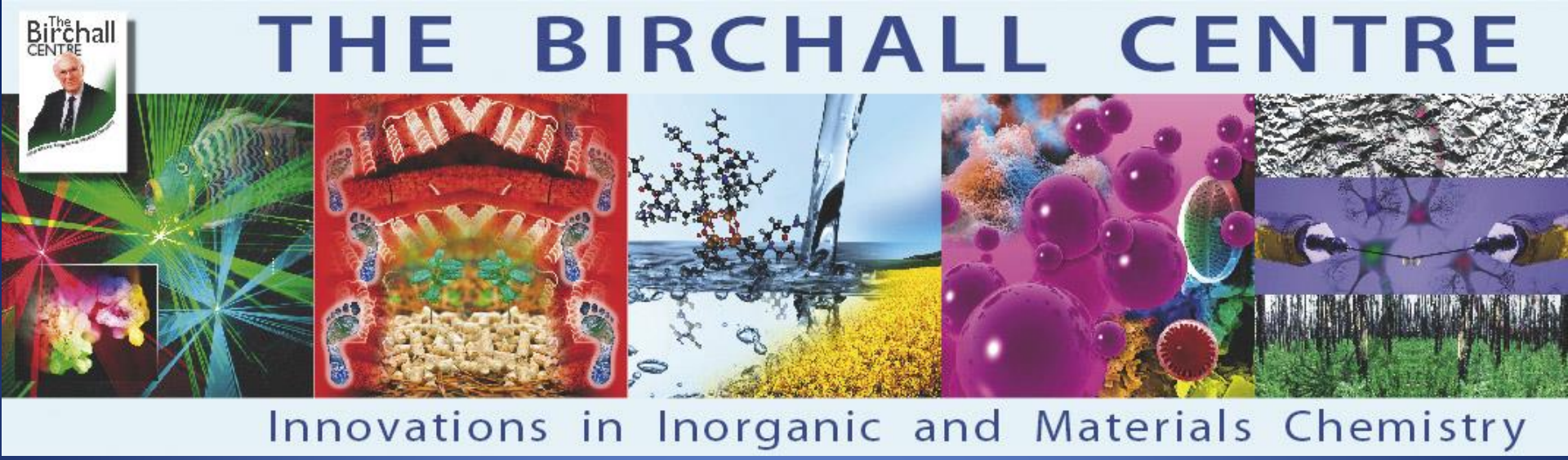


Human Exposure to Aluminium

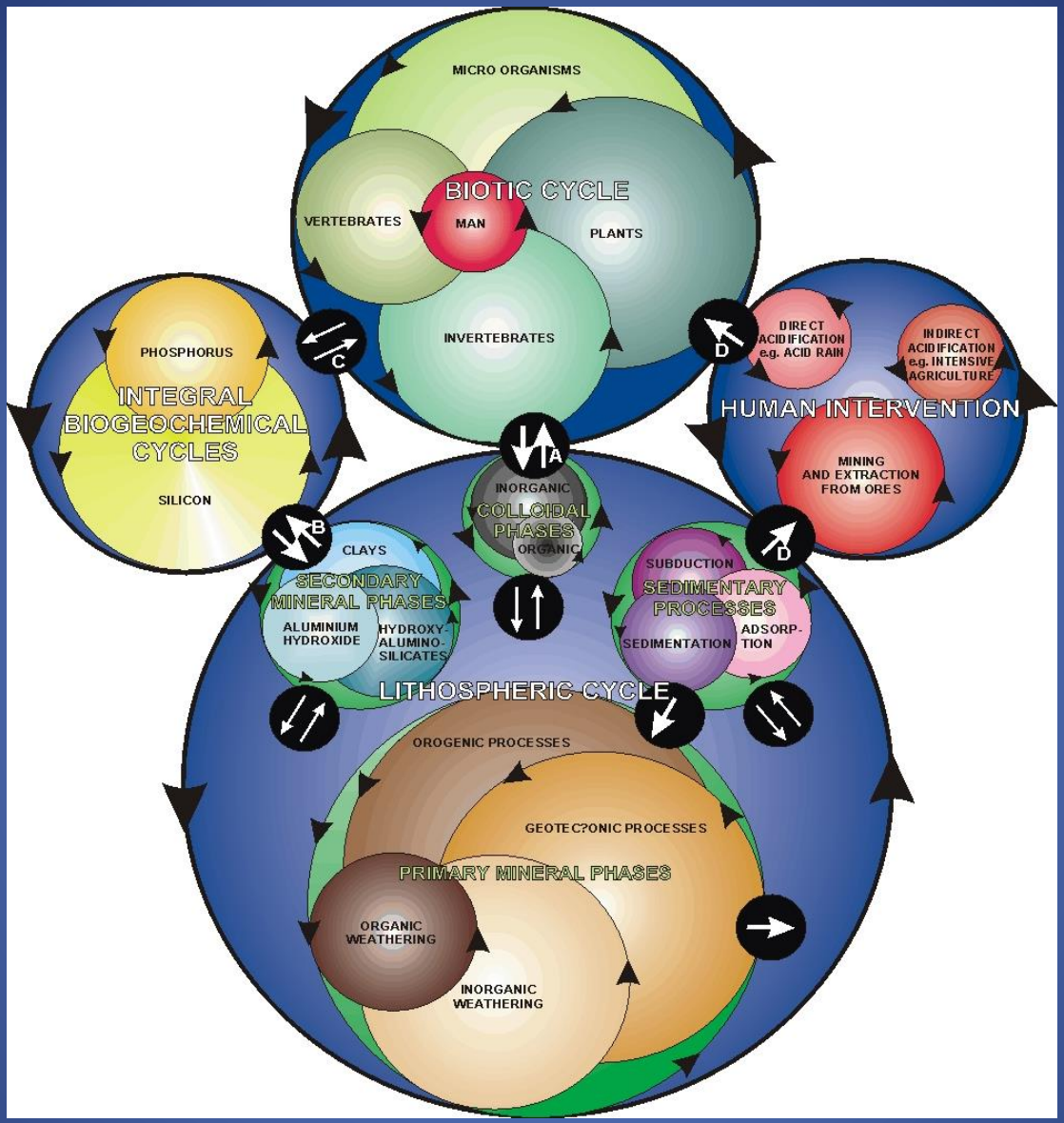
Aluminium Adjuvants and Immunotherapy

Christopher Exley PhD

The Birchall Centre, Keele University,
Staffordshire, ST5 5BG, UK.

