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**INSERM U955 -team 10**  
Cell Interactions  
in Neuromuscular  
System

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**Macrophagic myofasciitis**  
**New insights on the long-term safety**  
**of aluminum adjuvants**

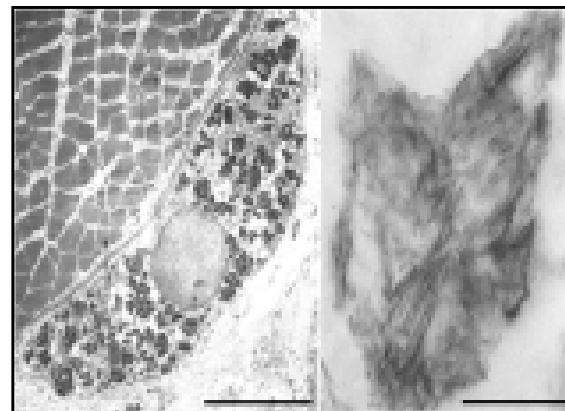
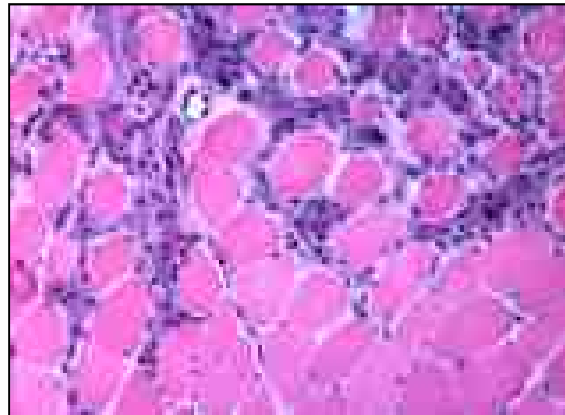
FJ AUTHIER

Reference Center for Neuromuscular Diseases GNMH,  
Henri Mondor University Hospital, Créteil, France

# 1. Macrophagic myofasciitis (MMF): A specific lesion in deltoid muscle

## Macrophagic myofasciitis: an emerging entity

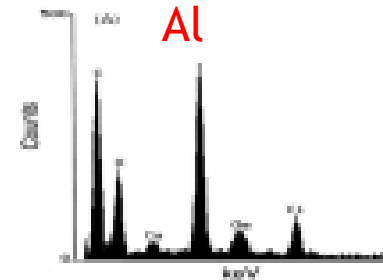
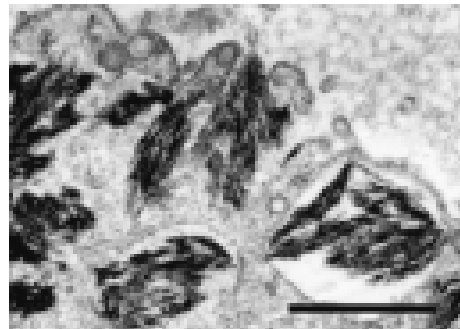
R. R. Gherardi, M. Coquet, P. Chélin, F. J. Authier, P. Lefebvre, L. Bélec, D. Figarella-Branger, JM. Masson, JF. Pellissier, M. Fardoux, for the Groupe d'Études et Recherches sur les Maladies Musculaires Acquises et Dysimmunitaires



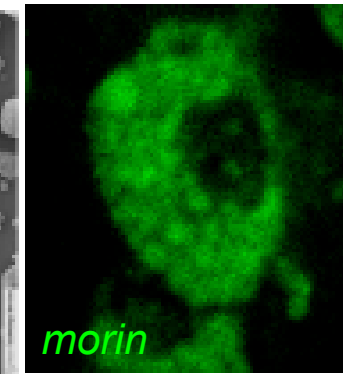
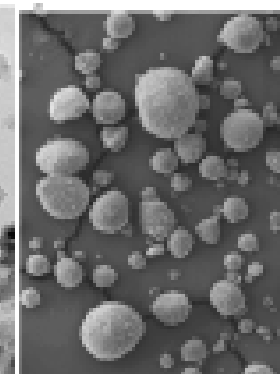
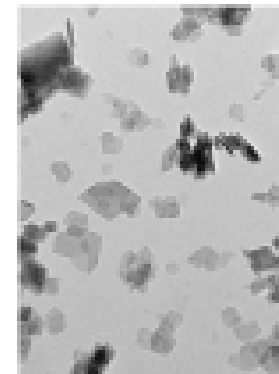
Lancet 1998; 352: 347-52

## Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle

R. R. Gherardi<sup>1</sup>, M. Coquet<sup>1</sup>, B. Flacco<sup>2</sup>, L. Bélec<sup>3</sup>, P. Lefebvre<sup>4</sup>, J. A. Berthiaud<sup>5</sup>, J. F. Pellissier<sup>6</sup>, P. Chélin<sup>7</sup> and R. R. Gherardi<sup>1</sup>



HBV  
TT  
HAV



Brain (2001), 124, 1821-1831

## スライド 2

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FJ10

Macrophagic myofasciitis is an emerging condition characterized by specific lesions at muscle biopsy made of focal macrophagic infiltrates  
Authier, 2007/06/25

## 2. MMF-associated Clinical Syndrome

Up to 17 alum shots (mean 5.2) in past 10yrs

Delayed clinical onset (mean 12mo) from last shot

Delayed muscle biopsy (mean 66 mo) from last shot

**Myalgia (88%) + Chronic fatigue (87%) + Cognitive impairment (96%)**

± overt autoimmune disease (20%) : **Multiple sclerosis (9%), DM, thyroiditis...**)

1. Significant association between **myalgias** and **MMF**: Gherardi et al, Brain 2001
2. Significant association between **fatigue** and **MMF**
  - case-control study: AFSSAPS, 2003
  - Total and Cognitive Fatigue scores (Impact Fatigue Scale) higher in MMF
3. Most **MMF patients fulfill criterias for Chronic Fatigue Syndrome**
  - Authier et al, Arthritis Rheum 2003
  - fatigue 93%, myalgias 87%, arthralgias 55%
  - CFS criteria (CDC/Oxford) 53%

### 3. MMF after anti-HPV immunization

8 girls referred to Henri Mondor hospital

- Age: at onset 15-18 yrs  
at evaluation : 16-23 yrs

Vaccines:

**GARDASIL 8/8**

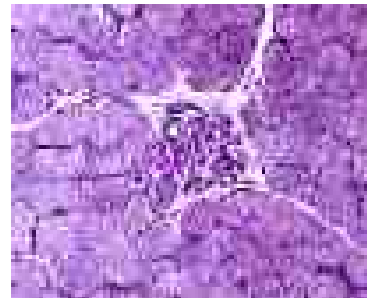
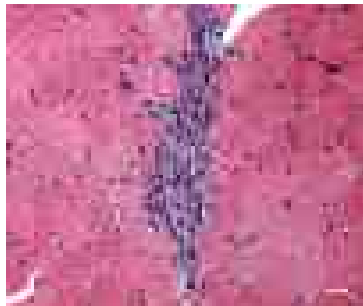
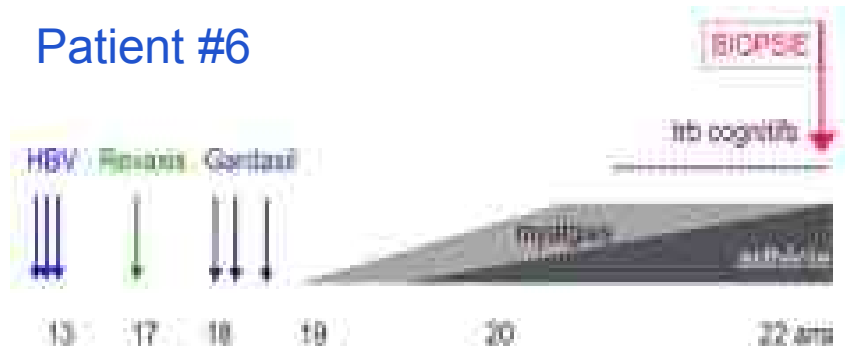
REVAXIS (DTP) 3/8

