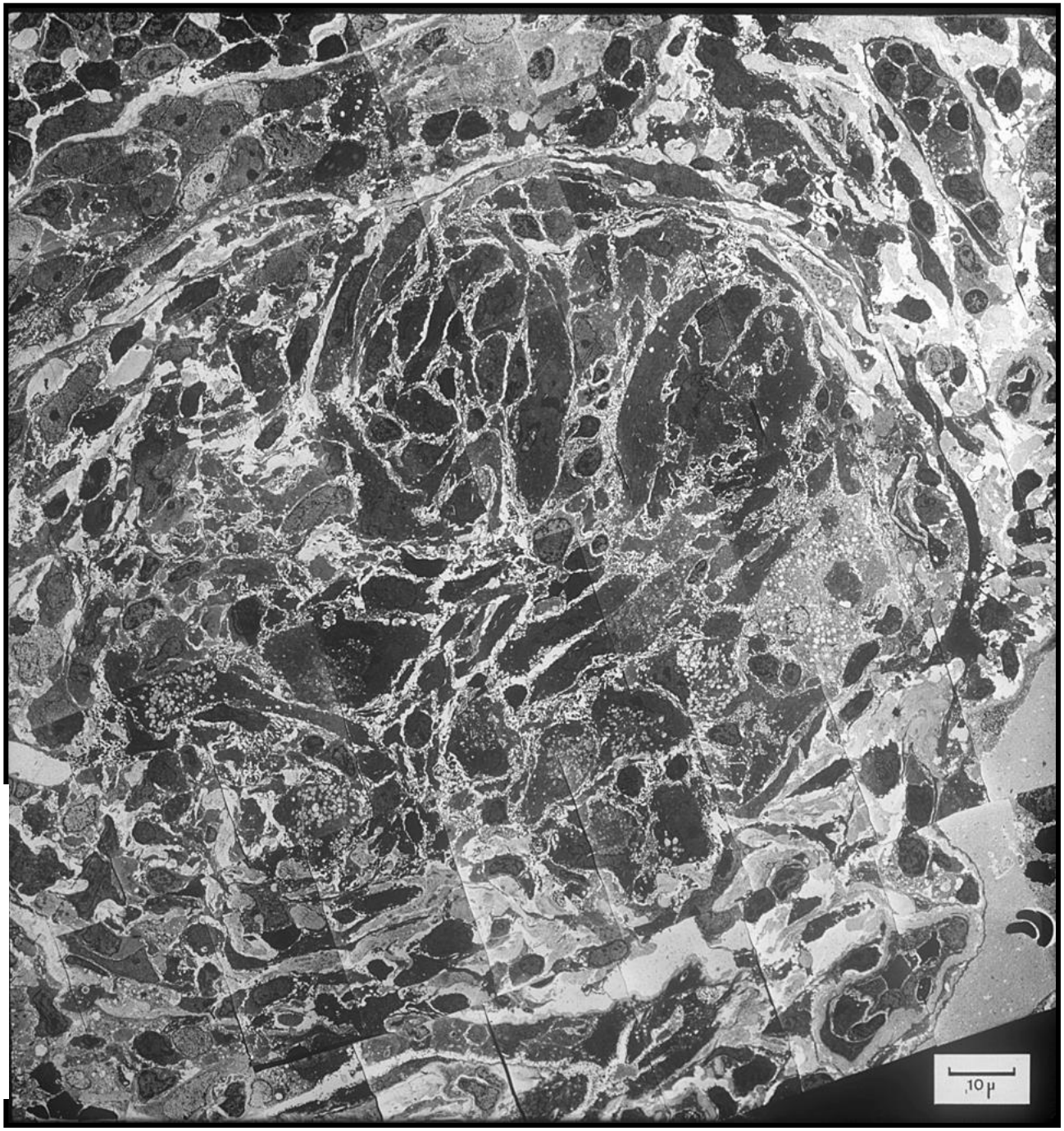
MORPHOLOGY AND DISTRIBUTION OF THE CELLS OF A SARCOID GRANULOMA: ULTRASTRUCTURAL STUDY OF SERIAL SECTIONS

P. Soler and F. Basset

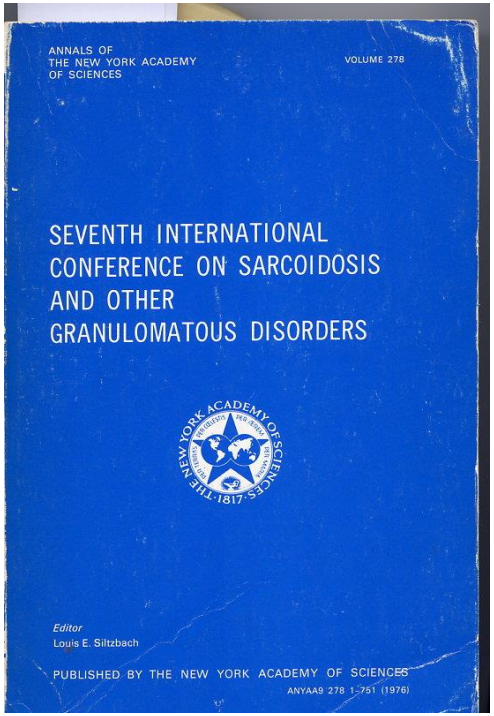
Groupe de Recherches U 82
Institut National de la Santé
et de la Recherche Médicale
Hôpital Bichat
Paris, France

J. F. Bernaudin and J. Chretien

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



1976



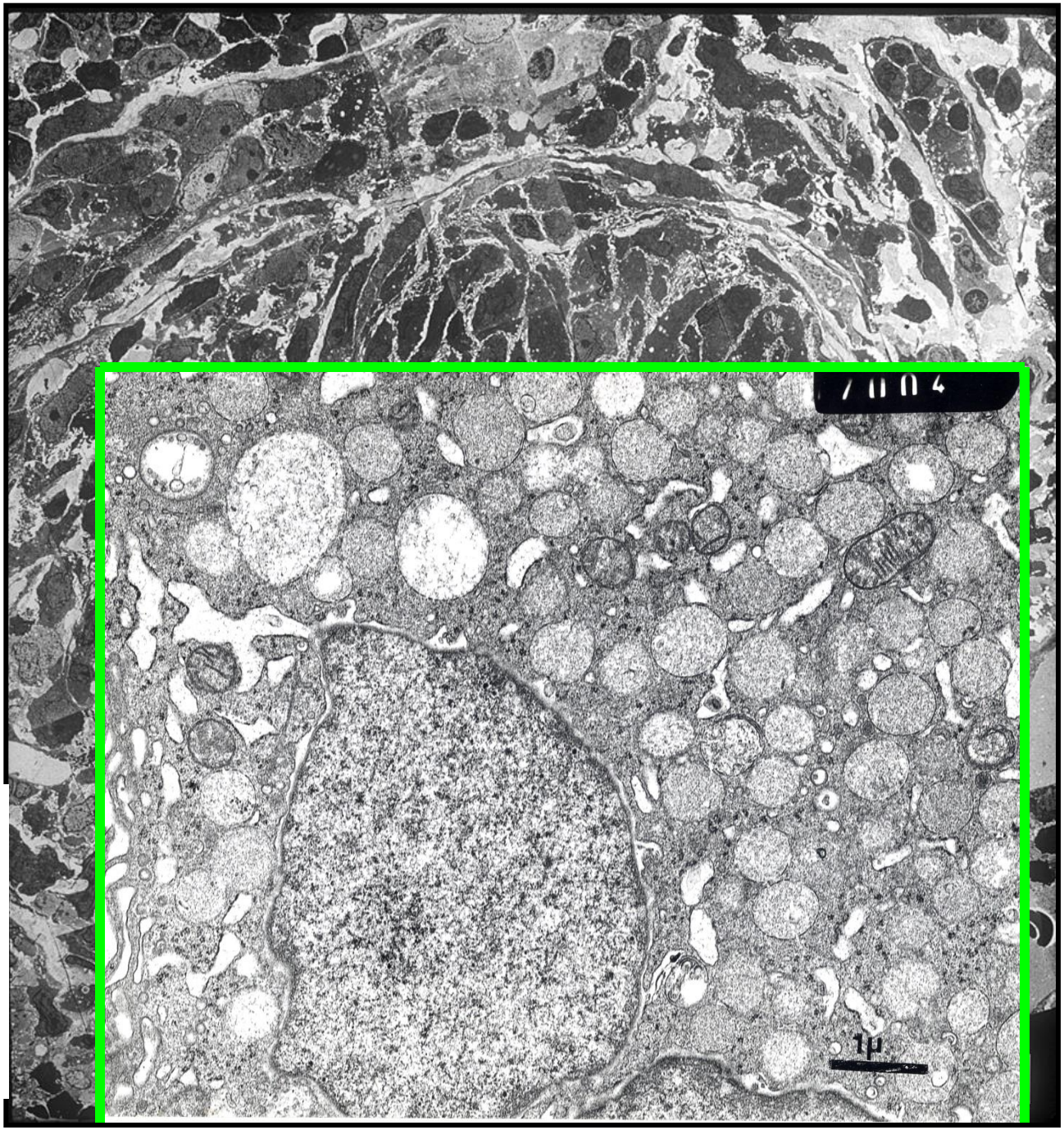
MORPHOLOGY AND DISTRIBUTION OF THE CELLS OF A SARCOID GRANULOMA: ULTRASTRUCTURAL STUDY OF SERIAL SECTIONS

P. Soler and F. Basset

Groupe de Recherches U 82
Institut National de la Santé
et de la Recherche Médicale
Hôpital Bichat
Paris, France

J. F. Bernaudin and J. Chretien

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



Inflammation aiguë

(poly N → macrophages)

élimination de l'Agent agresseur → résolution

Agression

persistance de l'Agent agresseur

inflammation chronique

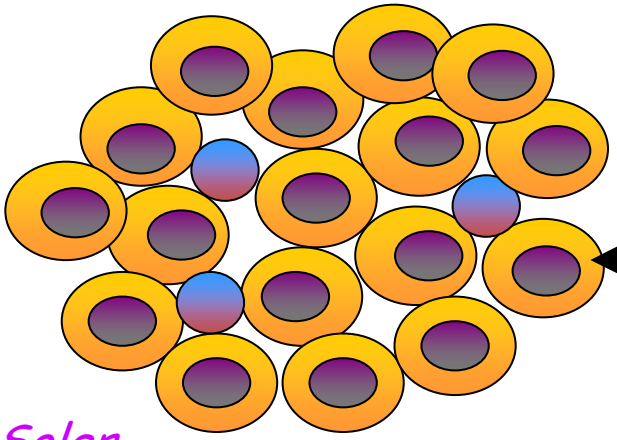
(macrophages)

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

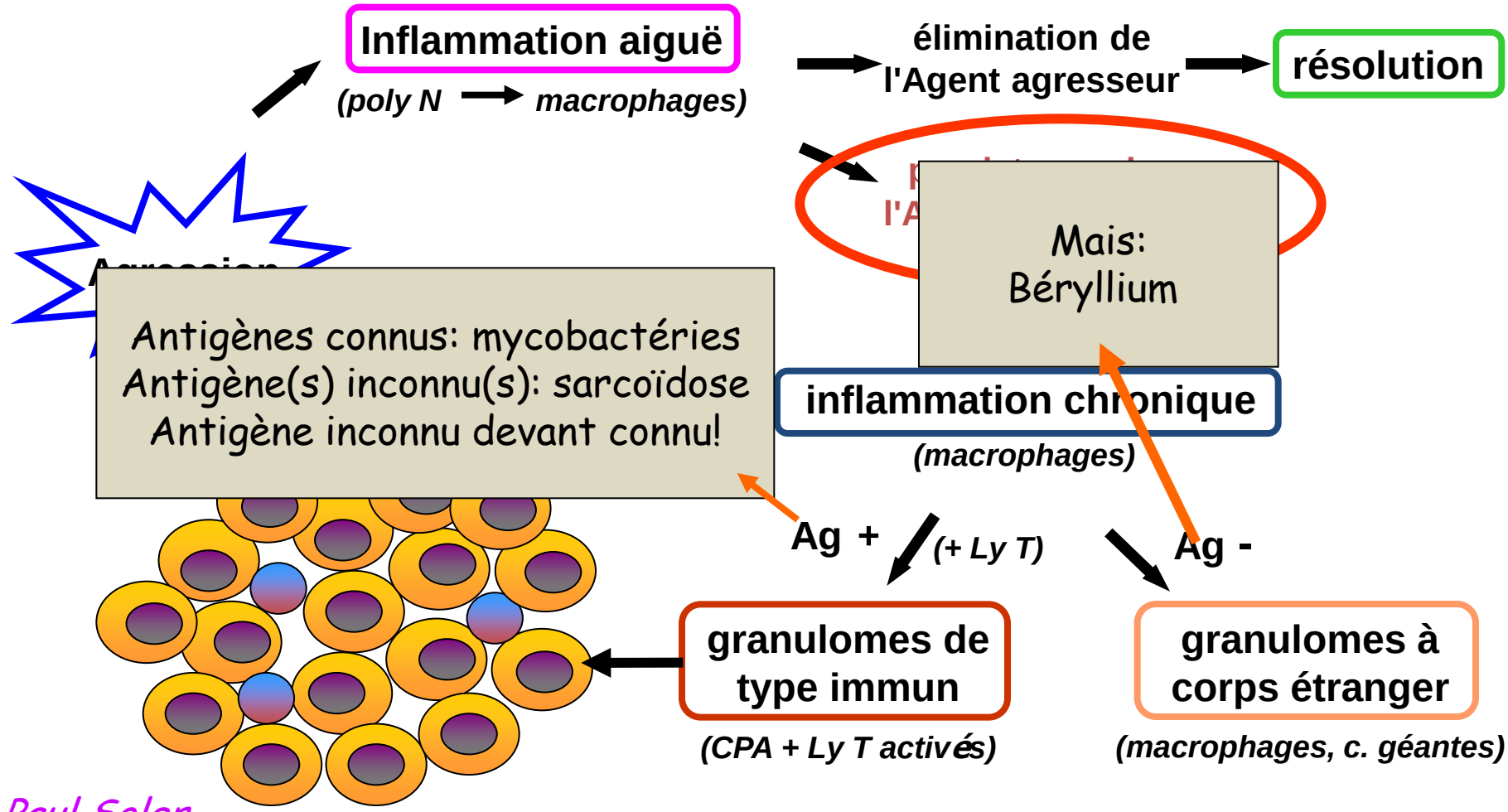
(CPA + Ly T activés)

Ag - → granulomes à corps étranger

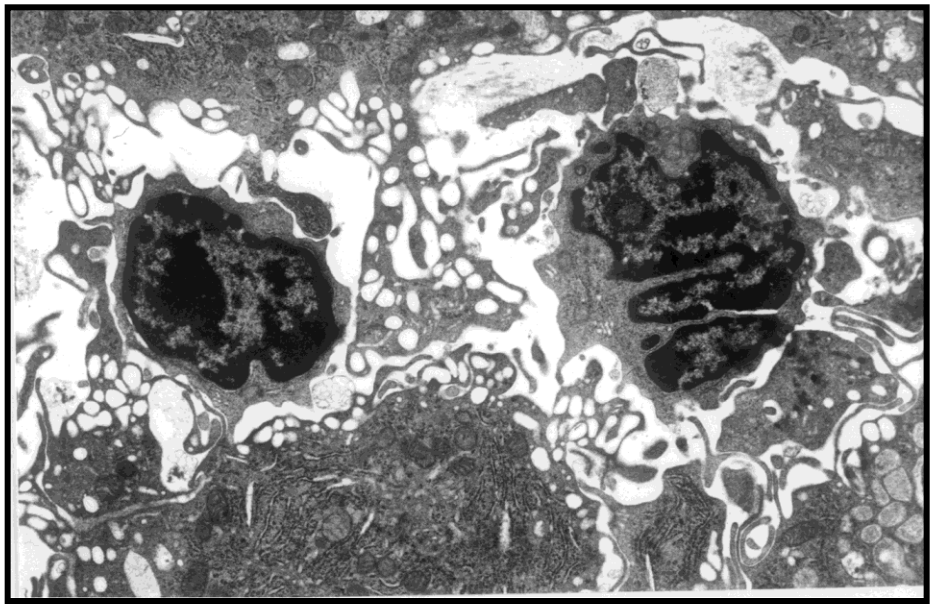
(macrophages, c. géantes)