http://www.keele.ac.uk/aluminium/

EAACI Copenhagen June 2014

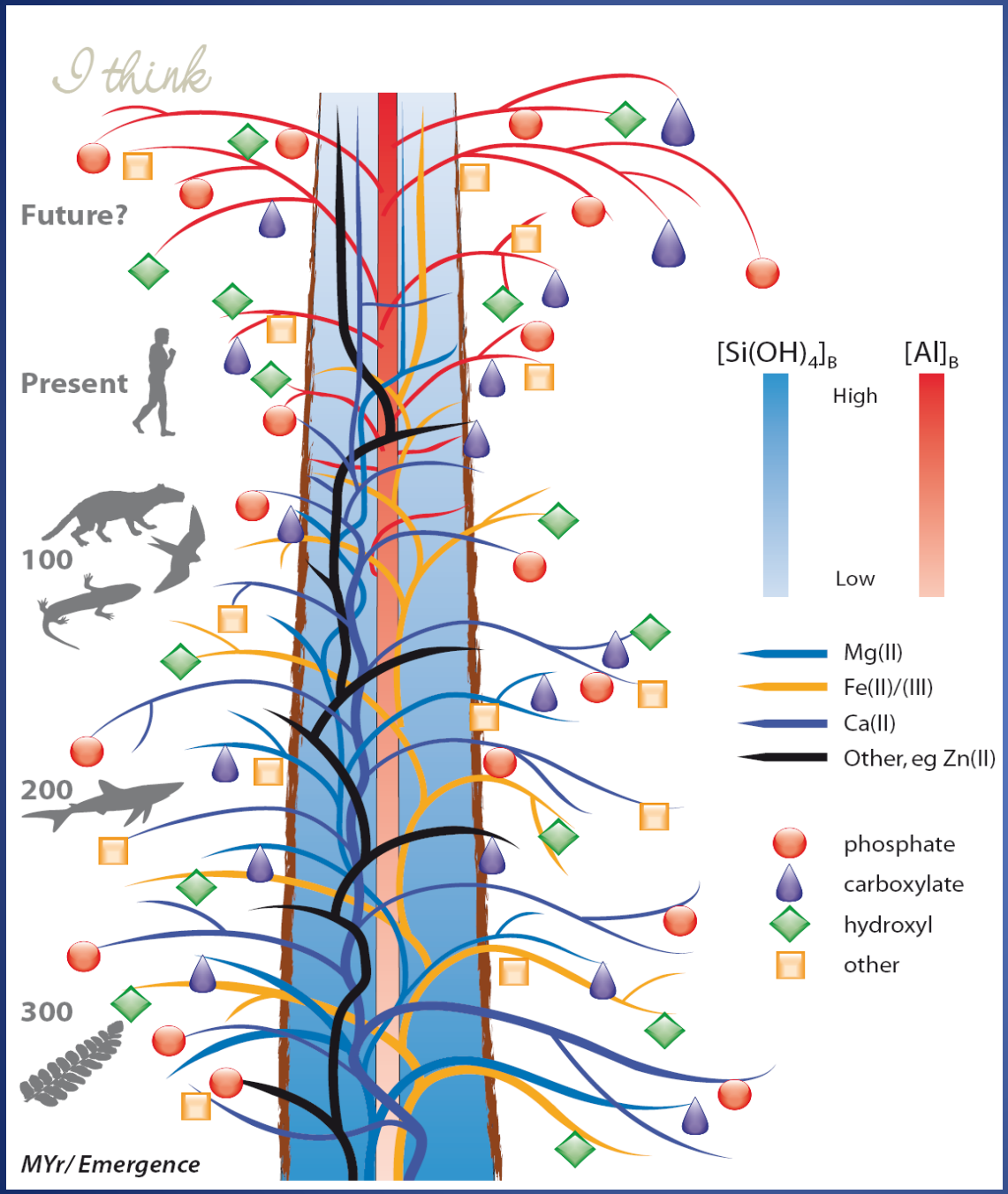


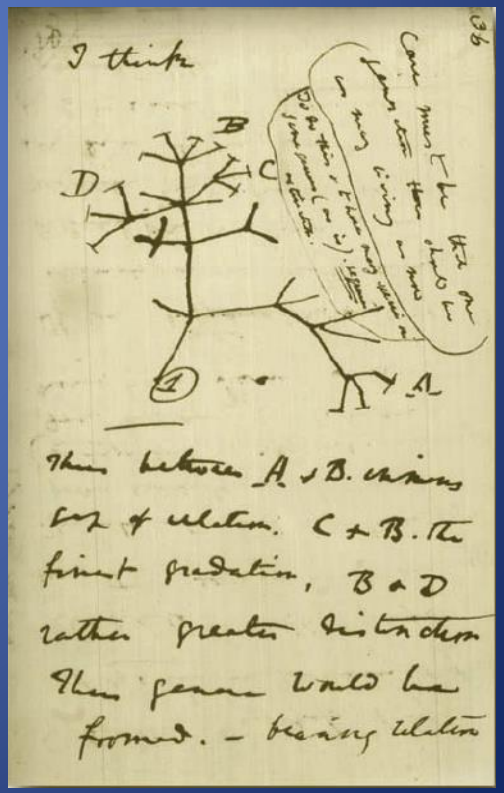
THE BIOGEOCHEMICAL CYCLE OF ALUMINIUM

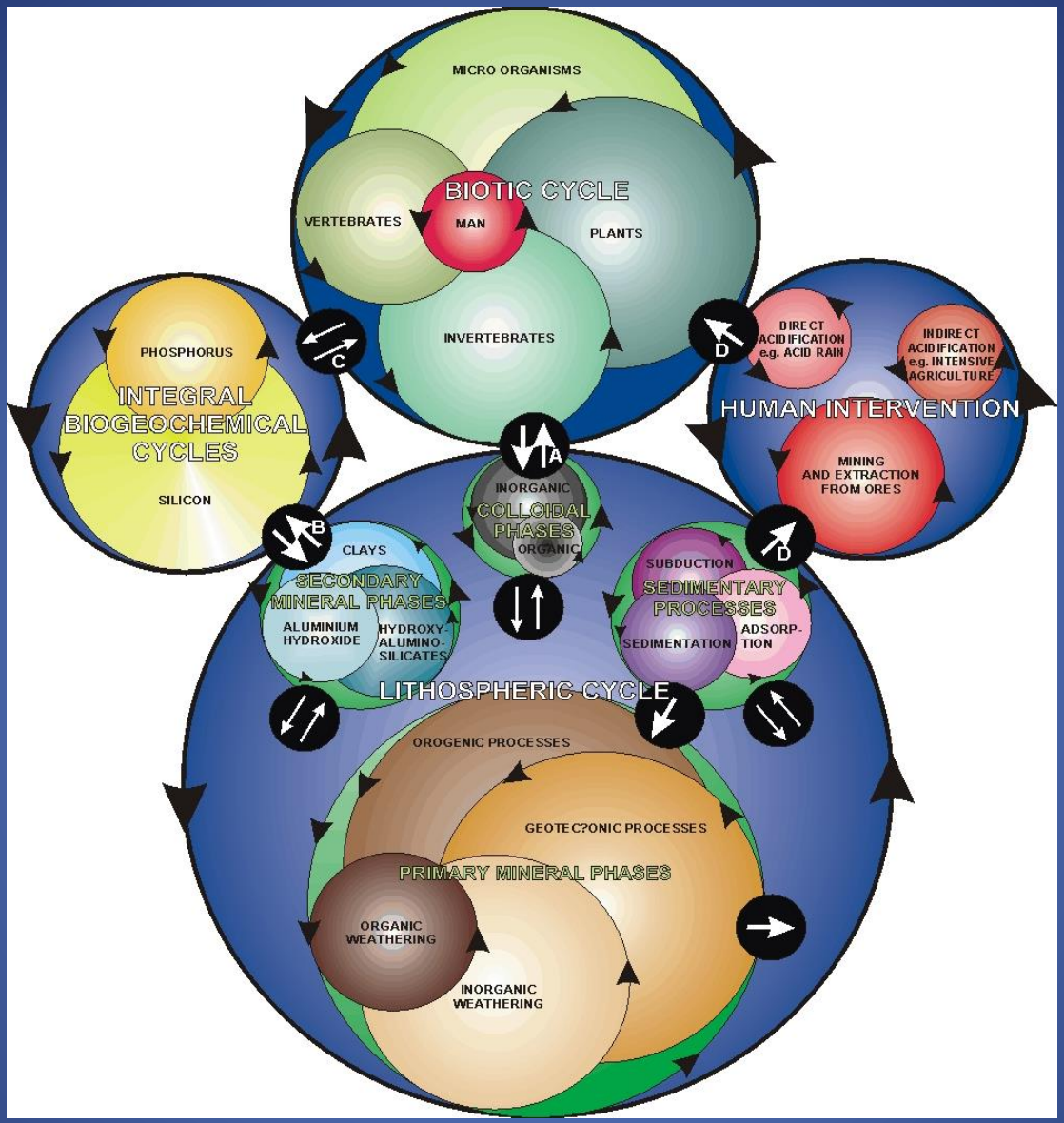
Exley C (2003) A biogeochemical cycle for aluminium ? J. Inorg. Biochem. 97, 1-7.

A Biochemical ‘Tree of Life’ for the Natural Selection of Aluminium

Exley C (2009) Darwin, natural selection and the biological essentiality of aluminium and silicon. Trends in Biochemical Sciences 34, 589-593.