HBV 2/8

- Deltoid muscle biopsy (7/8): normal: 5/7

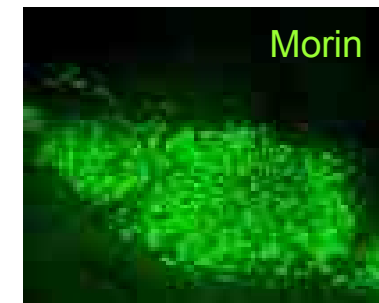
**Macrophagic myofasciitis 2/7**

#### Patient #6

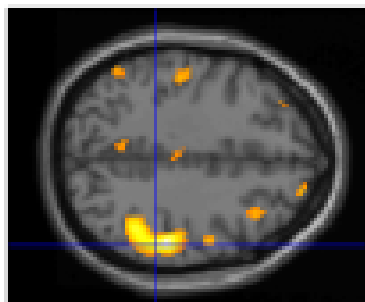
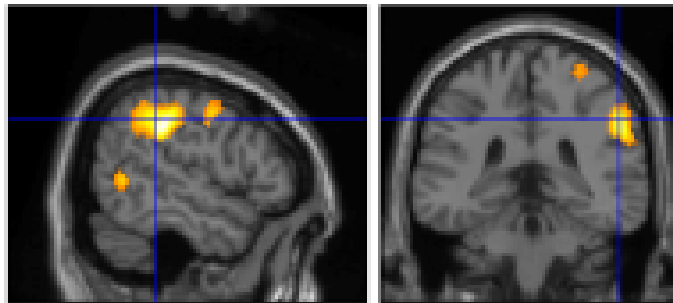
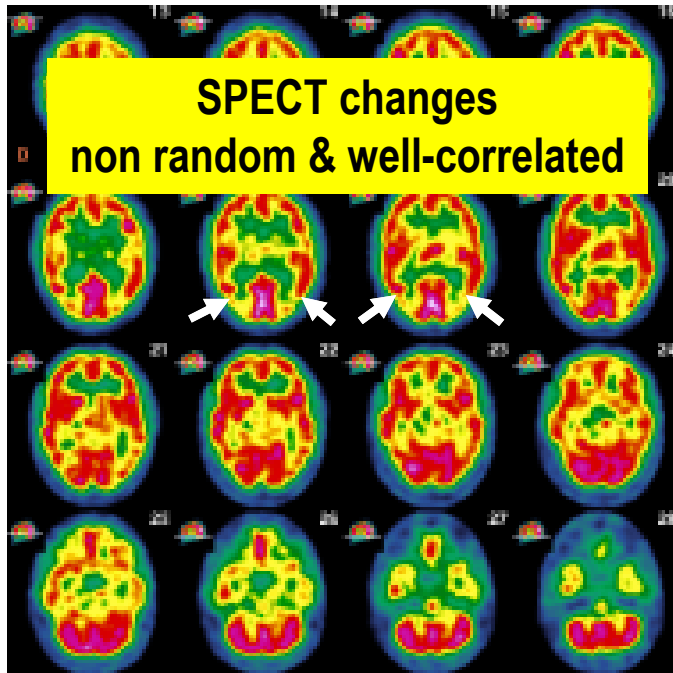


#### Experimental MMF lesion induced by i.m. injection of Gardasil

- C57.BL6 mouse
- i20  $\mu$ l Gardasil i.m. in *Tibialis anterior*
- Sampling at D+28