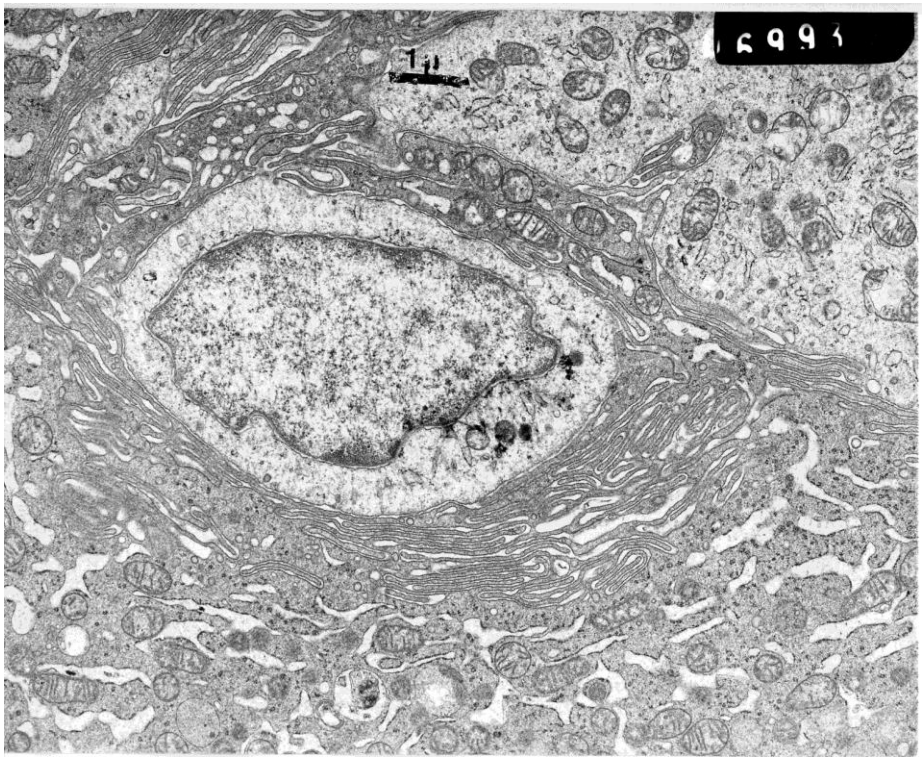


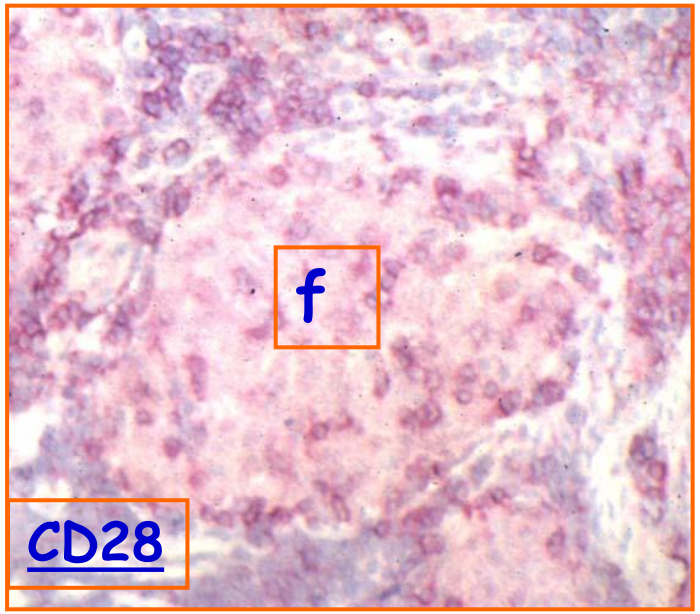
Paul Soler


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



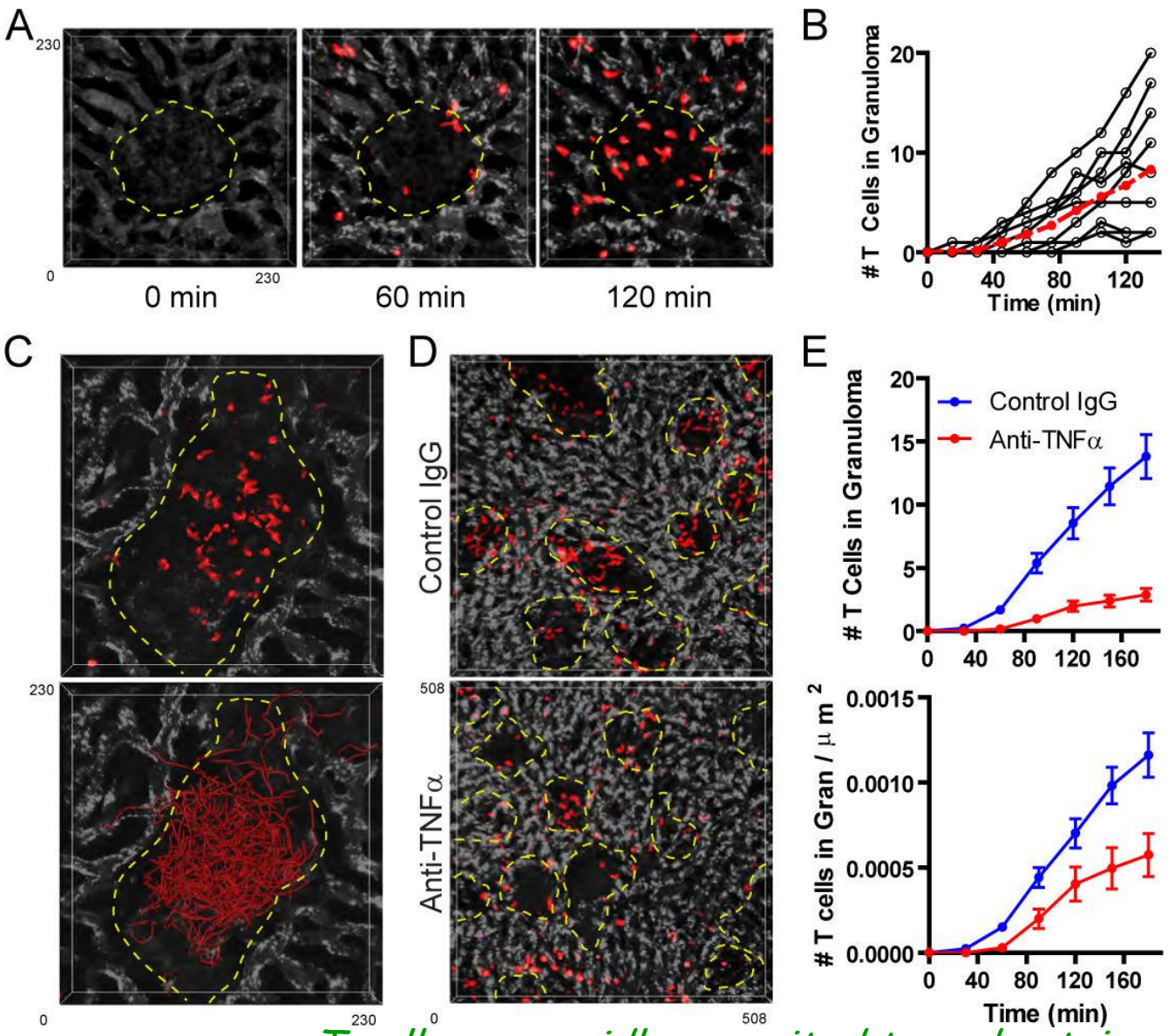




P Soler,

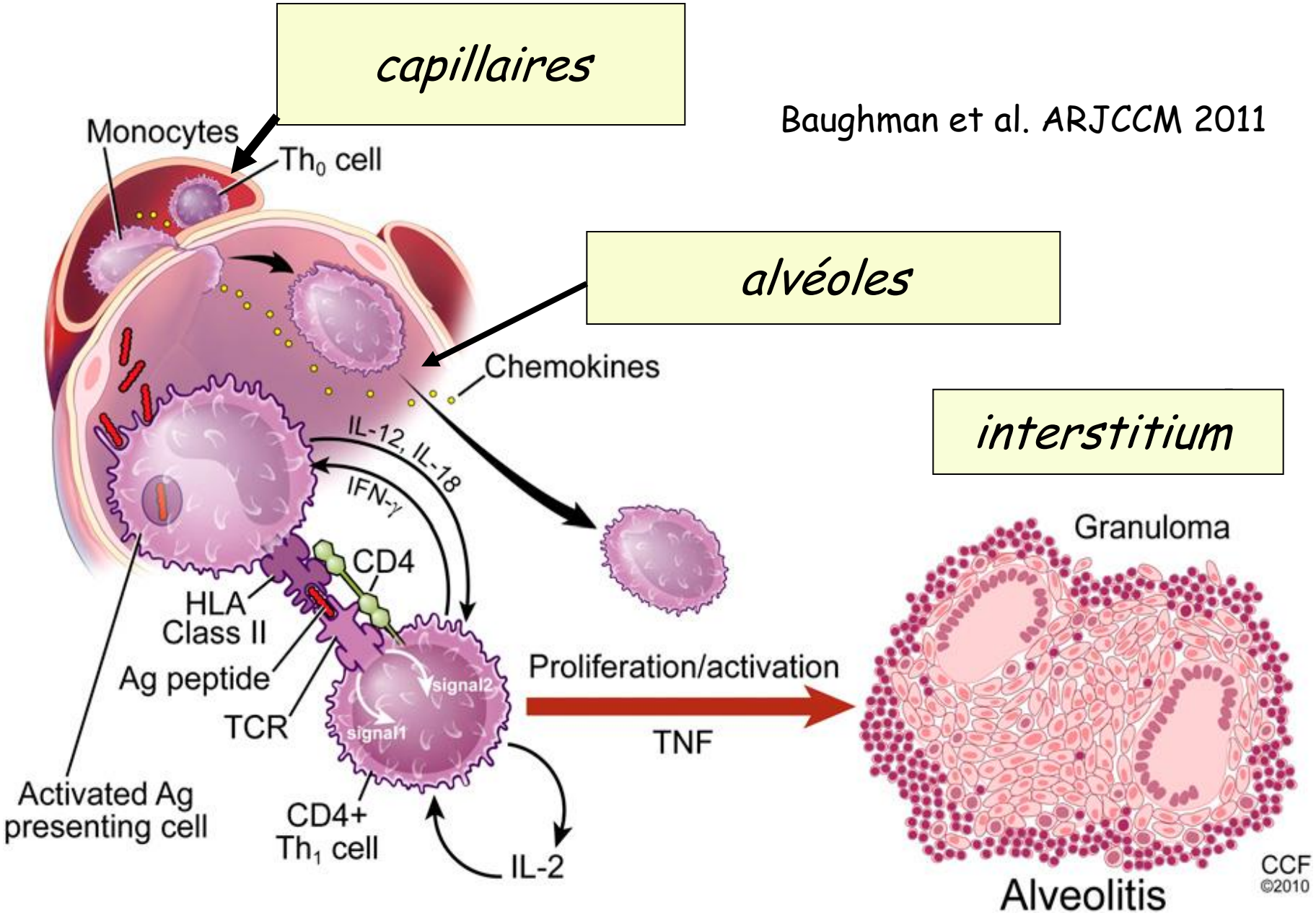
lymphocytes CD4+ / CD45RO+ / αβ
exprimant le CD28 ligand de CD80, CD86

P Soler



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


Mise en place dans la sarcoidose


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

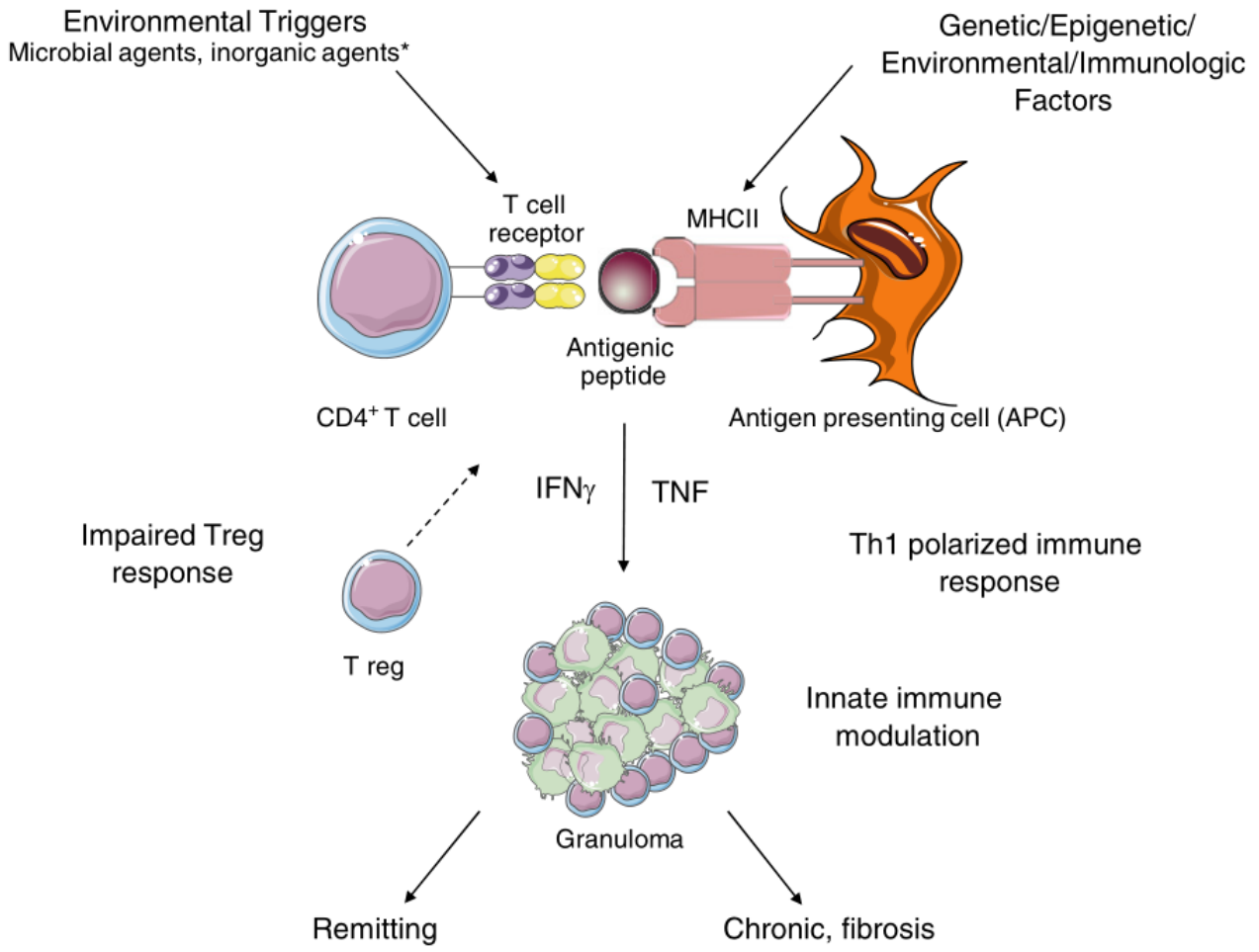


Figure 1. Schematic of the current state of the genetic, immunological, and environmental basis of

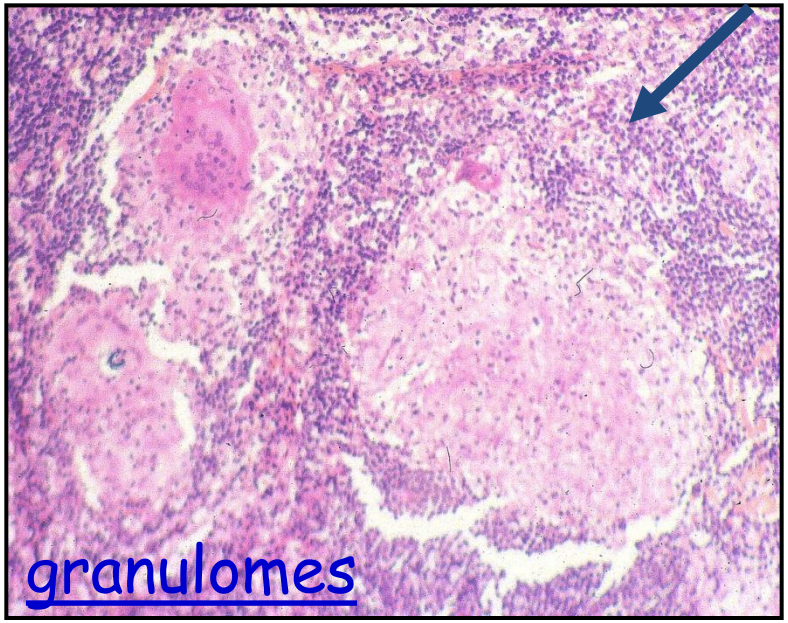
D Moller et al.2017

ALVEOLITIS AND GRANULOMAS: SEQUENTIAL COURSE IN PULMONARY SARCOIDOSIS

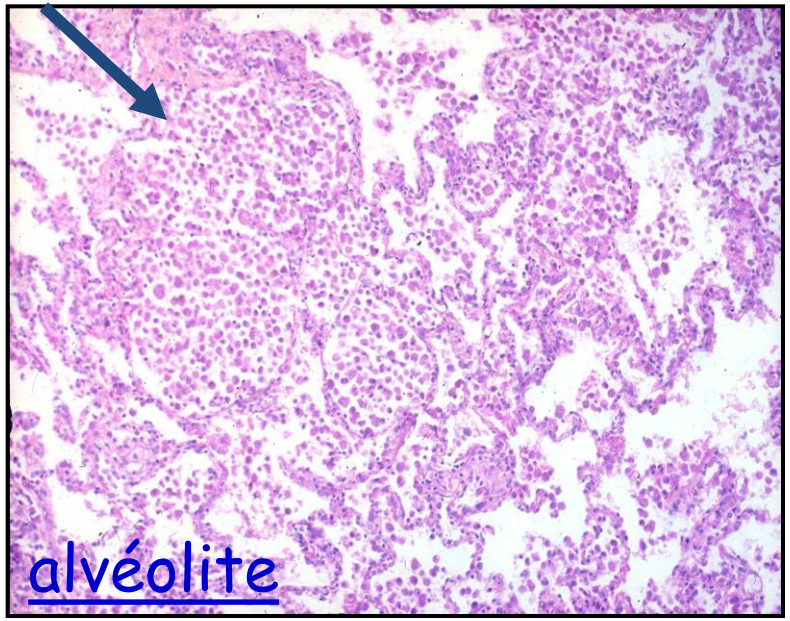
J. LACRONIQUE*, J.-F. BERNAUDIN**, P. SOLER***, F. LANGE**, O. KAWANAMI†, G. SAUMON***, R. GEORGES***, F. BASSET***