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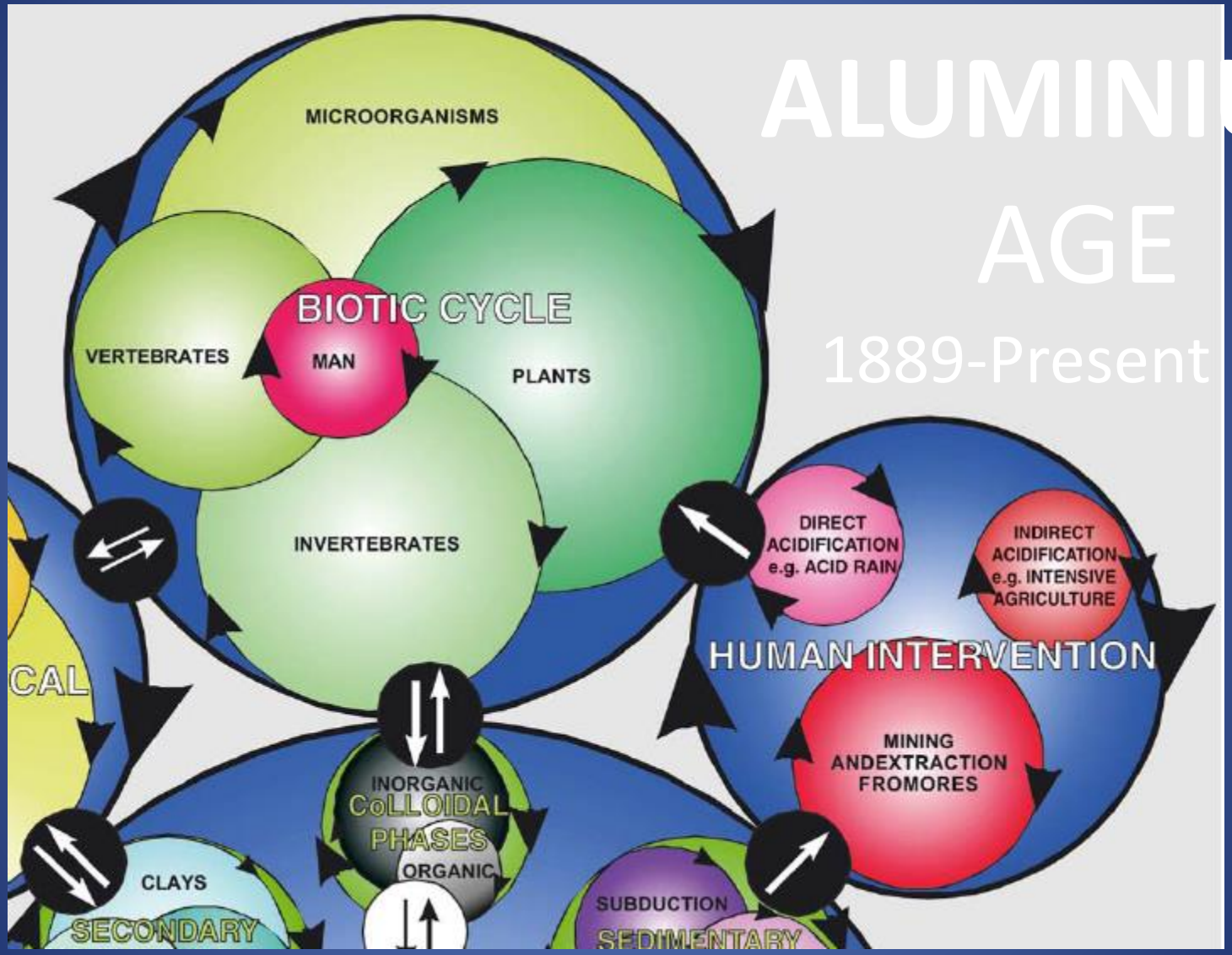