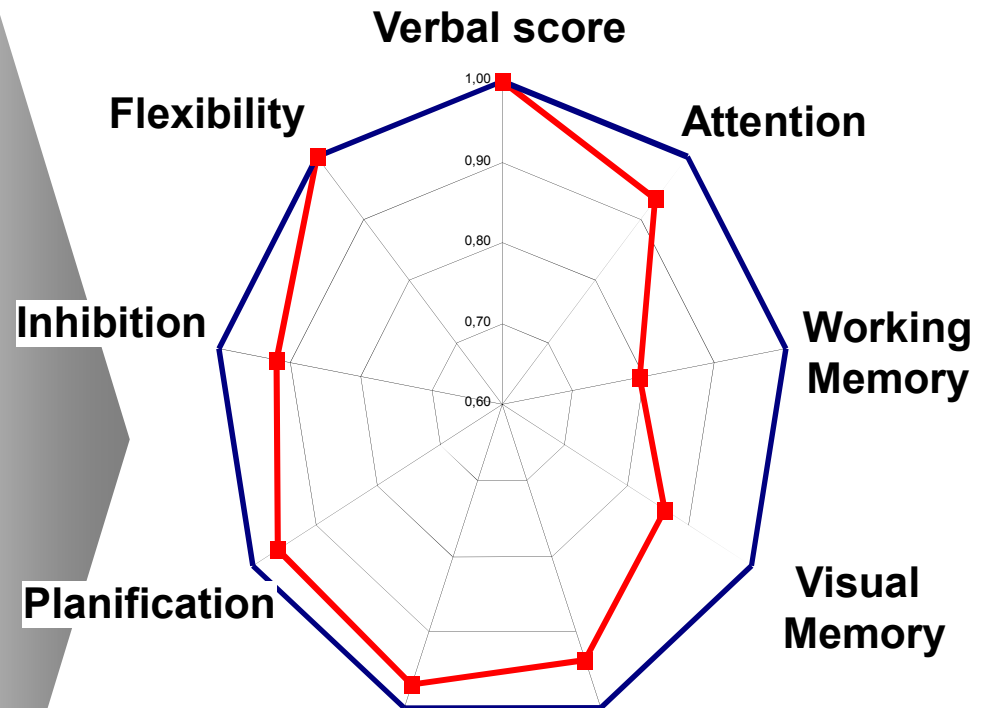


# 4. MMF is associated with Cognitive Dysfunction (MCI)



**Associative posterior cortex**  
Itti & Authier  
(in préparation)

- quasi-constant (95%)
- stereotyped, dysexecutive type
- reported in workers exposed to inhaled AI



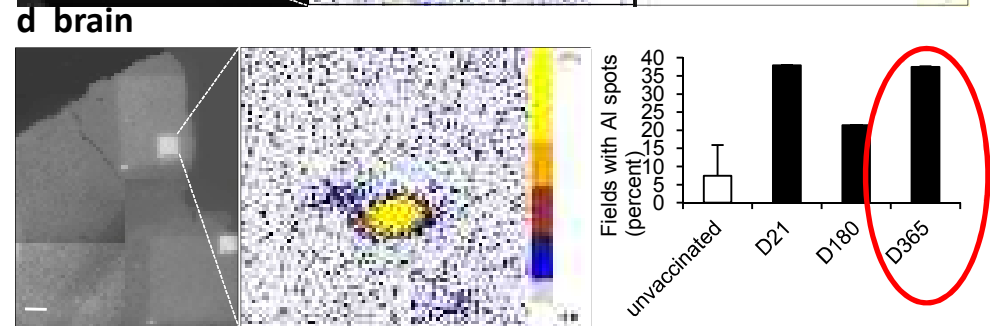
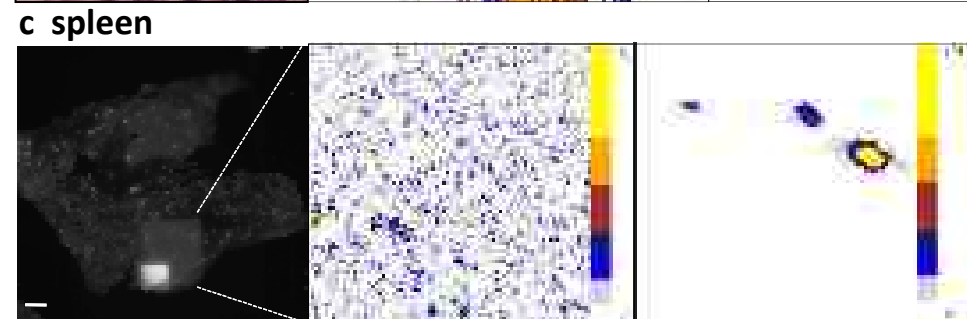
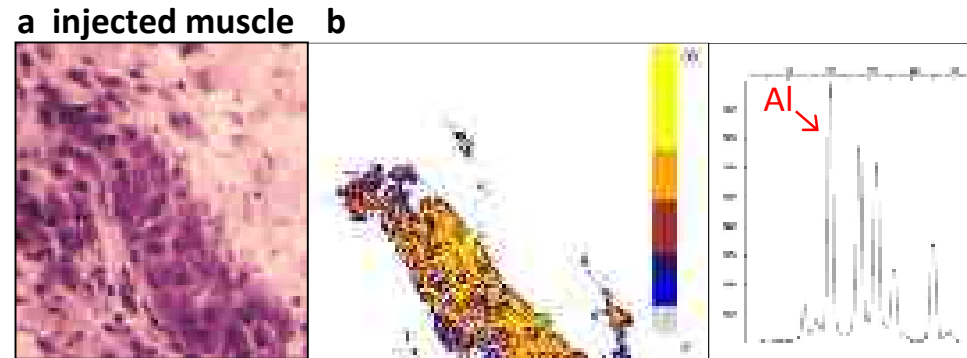
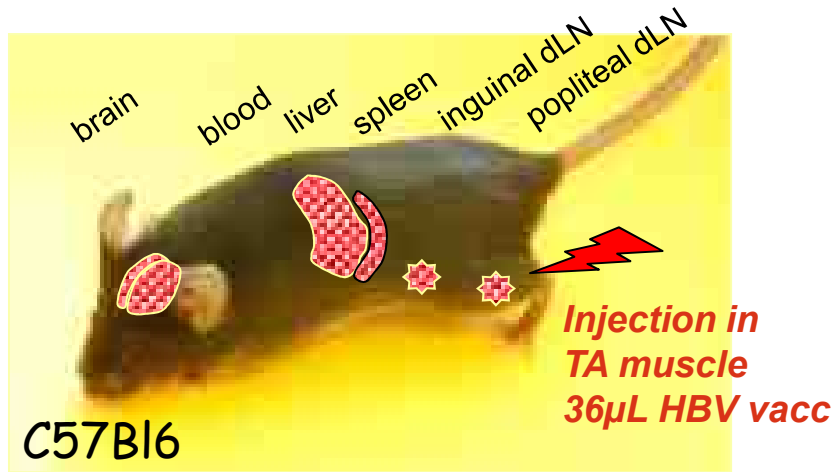
Perceptual Organisation      Verbal memory