* 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) pp 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

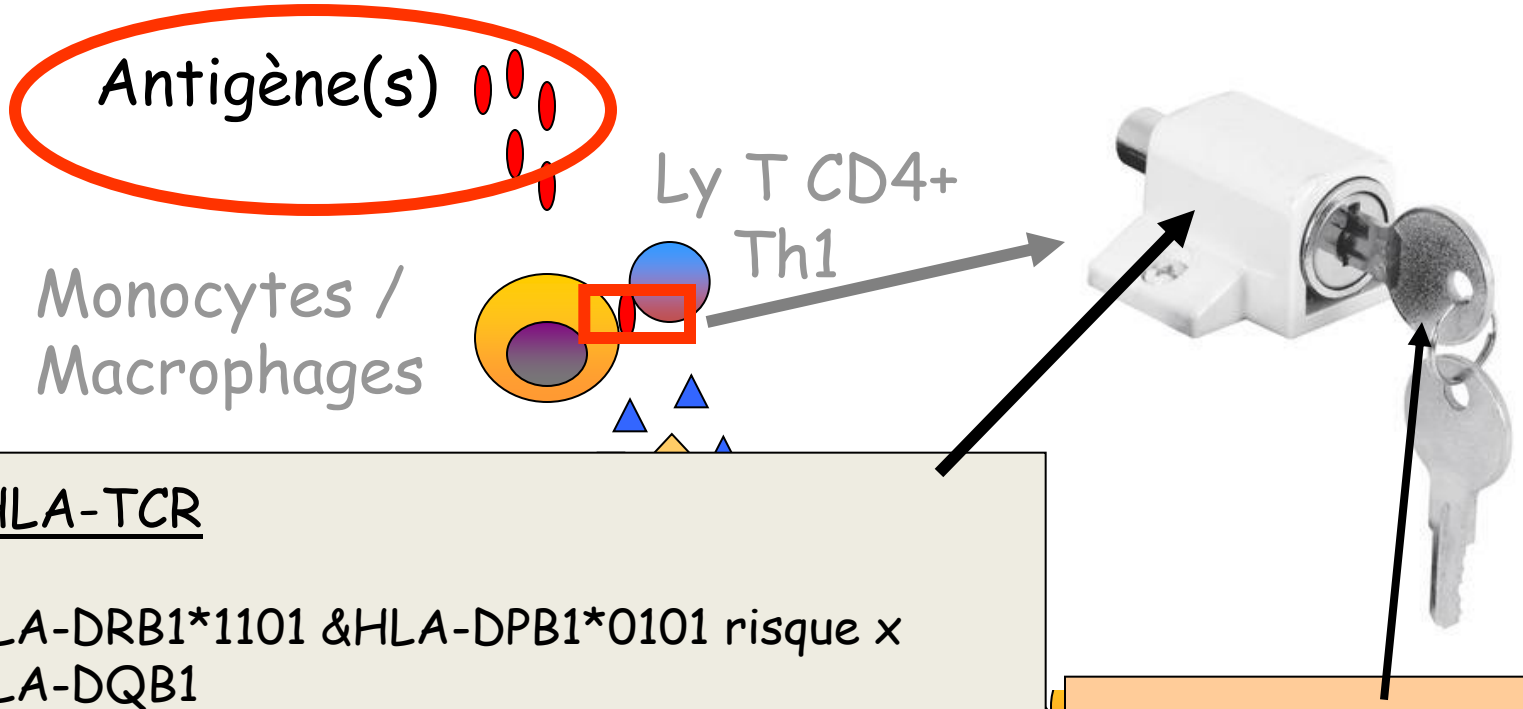
Definition of abbreviations: AM = alveolar macrophages; ly = lymphocytes.
* Values are medians (range).
Mann-Whitney U test analysis: †$p < 0.001$ versus controls; ‡$p < 0.01$ versus the other groups.

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



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

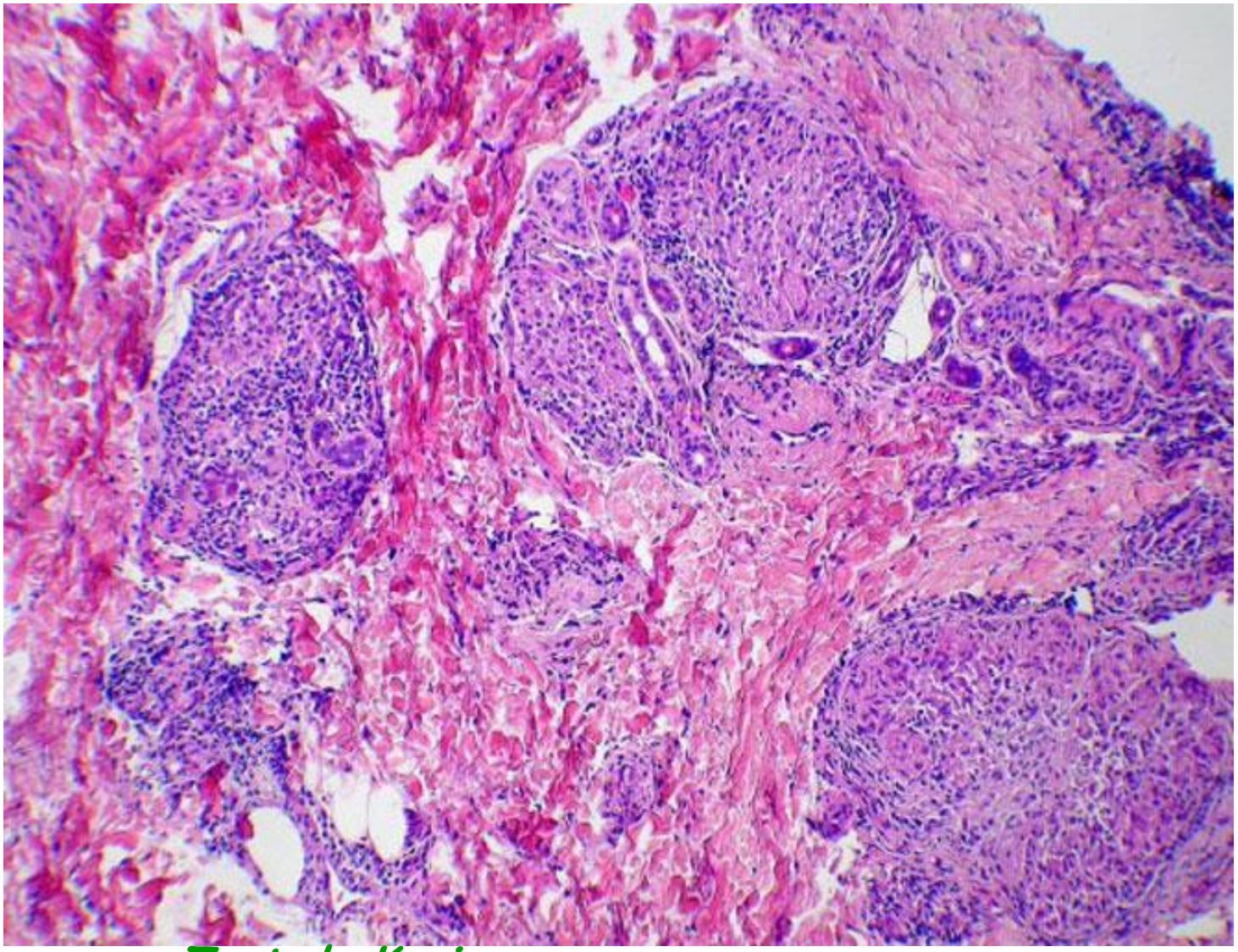
Propionibacterium acnes
Mycobacterium tuberculosis

- 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

- 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

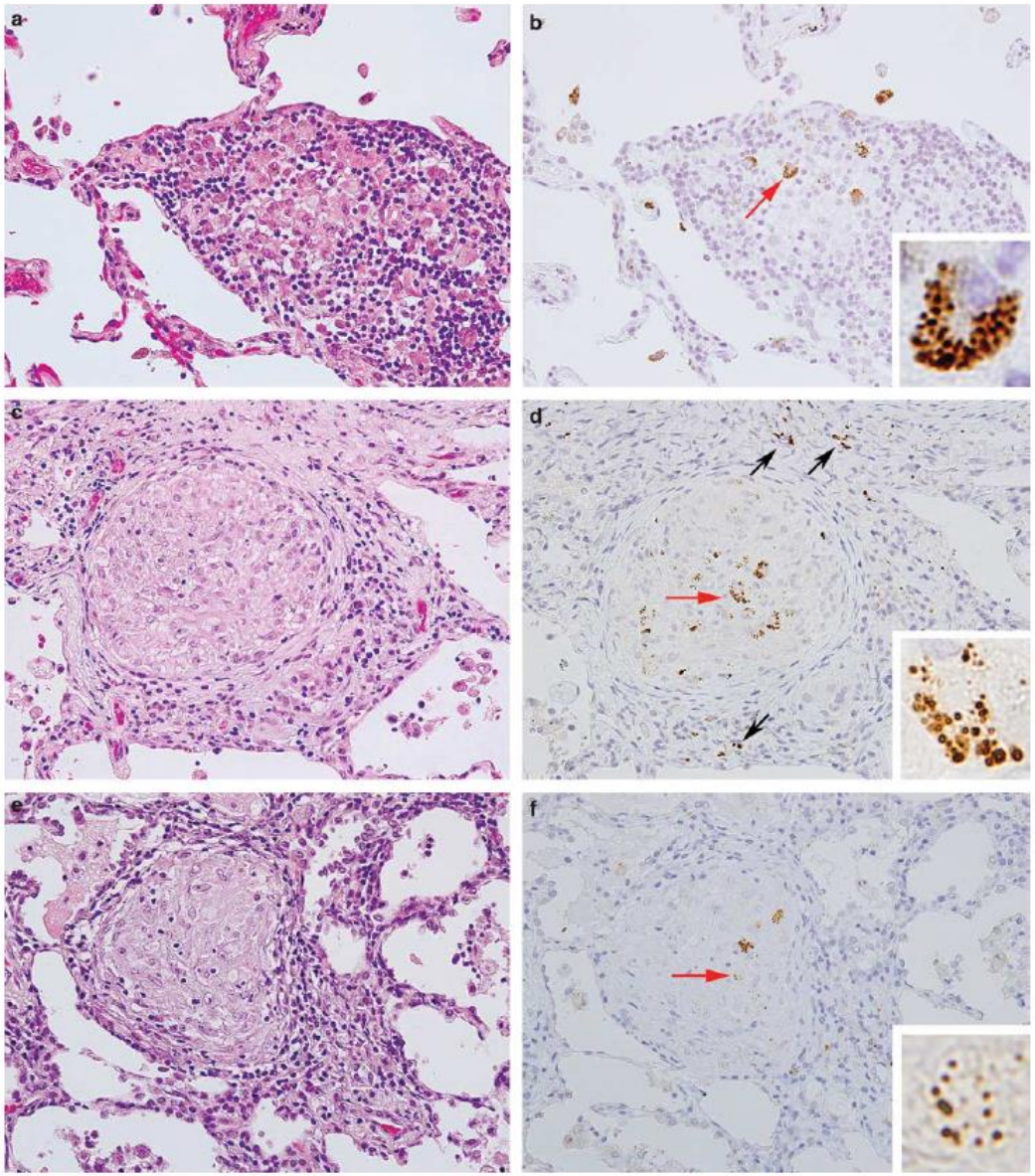


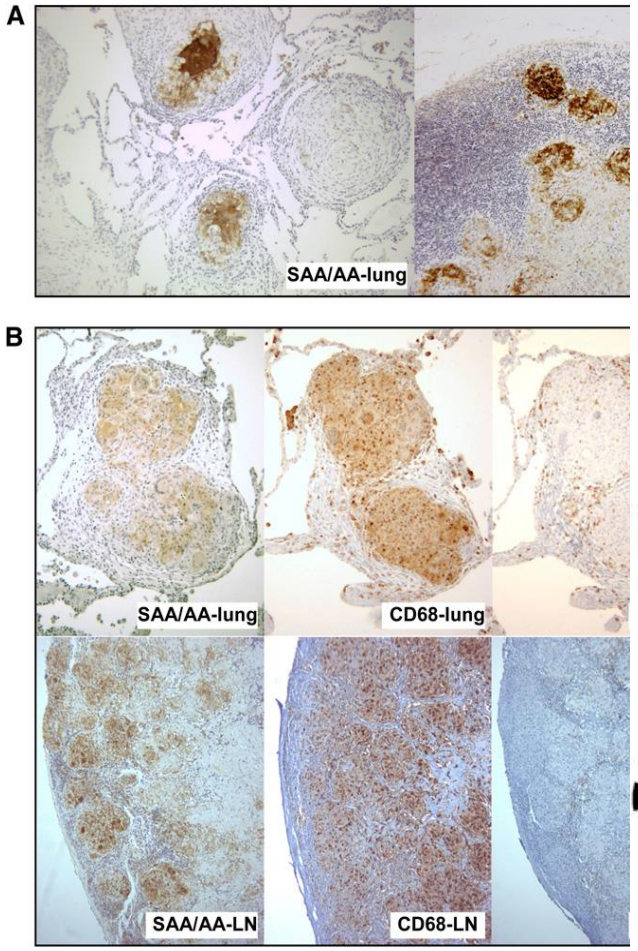
Figure 2 *P. acnes* within sarcoid granulomas of the lungs. Hematoxylin and eosin staining (left) and immunostaining with PAB antibody

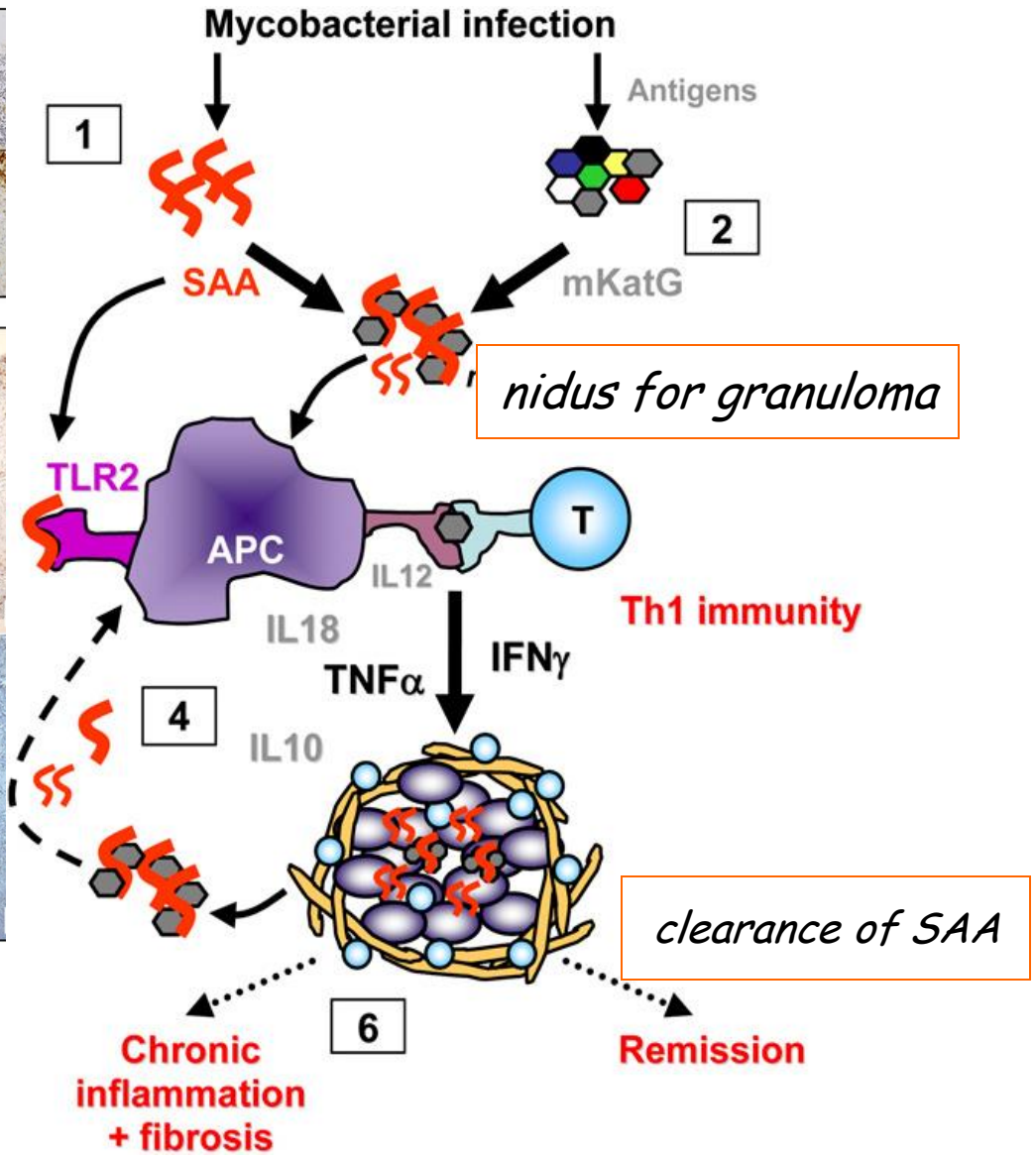
1284 MODERN PATHOLOGY (2012) 25, 1284–1297