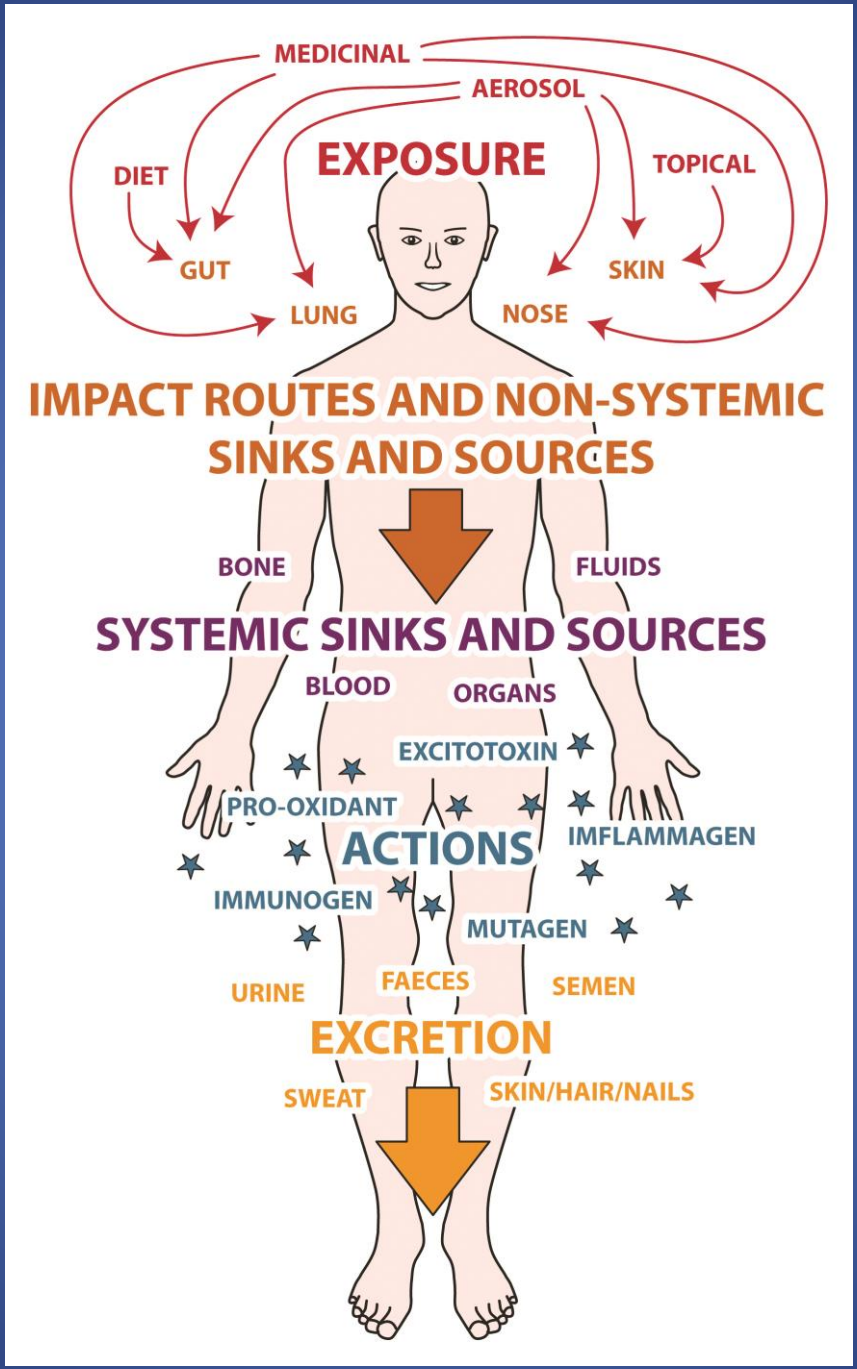
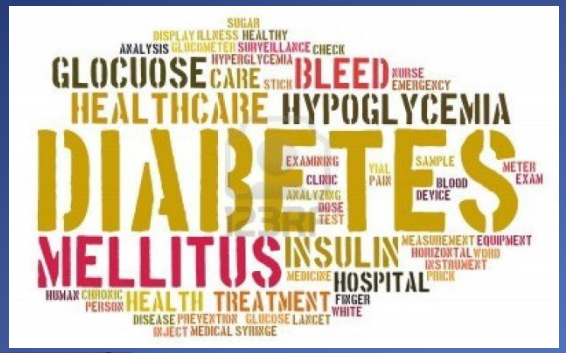
THE ALUMINIUM AGE

