Annotation of powerpoint presentation

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Biopersistence and biodistribution of particles injected into muscle: application to Alum safety

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French myopathologists have identified in 1998 a condition called macrophagic myofasciitis (MMF), pointing to the lack of knowledge on the fate, systemic diffusion, and long-term safety of Alum particles injected into muscle. MMF was initially described as an emerging condition of unknown cause characterized by a stereotyped lesion at muscle biopsy detected in middle-aged adult patients with diffuse myalgias and fatigue.

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Macrophages, the major immune cell type in the lesion, enclosed agglomerates of nanocrystals in their cytoplasm, subsequently found to represent Al hydroxide

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These crystals corresponded to Alum derived from hepatitis B, hepatitis A and tetanus toxoid vaccines. It is now widely accepted that MMF is a specific histologic lesion assessing long-term persistence of Alum at site of previous i.m. immunization.

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Alum residence time is very long in affected individuals with a mean delay from the last vaccination to biopsy of 53 months (up to >12years). Only a small minority of cases appear to represent chance association due to recent immunization in a patient with unrelated neuromuscular disease. In rats, experimental MMF shrinks progressively with time, and has very small size at 12 months. WHO has suggested that patients with longstanding post-vaccinal MMF could have individual inability to clear Alum out of the body.

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This was supported by marked influence of the rat genetic background on the size of vaccine-induced experimental MMF.

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About 1000 patients with MMF have been identified in France. Adult patients with MMF collected in our Center (>250), usually presented with diffuse arthromyalgias and chronic fatigue. A case control study conducted by AFSSAPS pointed out chronic fatigue as more frequent and more pronounced in patients with than without MMF in the deltoid muscle.

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Adult MMF patients with diffuse arthromyalgias, chronic fatigue, and cognitive complaints, often fulfilled international criteria for chronic fatigue syndrome. They usually lack fibromyalgic tender points. About 10% have concurrent demyelinating CNS involvement similar to multiple sclerosis.

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Neuropsychological tests have shown cognitive alterations in almost all MMF patients. Compared to arthritis controls matched for pain severity and duration, depression and educational level, MMF patients displayed more severe and distinctive impairment of visual memory, working memory and dichotic listening, suggesting organic brain damage. Similar cognitive alterations occur in foundry workers exposed to inhaled Al fumes or powder.

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In contrast to arthritic controls, most MMF patients had some altered neuropsychological tests reaching the dementia threshold.

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In 2003 we observed that the "Gulf war syndrome", which, in UK, has been linked to exposure to multiple vaccinations, including the Alum-adjuvanted anthrax vaccine, had symptoms strikingly similar to those observed in our MMF patients. Similarity is also obvious with clinical manifestations in silicone implant-associated autoimmune conditions. This recently led to individualization by Yehuda Shoenfeld of the so-called Autoimmune/inflammatory Syndrome Induced by Adjuvants (ASIA).

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Although a set of clinical manifestations (ASIA) is typically observed in adult patients with longstanding MMF lesion in the deltoid muscle, significance of the association remains unclear as nobody has characterized the biodistribution pattern of particles injected into muscle. Admittedly, Alum safety concerns crucially depend on whether the particulate compound will entirely remain localized at site of injection or can diffuse and accumulate in distant organs,

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Nanosized particles (NSPs) have various innovative medical applications in fields such as, imaging contrast fluids, topic antimicrobials, surgery tools, and drug or gene delivery, and vaccine. In balance with these promising applications, safety issues need to be very carefully assessed. Due to the rapidly growing number of novel compounds and formulations, questions relative to biodistribution, persistence and toxicity of most nanomaterials have not been thoroughly explored, and long-term data are lacking. Therefore, the understanding of general mechanisms that may underlie beneficial/adverse effects of NSPs, especially those interacting with immune cells, is mandatory.

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Alum is nano-crystaline particle composed of Aluminium hydroxide that has been introduced in vaccine for its immunologic adjuvant effect in 1927. Alum remains the most commonly used vaccine adjuvant although mechanisms by which it stimulates immune responses remain incompletely understood. Since biodistribution of particles injected into muscle has not been previously reported, biological likelihood of a cause to effect relationship between Alum i.m. injection and systemic manifestations remains elusive. Macrophages are now recognized to avidly take up Alum agglomerates and, in so-doing, become long-lived cells. Interaction of nanomaterials with immune cells may strongly interfere with their biodisposition. We wondered if a proportion of particles injected into muscle could translocate to distant organs as part of a general mechanism linked to phagocytosis.

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We recently observed that muscle envelopes host most of the so-called resident muscle macrophages

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These macrophages differ from exudate macrophages by their abundant production of KC and MCP-1, two potent chemokines attracting neutrophils and circulating monocytes, respectively.

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Thus, upon muscle injury or other danger signal, resident MPs first accumulate in fascia, then release chemokines, thus eliciting huge muscle infiltration by exudate MO/MPs. Phagocytosis of debris, is followed by a phenotypic switch of MO/MPs into alternatively activated MPs, helping myorepair, and migration to lymphoid organs

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These migrating cells derived from circulating MOs are known as 'inflammatory' dendritic cells, and substitute to classical migrating dendritic cells present in tissues other than muscle (such as dermis).

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After i.m. injection of Alum-containing vaccines in mice, muscle Al content decreases by 50% within 4 days after injection and then remains stable once the granuloma of Alum-loaded phagocytes is formed. To examine if and how particles injected into muscle can also translocate to distant sites, we used two types of fluorescent particles: exploratory polychromatic fluorescent latex beads (FLBs), and a confirmatory Alum-relevant nanohybrid (Al-rho) in which Al(OH)3 is coupled with rhodamine.

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Our preliminary results indicate that :

- After i.m. injection particles are captured by phagocytes(MO/MPs) within hours.
- Some particle-loaded cells form stable local granuloma in fascia; other ones migrate through lymphatics to the draining lymph nodes (initial lymphatic biodistribution).
- Migratory particle-loaded cells then exit LNs via the thoracic duct, gain access to the blood stream and distribute to distant organs (secondary hematogenous distribution).
- Incorporation into brain is delayed, and slowly accumulative.
- Neurodelivery is achieved through a MCP-1-dependant Trojan horse mechanism.
- A similar elementary mechanism has been previously shown for neurodelivery of viral particles (HIV, HCV, possibly EBV).
- This might constitute a common pathway at play in chronic fatigue syndrome / ASIA syndrome induced by a variety of infectious or mineral particles, including vaccine adjuvants such as Al(OH)3.

Implication of this mechanism of particle neurodelivery in pathophysiology of neuroinfllamatory (MS) and neurodegenerative (AD) diseases desserves investigation.

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