Open

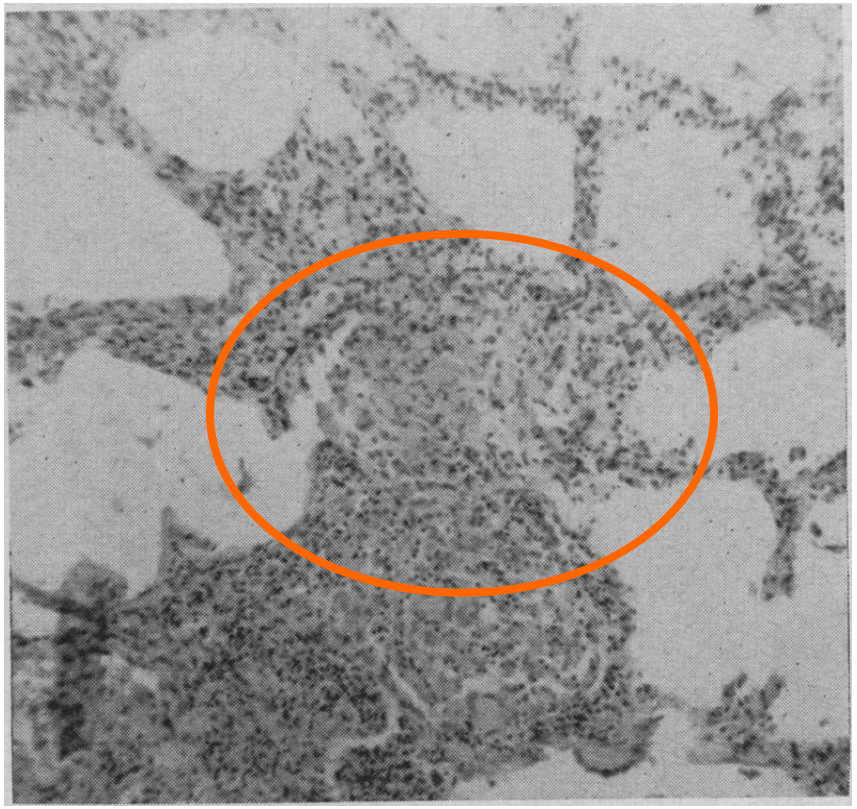
Localization of *Propionibacterium acnes* in granulomas supports a possible etiologic link between sarcoidosis and the bacterium

Mariko Negi[1], Tamiko Takemura[2], Josune Guzman[3], Keisuke Uchida[1], Asuka Furukawa[1], Yoshimi Suzuki[1], Tadatsune Iida[1], Ikuo Ishige[1], Junko Minami[4], Tetsuo Yamada[1], Hiroshi Kawachi[1], Ulrich Costabel[5] and Yoshinobu Eishi[1]





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



PULMONARY GRANULOMATOSIS
OF BERYLLIUM WORKERS
J. W. STURTRIDGE
Canad. M. A. J. Aug. 15, 1956, vol. 75

HLADPB1*0201
(HLADPGlu69 Chaine β)

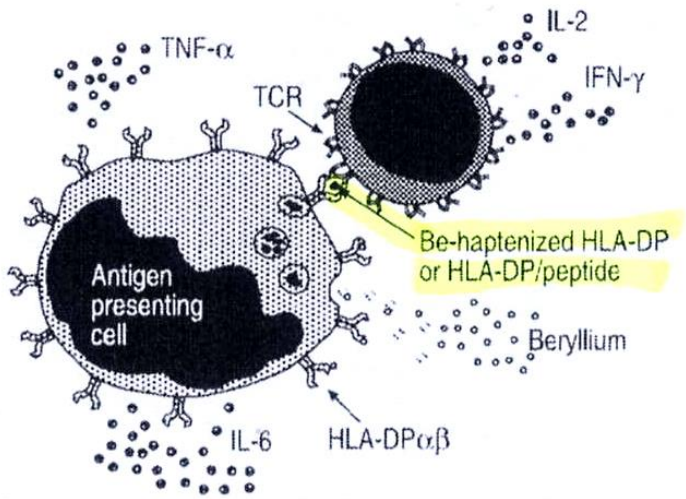


Fig. 4. – Schematic diagram of the immune response to Be in beryllio-sis. TNF-α: tumour necrosis factor-alpha; TCR: T-cell receptor; IL: in-terleukin; IFN-γ: interferon-gamma; HLA: human leukocyte antigen.

Saltini C et al ERJ 1988

292

Seven cases
phagus are re
nosis and trea
The results
cadaveric oesc
the mechanism
sudden rise of
to a relaxed
obstructed.

Addendum
publication a
the oesophagu
at St. George'
of 52 years wi
phagus on the
azygos vein, w
would like to
mention this p

Acknowled
Mearns Milne
for permissio
like to thank
to use post-m
work and Dr.
radiological as

SKIN GRANULOMATA DUE TO BERYLLIUM OXIDE*

By W. JONES WILLIAMS
SENIOR LECTURER IN PATHOLOGY

J. H. LAWRIE
LECTURER IN SURGERY

WELSH NATIONAL SCHOOL OF MEDICINE, THE ROYAL INFIRMARY, CARDIFF

AND H. J. DAVIES
H.M. MEDICAL INSPECTOR OF FACTORIES

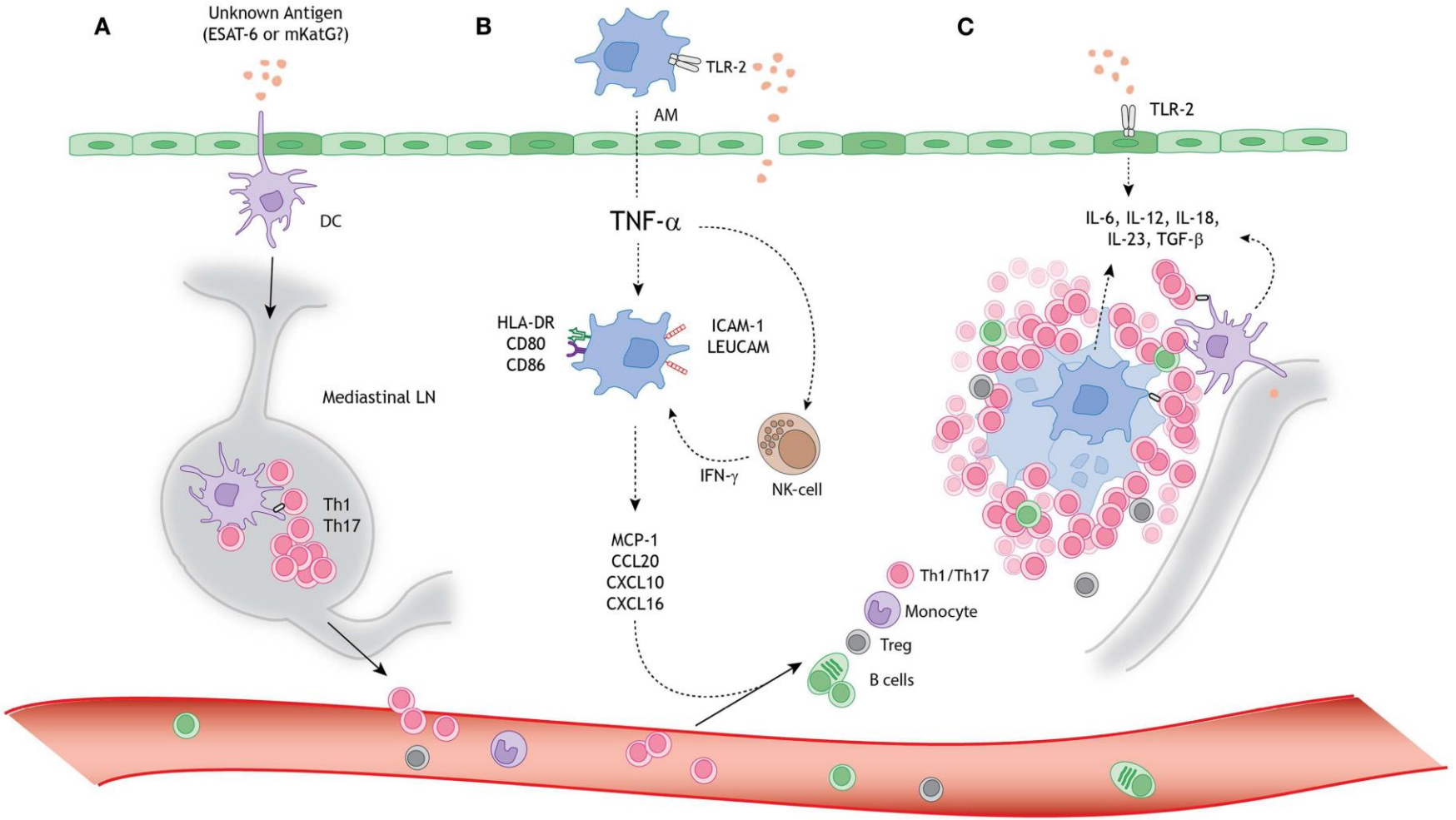
We would like to emphasize the serious results that may follow the accidental introduction of beryllium into the skin. Two main varieties of beryllium skin disease are described by Tepper, Hardy, and Chamberlin (1961): (1) acute types including contact dermatitis and beryllium ulcer, which show non-specific 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 phos-phors 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 erythro-mycin. He was treated with an initial course of erythro-mycin 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.



Caroline E Broos et al. Frontiers Immunology 2013

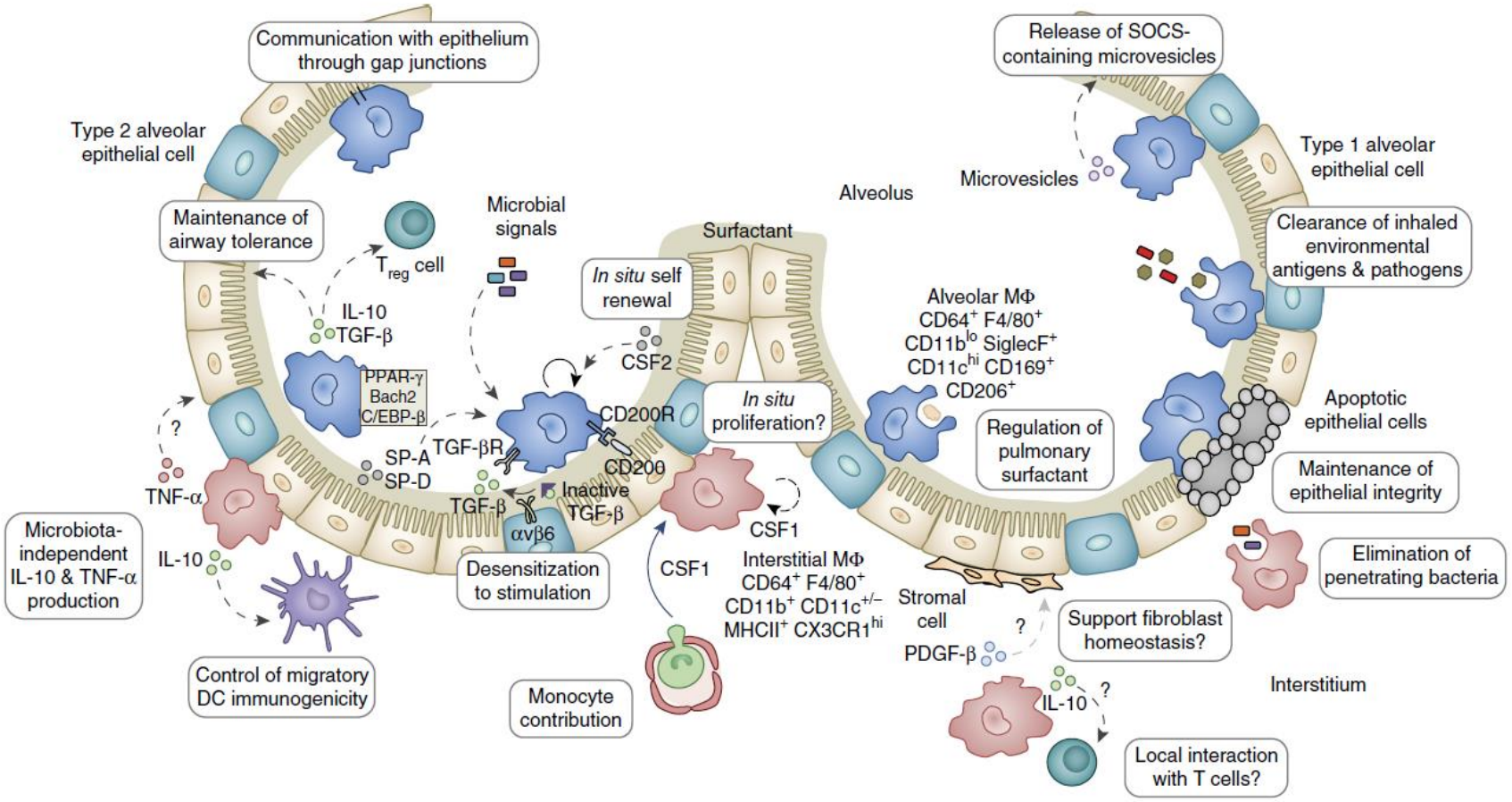


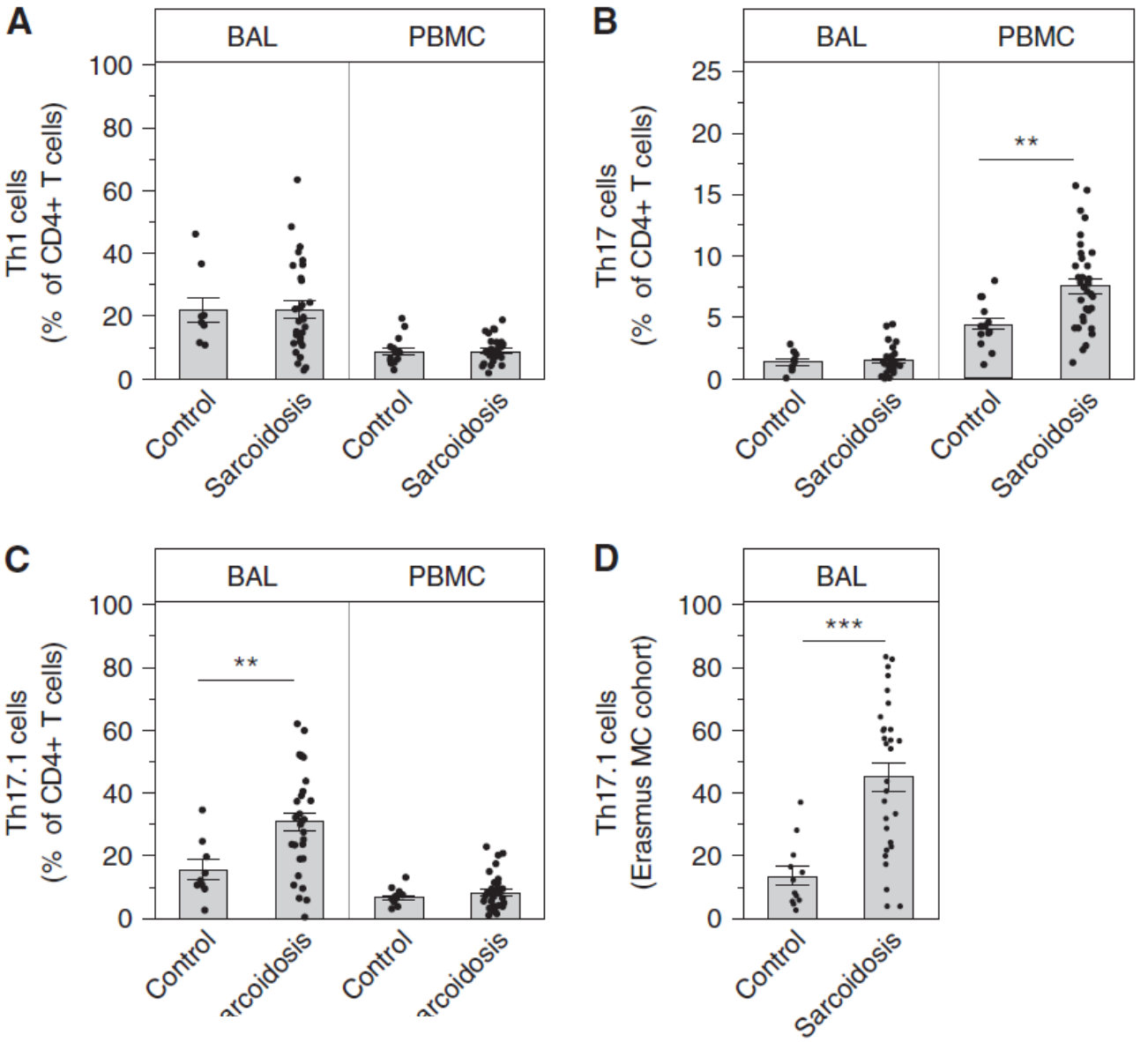
Figure 2 Alveolar macrophages in the lung are crucial for maintaining the patency of the alveolar space, where they regulate surfactant levels and phagocytose inhaled microbes and other particulate materials[59,61]. They communicate intimately with alveolar epithelial cells, removing dead

nature medicine

Barrier-tissue macrophages: functional adaptation to environmental challenges

Allan McI Mowat[1], Charlotte L Scott[1–3] & Calum C Bain[4]