Joint dis. : ——— (blue line)  
MMF: ——— (red line) (normalized values)

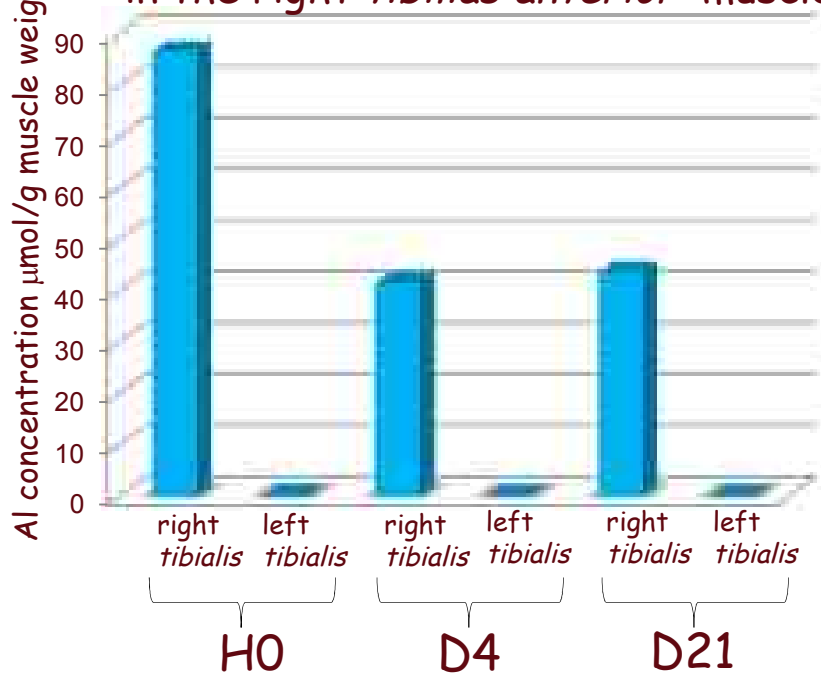
Couette *et al.* J. Inorg. Biochem. 2009  
Passeri *et al.* J. Inorg. Biochem. 2011



# 5. IM injection of alum-vaccine is followed by entry of Aluminum in brain



muscle Al content after vaccine injection in the right *tibialis anterior* muscle



- Costantini et al (1989): rat, Al-lactate, IP
- Redhead et al (1992): rat, Al(OH)<sub>3</sub>, IP
- Flarend et al (1997): rabbit, 26Al(OH)<sub>3</sub>, IM



## 6. Neuromigration of alum particles is an active process

- Alum particles can be transported by monocyte-lineage cells to lymph nodes, blood and spleen, and, similarly to HIV, may use MCP1/CCL2-dependent mechanisms to penetrate the brain.
- This occurs at a very low rate in normal conditions explaining good overall tolerance of alum despite its strong neurotoxic potential.
- However, continuously escalating doses of the poorly biodegradable alum adjuvant in the population may become insidiously unsafe, especially in case of **overimmunization**
  - or **immature/altered blood brain barrier**
  - or **high constitutive CCL-2 production**.

**INSERM U955**

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MF Boisse

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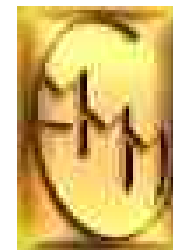
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**Claire DWOSKIN  
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