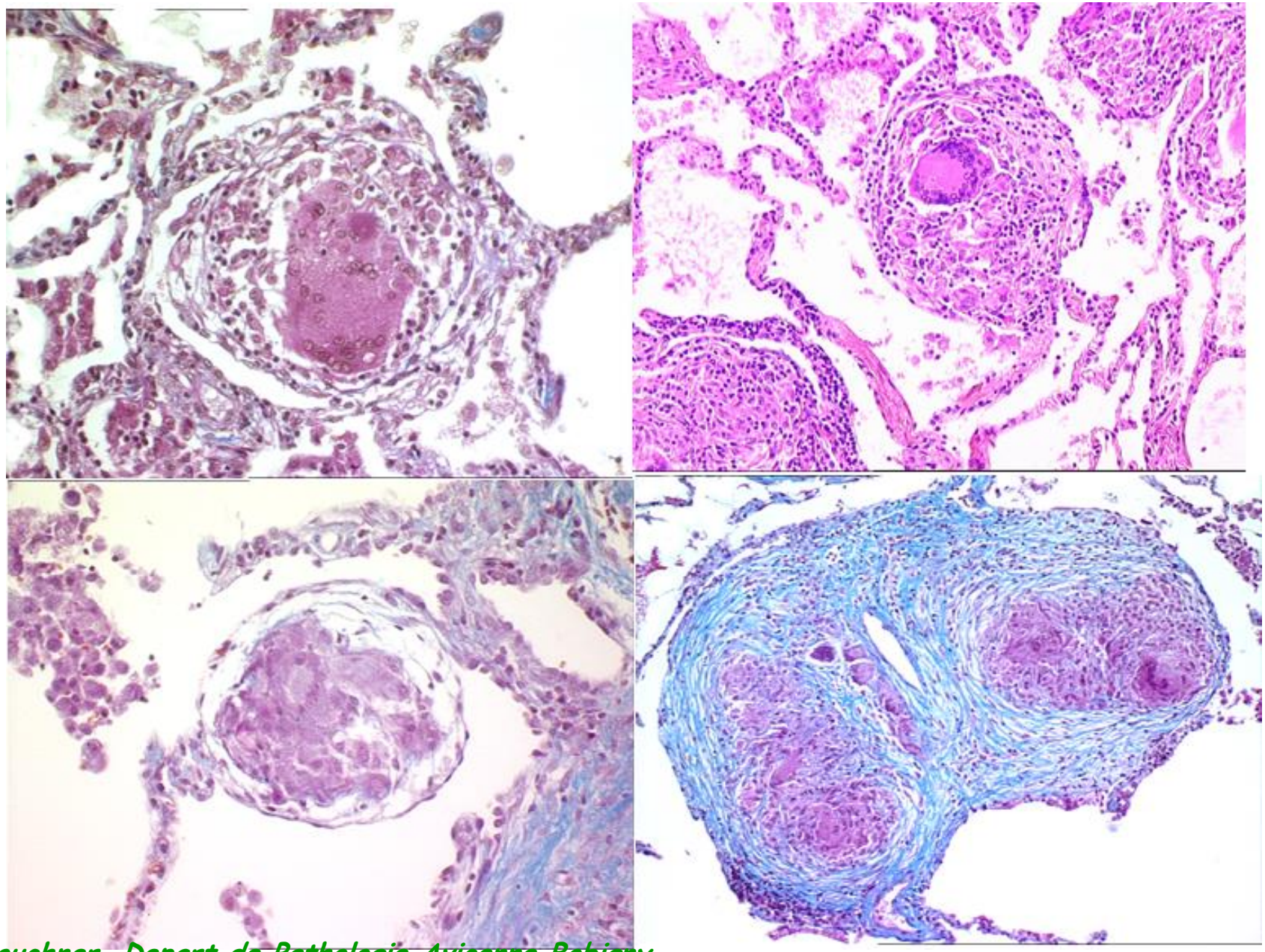
Mc Mowat a et al. November 2017



IFN-γ–Producing T-Helper 17.1 Cells Are Increased in Sarcoidosis and Are More Prevalent than T-Helper Type 1 Cells

Joris Ramstein[1*], Caroline E. Broos[2*], Laura J. Simpson[3,4], K. Mark Ansel[3,4], Sara A. Sun[1], Melissa E. Ho[1], Prescott G. Woodruff[1], Nirav R. Bhakta[1], Laura Christian[3,4], Christine P. Nguyen[1], Bobby J. Antalek[1], Bryan S. Benn[1], Rudi W. Hendriks[2], Bernt van den Blink[2], Mirjam Kool[2], and Laura L. Koth[1]

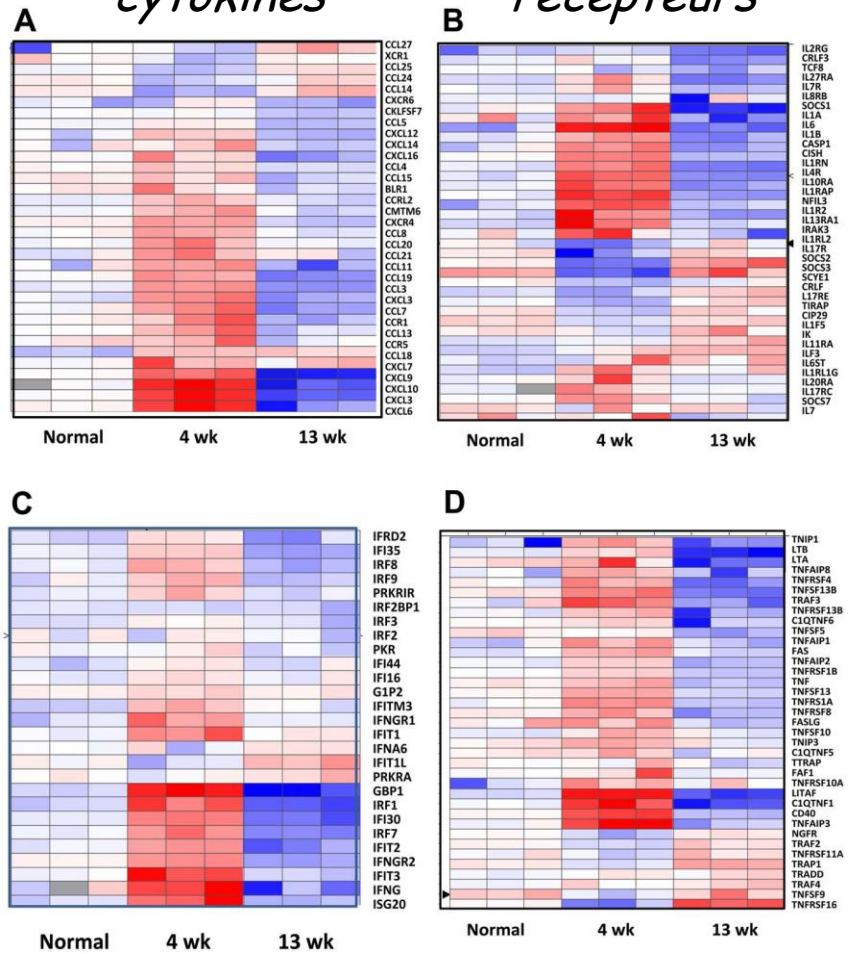
American Journal of Respiratory and Critical Care Medicine Volume 193 Number 11 | June 1 2016



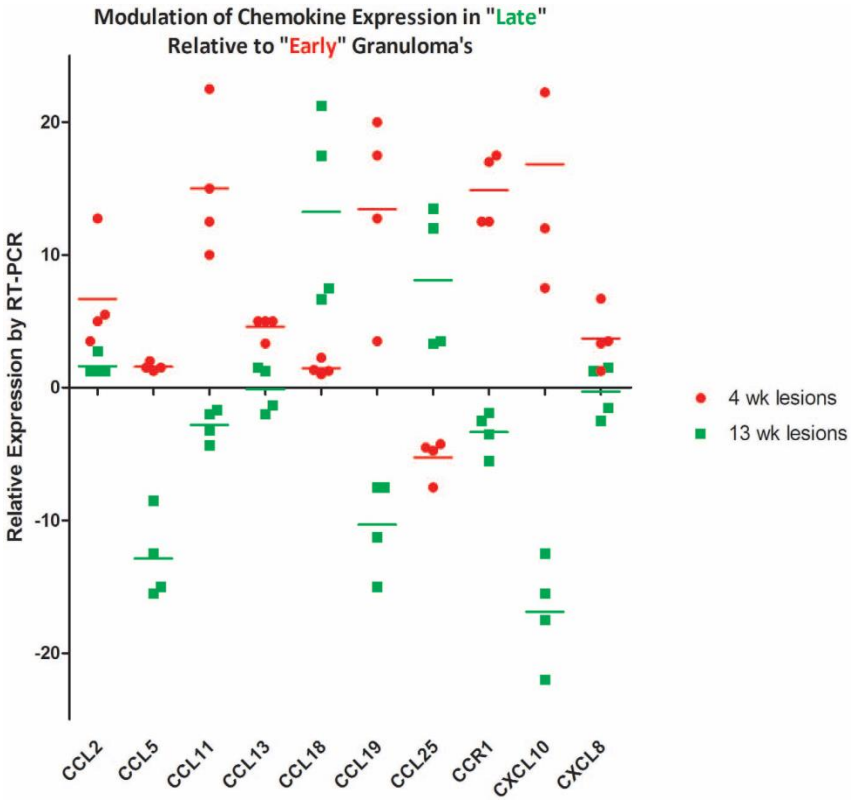
M Kambouchner, Depart de Pathologie Avicenne Bobigny

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

cytokines *récepteurs*

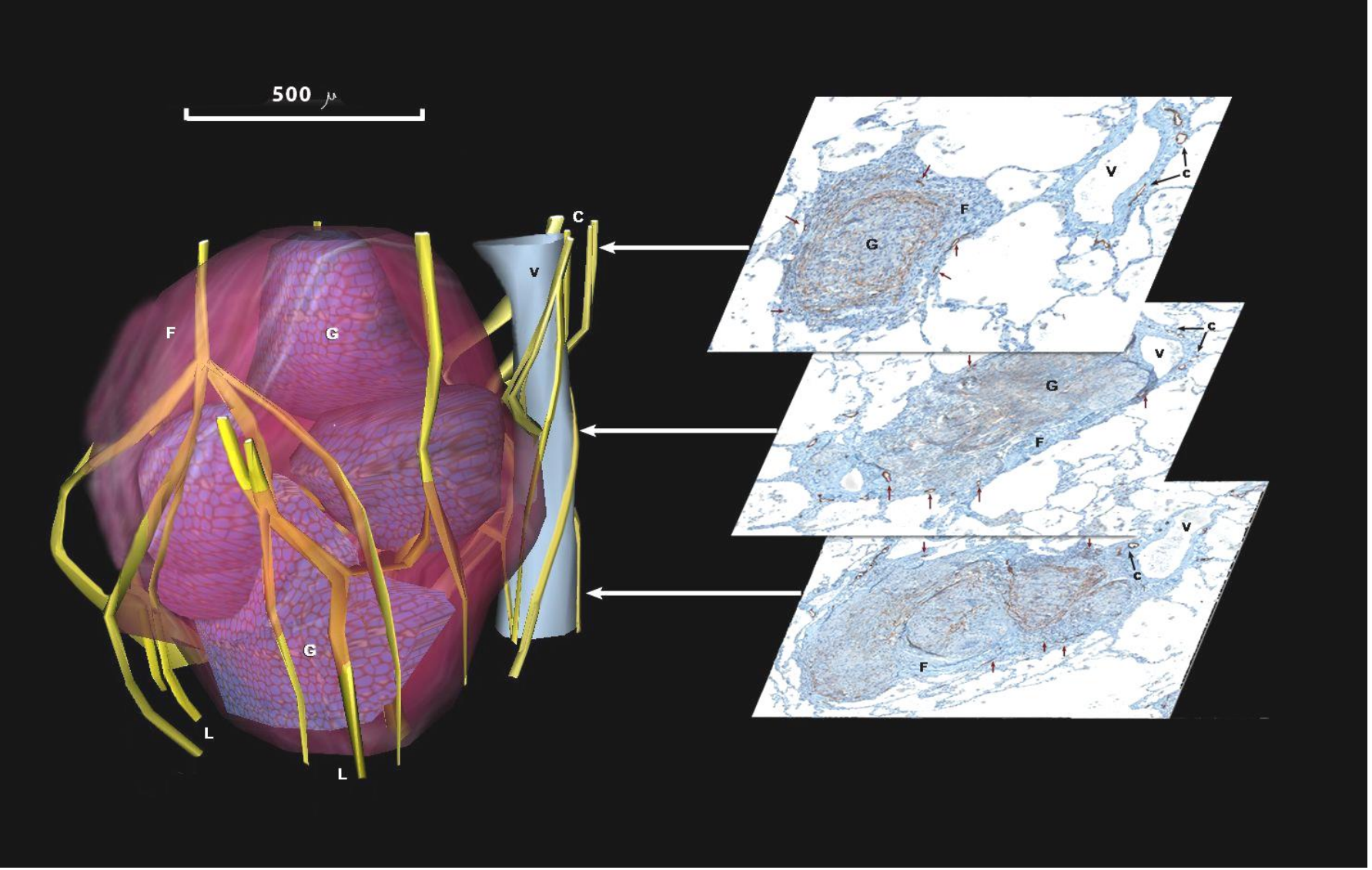


INFγ network *TNFα network*

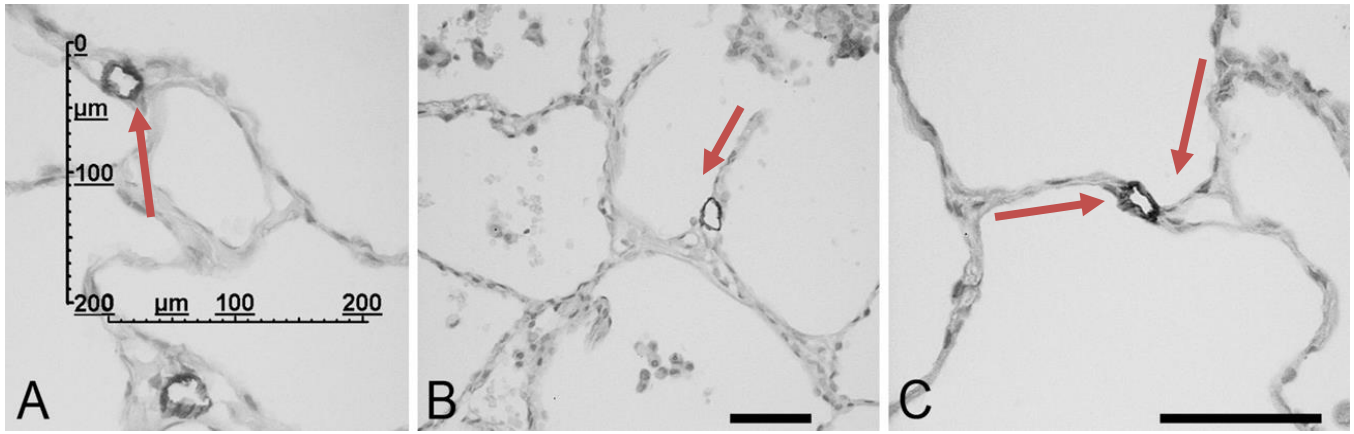


Aspects histo identiques à 4 et 13 semaines!


La proximité avec les lymphatiques



Kambouchner M et al. Lymphatic and blood microvasculature organisation in pulmonary sarcoid granulomas. Eur Respir J. 2011



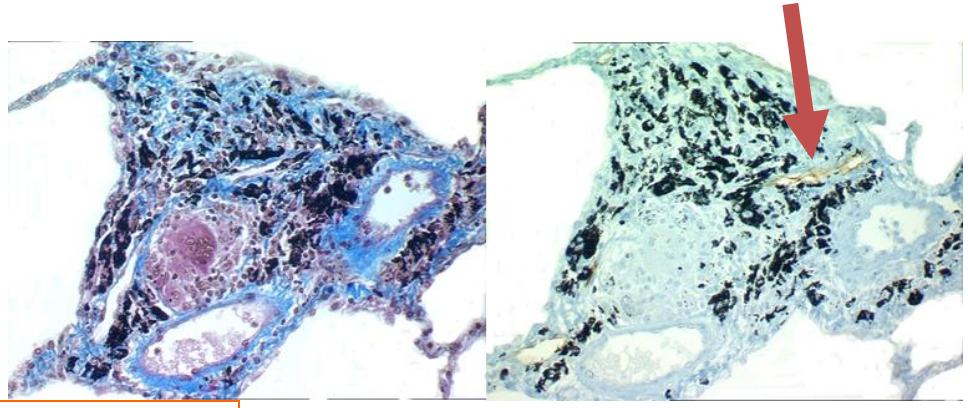
M Kambouchner & JFBernaudin
J Histochem Cytochem 2009

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*



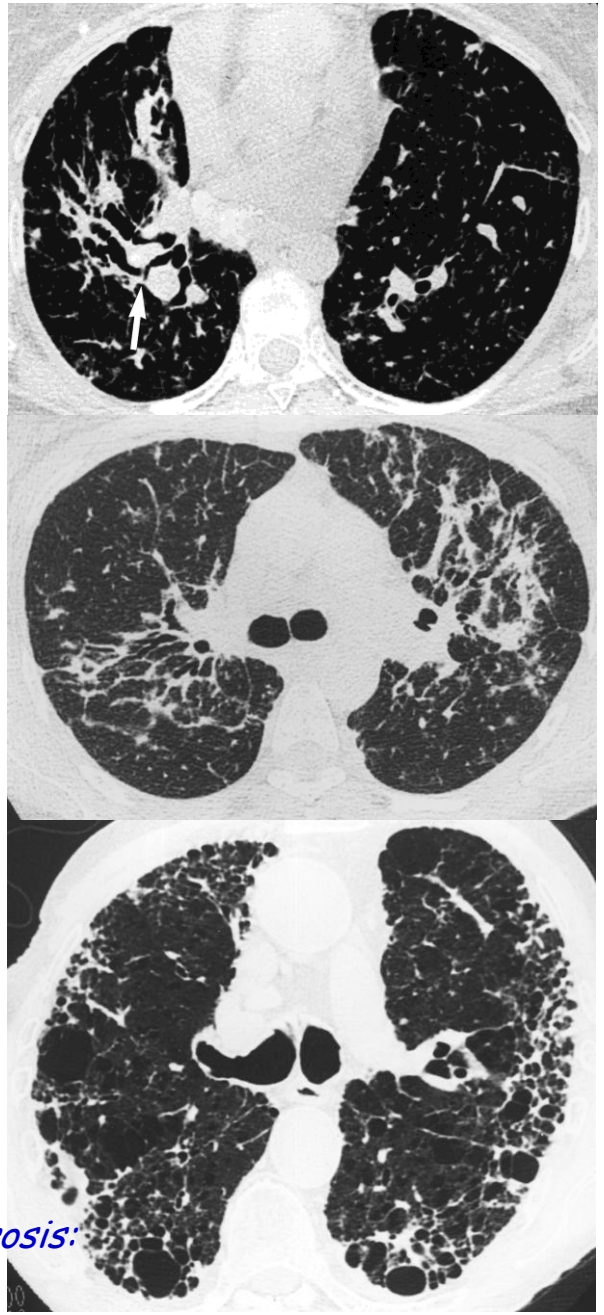
« sumps » puisards, zones de vidange
« initial foci of a wide variety of disease condition » (mycobac, poussières)


Du granulome à la fibrose

- *« Although granulomas may resolve with little consequence pulmonary fibrosis occurs in 20 to 25% of patients with sarcoidosis. The pathogenesis of pulmonary fibrosis remains uncertain »* *Ianuzzi MC et al. NEJM 2007*

- *« While there has been progress in sarcoidosis over the past few years, much is still unknown »* *Baughman R, et al AJRCCM 2011 under press*

- *1. distorsion des voies aériennes proximales*
- *2. opacités linéaires à extension périphérique*
- *3. rayon de miel*

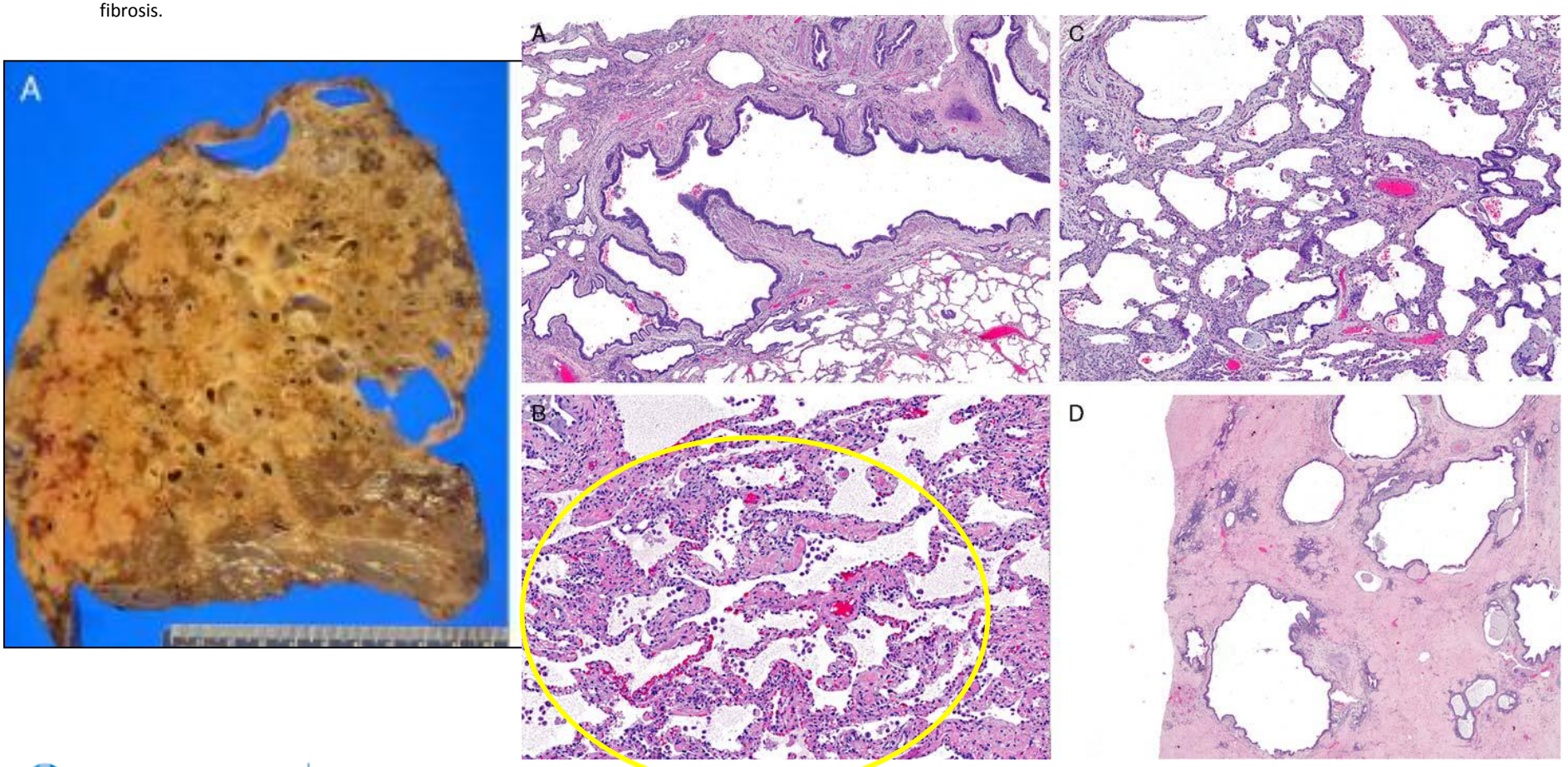


M Abehsera M, D Valeyre,P Grenier, H Jaillet, JP Battesti, M. Brauner. Sarcoidosis with Pulmonary Fibrosis: CT Patterns and Correlation with Pulmonary Function AJR 2000

End-stage Sarcoid Lung Disease Is Distinct From Usual Interstitial Pneumonia.
Xu, Lauren; Kligerman, Seth; Burke, Allen

American Journal of Surgical Pathology. 37(4):593-600, April 2013.
DOI : 10.1097/PAS.0b013e3182785a2d

FIGURE 5 . Pulmonary sarcoid, gross fibrotic patterns. A, Diffuse fibrosis with scattered cysts. B, Marked septal and peribronchial fibrosis. C, Marked subpleural, septal, and peribronchial hilar fibrosis.

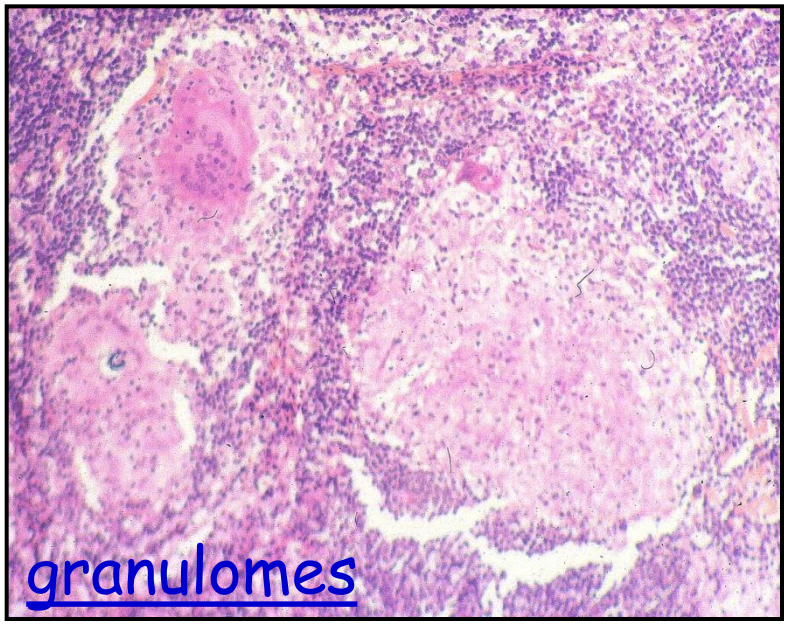


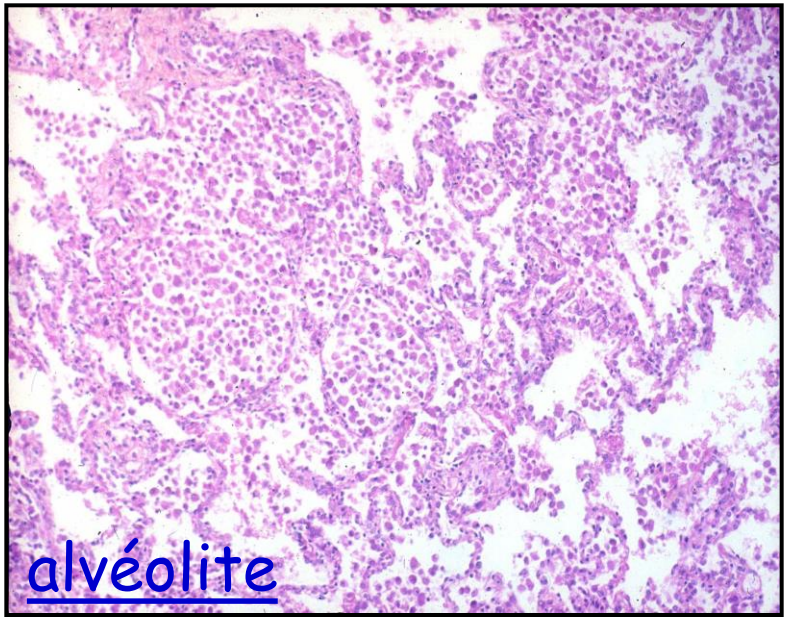
ALVEOLITIS AND GRANULOMAS: SEQUENTIAL COURSE IN PULMONARY SARCOIDOSIS

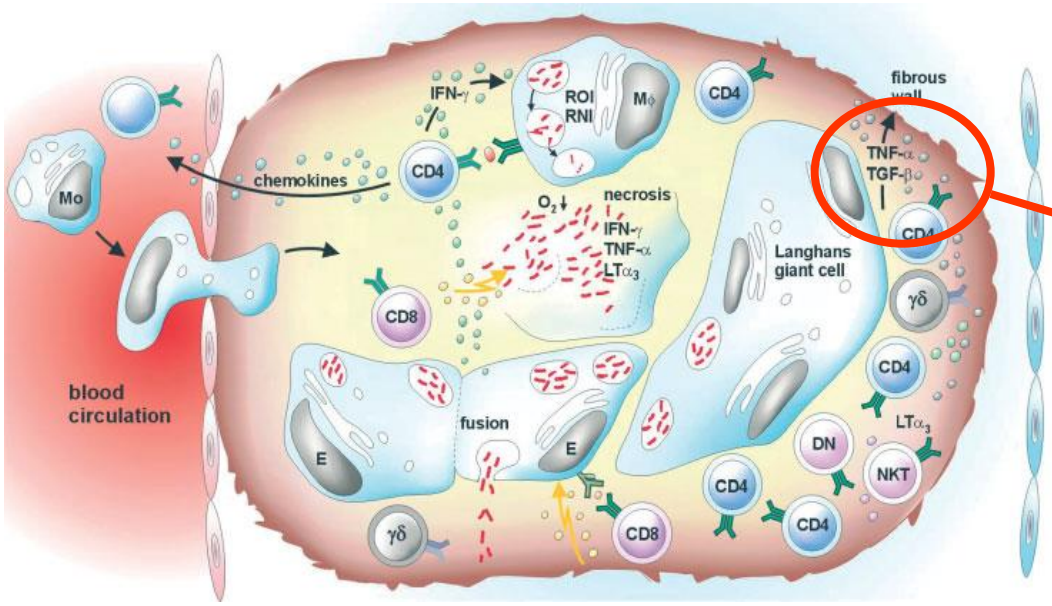
J. LACRONIQUE*, J.-F. BERNAUDIN**, P. SOLER***, F. LANGE**, O. KAWANAMI†, G. SAUMON***, R. GEORGES***, F. BASSET***

* 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.

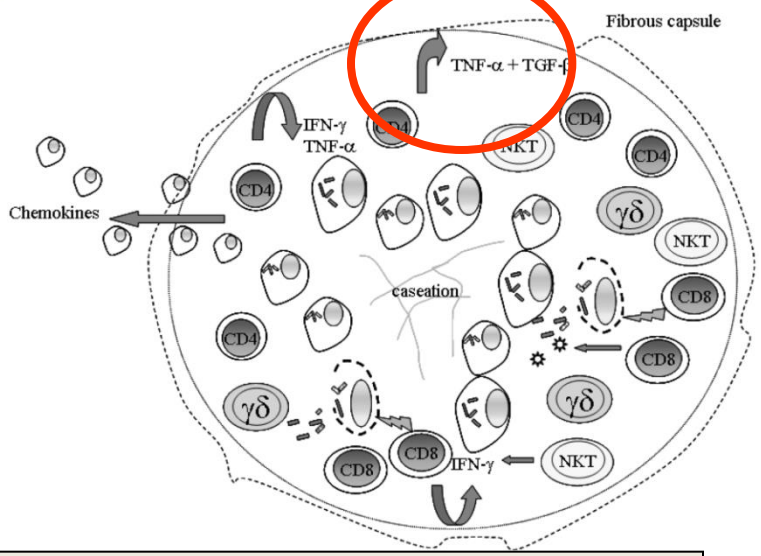
Sarcoidosis (1987) pp 36-42 Pergamon Press







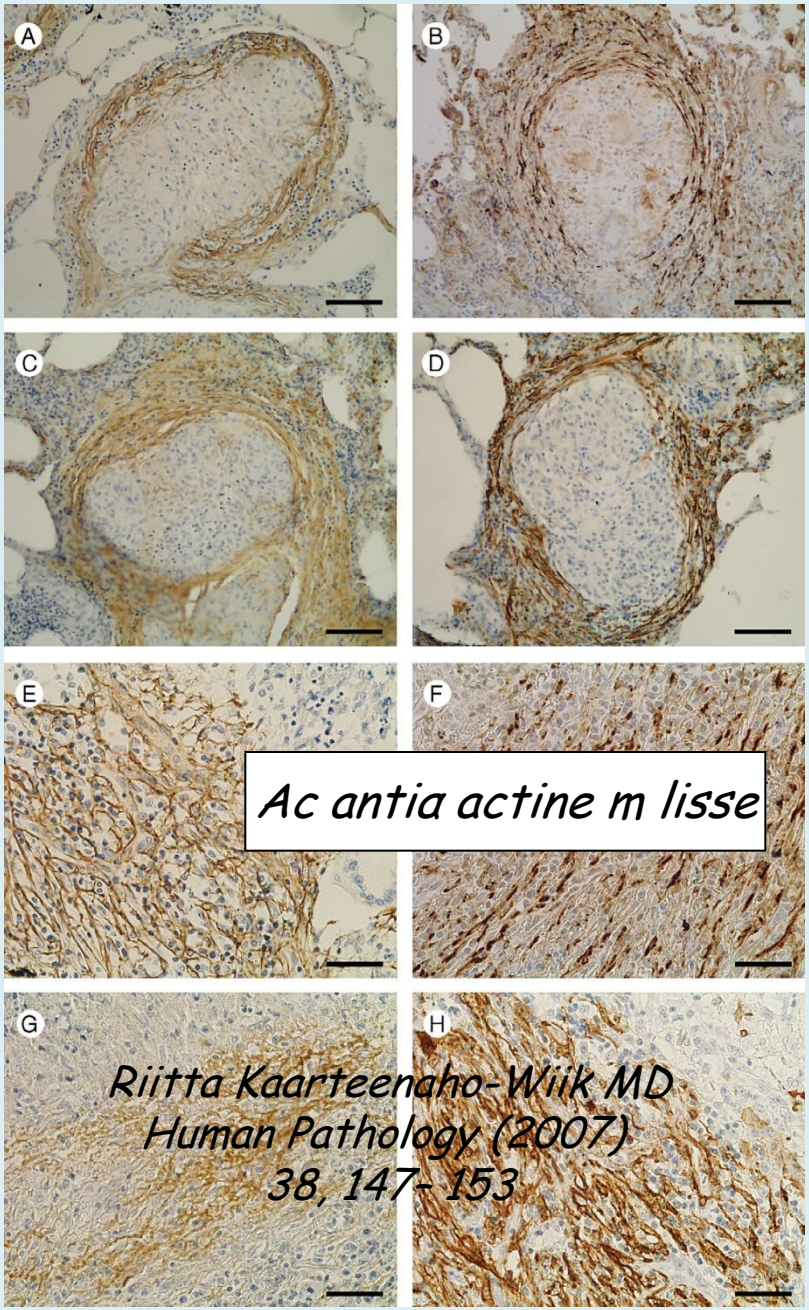
TGF β
TNF a

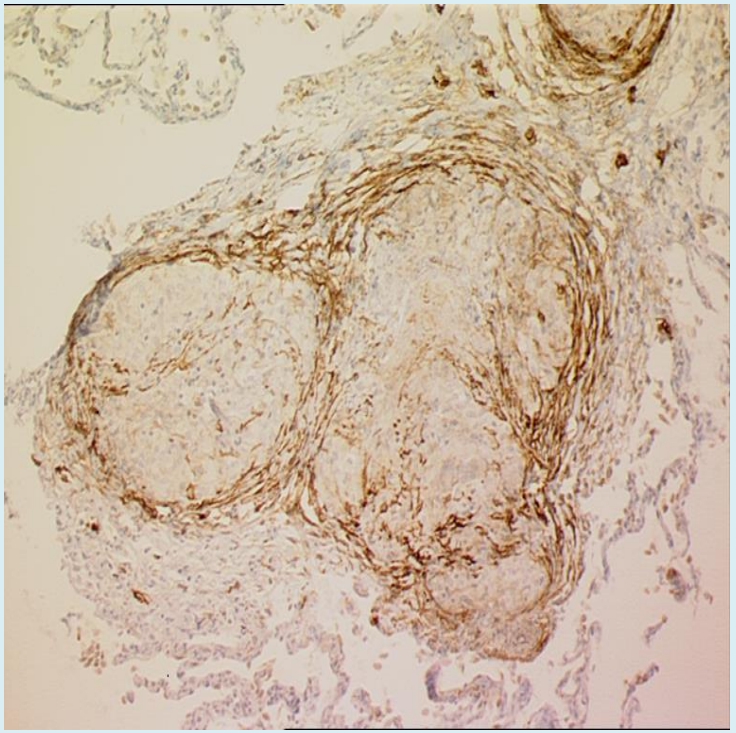


T Ulrichs, S HE Kaufmann. ***New insights into the function of granulomas in human tuberculosis***
J Pathol 2006; **208**: 261-269

encapsulation

TB Dheda K, Booth H
Lung Remodeling in Pulmonary Tuberculosis
JID 2005:192

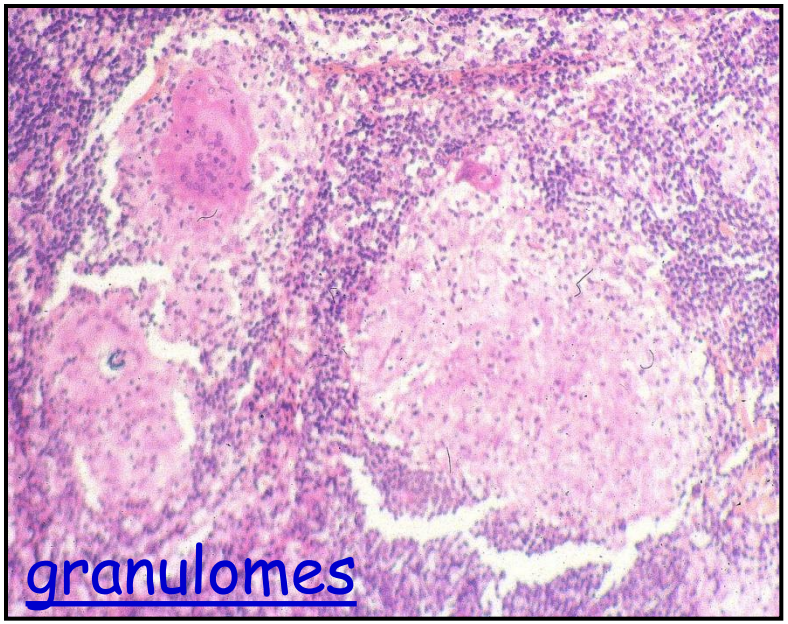




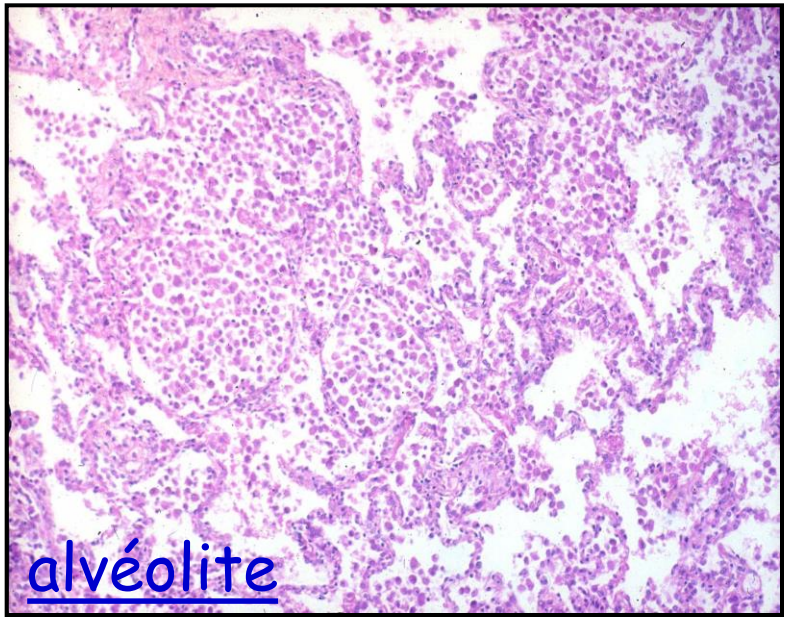
Ac anti podoplanine D2-40
MK &JFB

Couronne de myofibroblastes

évolution fibrosante liée à l'atteinte parenchymateuse hors granulomes?



granulomes



alvéolite

Shigemitsu H, Oblad JM, Sharma OP, Koss MN.
Eur Respir J. 2010 Mar;35(3):695-7

Chronic interstitial pneumonitis in end-stage sarcoidosis

- 7 poumons explants de transplantation pour « end-stage » sarcoïdose
- 2/7 aspect d'UIP terminale + 2/7 pneumopathie interstitielle avec foyers fibroblastiques
- durée d'évolution avant transplantation
  - 17, 20, 33 ans en absence de pneumopathie interstitielle inflammatoire (explant)
  - 3,3,6,7 ans si présence de pneumopathie interstitielle inflammatoire et/ou rayons de miel

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

AJRCCM. 2010 181

Gene Set Analysis of Lung Samples Provides Insight into Pathogenesis of Progressive, Fibrotic Pulmonary Sarcoidosis

Helen E. Lockstone[1], Sharon Sanderson[2], Nina Kulakova[2], Dilair Baban[1], Andrew Leonard[3], Wai Ling Kok[2], Simon McGowan[4], Andrew J. McMichael[2], and Ling-Pei Ho[2,5]

sarc

- *Sarcoidoses*

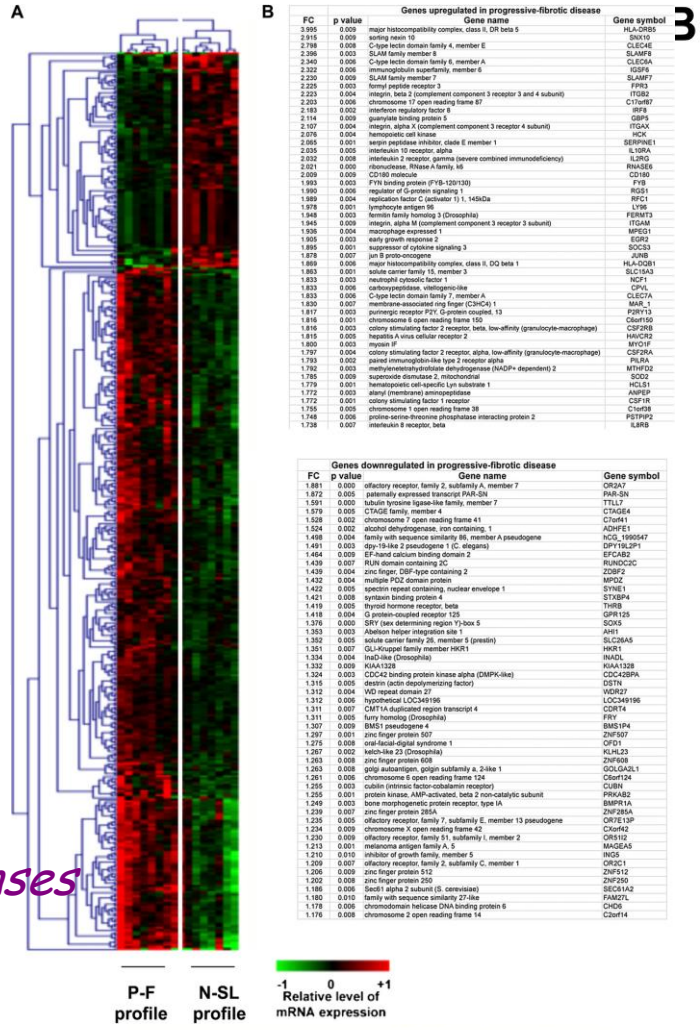
N-SL nodular self limited(8)

P-F progressive fibrosis (7)

29000gènes étudiés

↓

337 gènes
-activation immune
-mécanismes de défenses



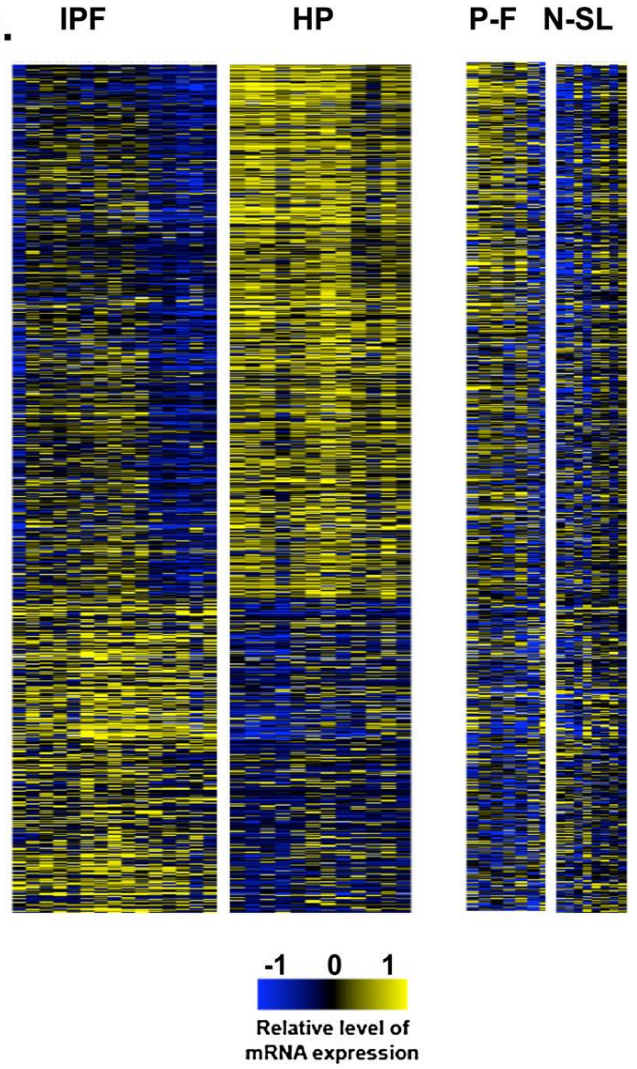
B

Genes upregulated in progressive-fibrotic disease

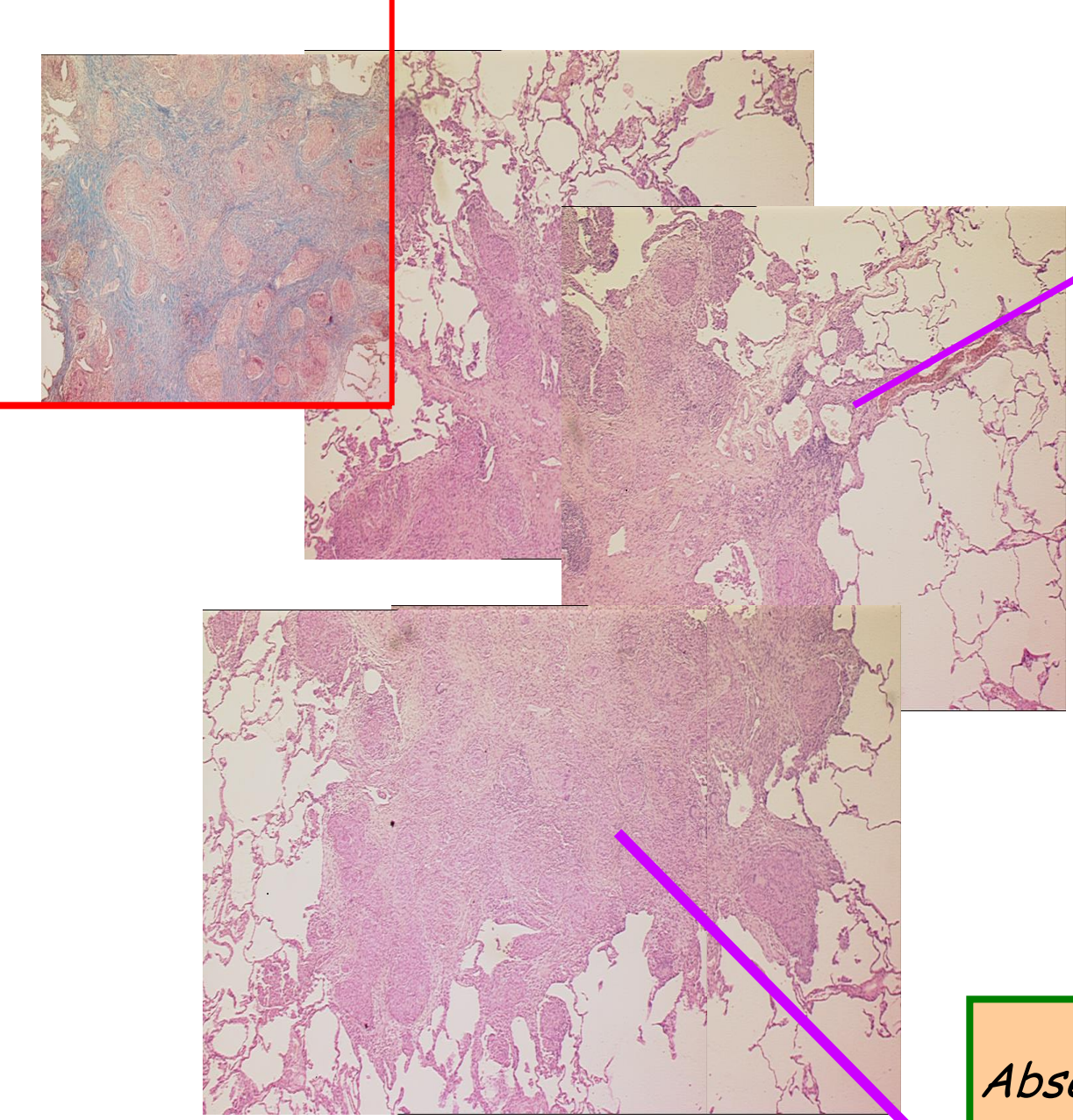
FC	p value	Gene name	Gene symbol
3.995	0.009	major histocompatibility complex, class II, DR beta 5	HLA-DRB5
2.915	0.009	sorting nexin 10	SNX10
2.798	0.008	C-type lectin domain family 4, member E	CLEC4E
2.396	0.003	SLAM family member 8	SLAMF8
2.340	0.006	C-type lectin domain family 6, member A	CLEC6A
2.322	0.006	immunoglobulin superfamily, member 6	IGSF6
2.230	0.009	SLAM family member 7	SLAMF7
2.225	0.003	formyl peptide receptor 3	FPR3
2.223	0.004	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)	ITGB2
2.203	0.006	chromosome 17 open reading frame 67	C17orf67
2.183	0.002	interferon regulatory factor 8	IRF8
2.114	0.009	guanylate binding protein 5	GBP5
2.107	0.004	integrin, alpha X (complement component 3 receptor 4 subunit)	ITGAX
2.076	0.004	hemopoietic cell kinase	HCK
2.065	0.001	serpin peptidase inhibitor, clade E member 1	SERPINE1
2.035	0.005	interleukin 10 receptor, alpha	IL10RA
2.032	0.008	interleukin 2 receptor, gamma (severe combined immunodeficiency)	IL2RG
2.021	0.000	ribonuclease, RNase A family, k6	RNASE6
2.009	0.009	CD180 molecule	CD180
1.993	0.003	FYN binding protein (FYB-120/130)	FYB
1.990	0.006	regulator of G-protein signaling 1	RGS1
1.989	0.004	replication factor C (activator 1) 1, 145kDa	RFC1
1.978	0.001	lymphocyte antigen 96	LY96
1.948	0.003	fermitin family homolog 3 (Drosophila)	FERMT3
1.945	0.009	integrin, alpha M (complement component 3 receptor 3 subunit)	ITGAM
1.936	0.004	macrophage expressed 1	MPEG1
1.905	0.003	early growth response 2	EGR2
1.895	0.001	suppressor of cytokine signaling 3	SOCS3
1.878	0.007	jun B proto-oncogene	JUNB
1.869	0.006	major histocompatibility complex, class II, DQ beta 1	HLA-DQB1
1.863	0.001	solute carrier family 15, member 3	SLC15A3
1.833	0.003	neutrophil cytosolic factor 1	NCF1
1.833	0.006	carboxypeptidase, vitellogenic-like	CPVL
1.833	0.006	C-type lectin domain family 7, member A	CLEC7A
1.830	0.007	membrane-associated ring finger (C3HC4) 1	MAR_1
1.817	0.003	purinergic receptor P2Y, G-protein coupled, 13	P2RY13
1.816	0.001	chromosome 6 open reading frame 150	C6orf150
1.816	0.003	colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)	CSF2RB
1.815	0.005	hepatitis A virus cellular receptor 2	HAVCR2
1.800	0.003	myosin IF	MYO1F
1.797	0.004	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)	CSF2RA
1.793	0.002	paired immunoglobin-like type 2 receptor alpha	PILRA
1.792	0.003	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2	MTHFD2
1.785	0.009	superoxide dismutase 2, mitochondrial	SOD2
1.779	0.001	hematopoietic cell-specific Lyn substrate 1	HCLS1
1.772	0.003	alanyl (membrane) aminopeptidase	ANPEP
1.772	0.001	colony stimulating factor 1 receptor	CSF1R
1.765	0.005	chromosome 1 open reading frame 38	C1orf38
1.748	0.006	proline-serine-threonine phosphatase interacting protein 2	PSTPIP2
1.738	0.007	interleukin 8 receptor, beta	IL8RB

Genes downregulated in progressive-fibrotic disease

FC	p value	Gene name	Gene symbol
1.881	0.000	olfactory receptor, family 2, subfamily A, member 7	OR2A7
1.872	0.005	paternally expressed transcript PAR-SN	PAR-SN
1.591	0.000	tubulin tyrosine ligase-like family, member 7	TTLL7
1.579	0.005	CTAGE family, member 4	CTAGE4
1.528	0.002	chromosome 7 open reading frame 41	C7orf41
1.524	0.002	alcohol dehydrogenase, iron containing, 1	ADHFE1
1.498	0.004	family with sequence similarity 86, member A pseudogene	hCG_1995047
1.491	0.003	dpy-19-like 2 pseudogene 1 (C. elegans)	DPY19L2P1
1.464	0.009	EF-hand calcium binding domain 2	EFCAB2
1.439	0.007	RUN domain containing 2C	RUNDC2C
1.439	0.004	zinc finger, DBF-type containing 2	ZDBF2
1.432	0.004	multiple PDZ domain protein	MPDZ
1.422	0.005	spectrin repeat containing, nuclear envelope 1	SYNE1
1.421	0.008	syntaxin binding protein 4	STXBP4
1.419	0.005	thyroid hormone receptor, beta	THRB
1.418	0.004	G protein-coupled receptor 125	GPR125
1.376	0.000	SRY (sex determining region Y)-box 5	SOX5
1.353	0.003	Abelson helper integration site 1	AHI1
1.352	0.005	solute carrier family 26, member 5 (prestin)	SLC26A5
1.351	0.007	GLI-Kruppel family member HKR1	HKR1
1.334	0.004	Ina2-like (Drosophila)	INADL
1.332	0.009	KIAA1328	KIAA1328
1.324	0.003	CDC42 binding protein kinase alpha (DMPK-like)	CDC42BPA
1.315	0.005	destrin (actin depolymerizing factor)	DSTN
1.312	0.004	WD repeat domain 27	WDR27
1.312	0.006	hypothetical LOC349196	LOC349196
1.311	0.007	CMT1A duplicated region transcript 4	CDRT4
1.311	0.005	furry homolog (Drosophila)	FRY
1.307	0.009	BMS1 pseudogene 4	BMS1P4
1.297	0.001	zinc finger protein 507	ZNF507
1.275	0.008	oral-facial-digital syndrome 1	OFD1
1.267	0.002	kelch-like 23 (Drosophila)	KLHL23
1.263	0.008	zinc finger protein 608	ZNF608
1.263	0.008	golgi autoantigen, golgin subfamily a, 2-like 1	GOLGA2L1
1.261	0.006	chromosome 6 open reading frame 124	C6orf124
1.255	0.003	cubilin (intrinsic factor-cobalamin receptor)	CUBN
1.255	0.001	protein kinase, AMP-activated, beta 2 non-catalytic subunit	PRKAB2
1.249	0.003	bone morphogenetic protein receptor, type IA	BMPR1A
1.239	0.007	zinc finger protein 285A	ZNF285A
1.235	0.005	olfactory receptor, family 7, subfamily E, member 13 pseudogene	OR7E13P
1.234	0.009	chromosome X open reading frame 42	CXorf42
1.230	0.009	olfactory receptor, family 51, subfamily I, member 2	OR51I2
1.213	0.001	melanoma antigen family A, 5	MAGEA5
1.210	0.010	inhibitor of growth family, member 5	ING5
1.209	0.007	olfactory receptor, family 2, subfamily C, member 1	OR2C1
1.206	0.009	zinc finger protein 512	ZNF512
1.202	0.008	zinc finger protein 250	ZNF250
1.186	0.006	Sec61 alpha 2 subunit (S. cerevisiae)	SEC61A2
1.180	0.010	family with sequence similarity 27-like	FAM27L
1.178	0.006	chromodomain helicase DNA binding protein 6	CHD6
1.176	0.008	chromosome 2 open reading frame 14	C2orf14



- *Le désordre dans les forces de tension*



traction

Absence de cycle respiratoire

MK, JFB, DV Avicenne

Table 1. Knowledge gaps in the pathogenesis of sarcoidosis

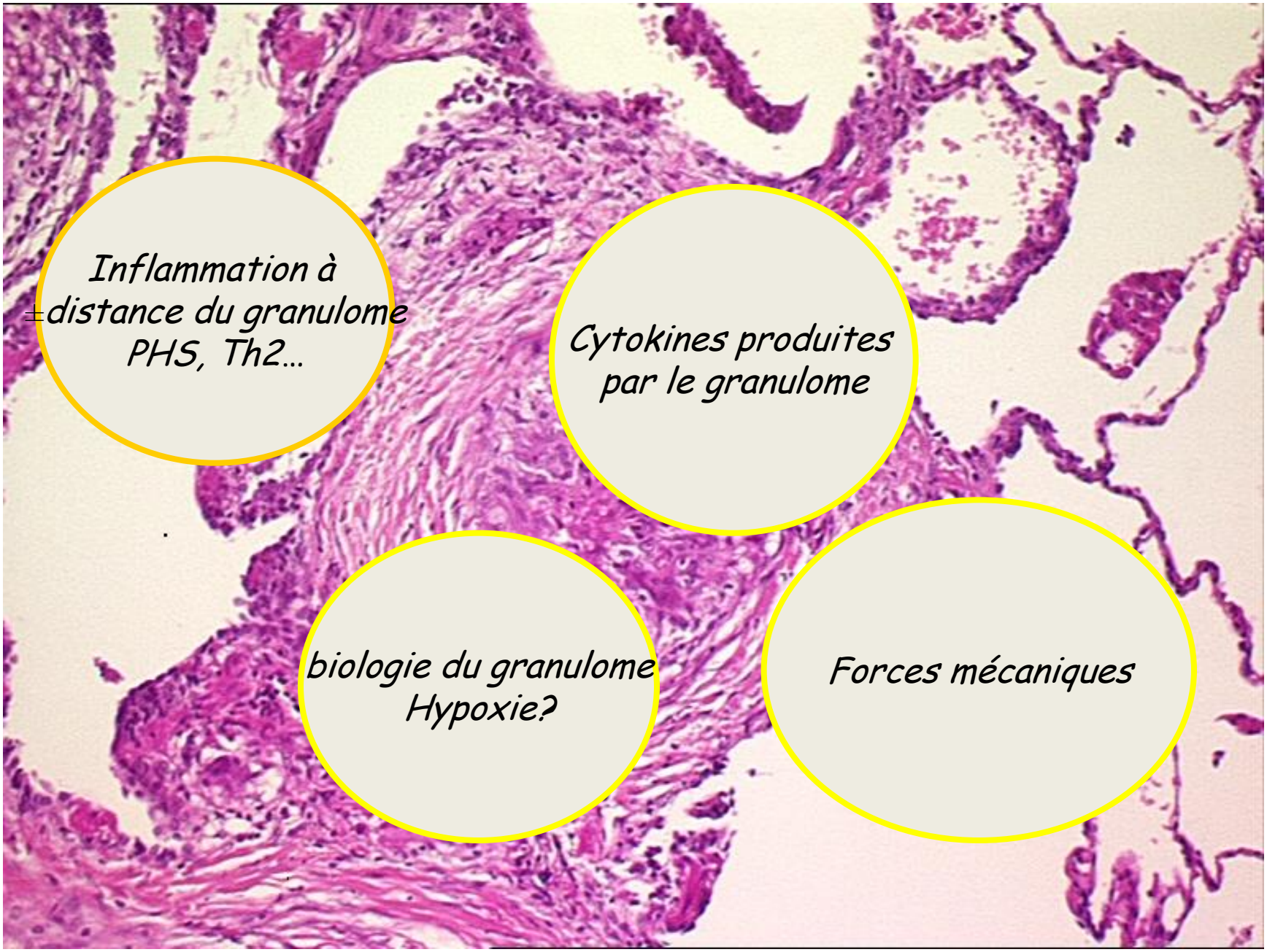
Genetic knowledge gaps
Understanding of the relationships between genotype and clinical phenotype is limited.
Understanding of genetic factors influencing immunologic variability is limited.
The role played by epigenetic factors (noncoding RNA, methylation, histone acetylation) in sarcoidosis is limited.
Knowledge gaps relating to environmental factors
The role of microbial and nonmicrobial antigens in the pathogenesis of sarcoidosis has not been firmly established.
Environmental factors that modify sarcoidosis disease course remain unknown.
The role played by the microbiome (lung, gastrointestinal tract) remains to be determined.
Knowledge gaps of the immunology of sarcoidosis
The role of T-cell subsets remains controversial.
The role of macrophage polarization in sarcoidosis granuloma formation is unclear.
The role of B cells remains largely unexplored.
The complex interaction among these cell lines during granuloma formation is difficult to model, and, as such, is largely unknown.

D Moller et al. 2017

Table 2. Summary recommendations for future research

Research Question to be Addressed	Recommended Scientific Approach
What is (are) the environmental exposure(s) causing sarcoidosis and influencing diverse clinical phenotypes?	Studies to identify environmental exposures that are associated with extreme disease phenotypes
What are the immune mechanisms, including incompletely understood local innate and adaptive immune responses, that could be targeted to more effectively treat sarcoidosis?	Support efforts to develop relevant animal and *in vitro* disease models Support hypothesis-driven research to identify molecular mechanisms and potential therapeutic targets
What is the genetic basis of severe sarcoidosis phenotypes?	Leverage high-throughput, low-cost genome-wide technology Genome-wide association studies Gene sequencing Epigenetics
How does the host microbiome influence the risk for sarcoidosis or severe sarcoidosis phenotypes?	Support studies to comprehensively evaluate the microbiome of the lungs and gastrointestinal tract and correlate with clinical and immunological sarcoidosis phenotypes
What are the molecular pathways and biomarkers that contribute to chronic multisystem sarcoidosis, and how can this information contribute to improved care?	Conduct longitudinal studies to assess various candidate biomarkers that would serve to assist in establishing the diagnosis, prognosis, and response to treatment
How do we account for the complex interactions of multiple environmental and host factors as they relate to the phenotypic variability of sarcoidosis?	Bioinformatic analysis of comprehensive data sets derived from large patient cohorts followed longitudinally

D Moller 2017


Inflammation à ±distance du granulome PHS, Th2…
Cytokines produites par le granulome
biologie du granulome Hypoxie?
Forces mécaniques

conclusion

« While there has been progress in sarcoidosis over the past few years, much is still unknown »
Baughman R, et al AJRCCM 2011

OPEN ACCESS Freely available online 2011 PLoS one

An *In Silico* Modeling Approach to Understanding the Dynamics of Sarcoidosis

Baltazar D. Aguda[1], Clay B. Marsh[2], Michael Thacker[3], Elliott D. Crouser[2]*

1 Neuro-Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, United States of America, **2** Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, The Ohio State University Medical Center, Columbus, Ohio, United States of America, **3** Department of Electrical and Computer Engineering, The Ohio State University Medical Center, Columbus, Ohio, United States of America

Abstract

AS

CrossMark ← click for updates

Mathematical model of sarcoidosis

Wenrui Hao[a], Elliott D. Crouser[b], and Avner Friedman[c,1]

[a]Mathematical Biosciences Institute, The Ohio State University, Columbus, OH; [b]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, The Ohio State University Medical Center, Columbus, OH; and [c]Mathematical Biosciences Institute & Department of Mathematics, The Ohio State University, Columbus, OH 43210

Contributed by Avner Friedman, September 17, 2014 (sent for review August 8, 2014; reviewed by Marc Judson and Reinhard C. Laubenbacher)

leads to a typical Th1 immune response that is initiated by macrophages. Activated macrophages secrete proinflammatory cytokines such as IL-12 (5) and TNF-α (6, 7) and anti-inflammatory cytokine IL-10 (8) and IL-13 (9); they and Th17 cells secrete chemokine (C-C motif) ligand 20 (CCL20) CCL20 (10, 11). The $CD4^+$ T cells in sarcoidosis are primarily Th1, Th17, and Treg. Th1 is activated by IL-12, and activated Th1 cells produce IFN-γ, which further activates macrophages; these processes are inhibited by IL-10 (12, 13). Cytokine CCL20 chemoattracts both Treg and Th17 cells (14) into the granuloma. Treg and Th17 are both activated by TGF-β (15). IL-2 secreted by Th1 (16) increases the proliferation of Th1 cells (16), blocks the proliferation of Th17 cells (17), and enhances the activation of Treg by TGF-β (18, 19); TGF-β is secreted by activated macrophages and Treg (20, 21).

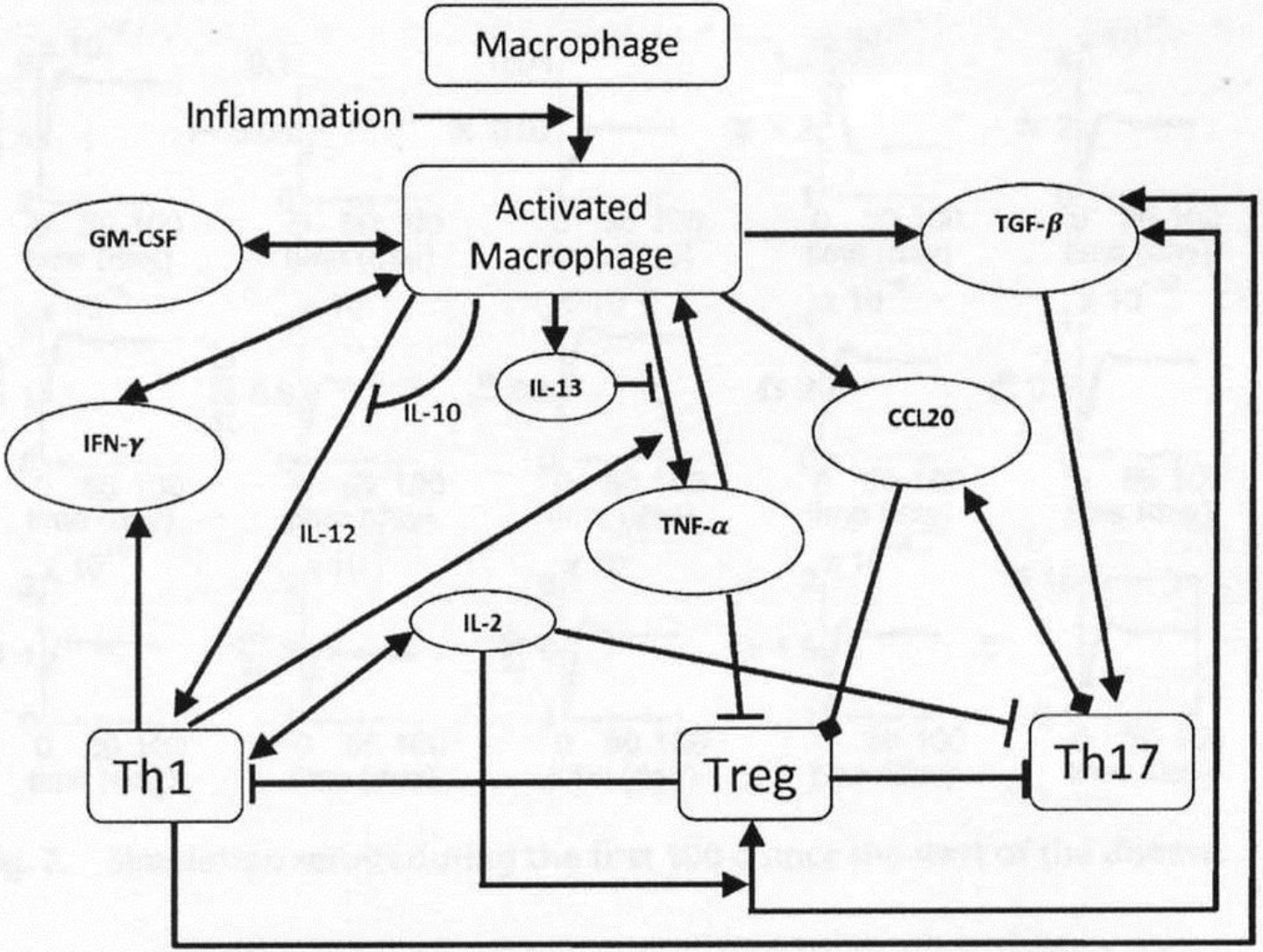


Fig. 1. Schematic network of sarcoidosis. Arrowhead means production or activation, rectangle means inhibition, and oval means chemoattraction

Remerciements à
Françoise Basset
Jacques Chrétien
Jean Bignon
Ron Crystal
Paul Soler
Jocelyne Fleury
Marianne Kambouchner
Dominique Valeyre