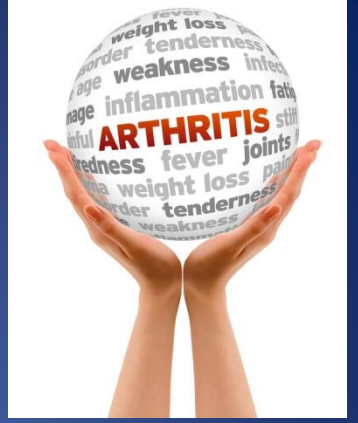
1889-Present Day

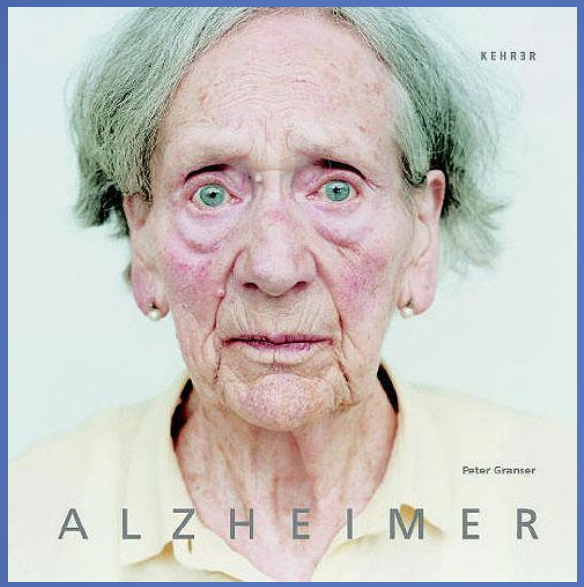


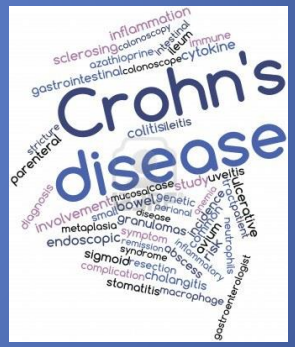


Exley C (2013) Human exposure to aluminium. Environmental Science:Processes and Impacts 15, 1807-1816.



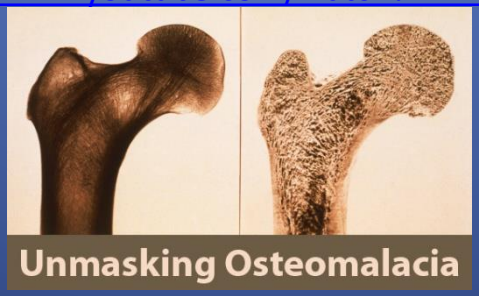






THE **ALUMINIUM** AGE?

http://www.youtube.com/watch?v=FrYxIVb3qPs



Editorial

What is the risk of aluminium as a neurotoxin?

Expert Rev. Neurother. Early online, 1–3 (2014)

Christopher Exley

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Aluminium is neurotoxic. Its free ion, $Al^{3+}_{(aq)}$, is highly biologically reactive and uniquely equipped to do damage to essential cellular (neuronal) biochemistry. This unequivocal fact must be the starting point in examining the risk posed by aluminium as a neurotoxin in humans. Aluminium is present in the human brain and it accumulates with age. The most recent research demonstrates that a significant proportion of individuals older than 70 years of age have a potentially pathological accumulation of aluminium somewhere in their brain. What are the symptoms of chronic aluminium intoxication in humans? What if neurodegenerative diseases such as Alzheimer's disease are the manifestation of the risk of aluminium as a neurotoxin? How might such an (outrageous) hypothesis be tested?

Aluminium is toxic, this is not open for debate. What we need to understand now are the conditions or situations under which the toxicity is exerted and manifested.

Exley C (2014) What is the risk of aluminium as a neurotoxin? Expert Review of Neurotherapeutics 14, 589-591.

Aluminium Adjuvants
How Do They Work?

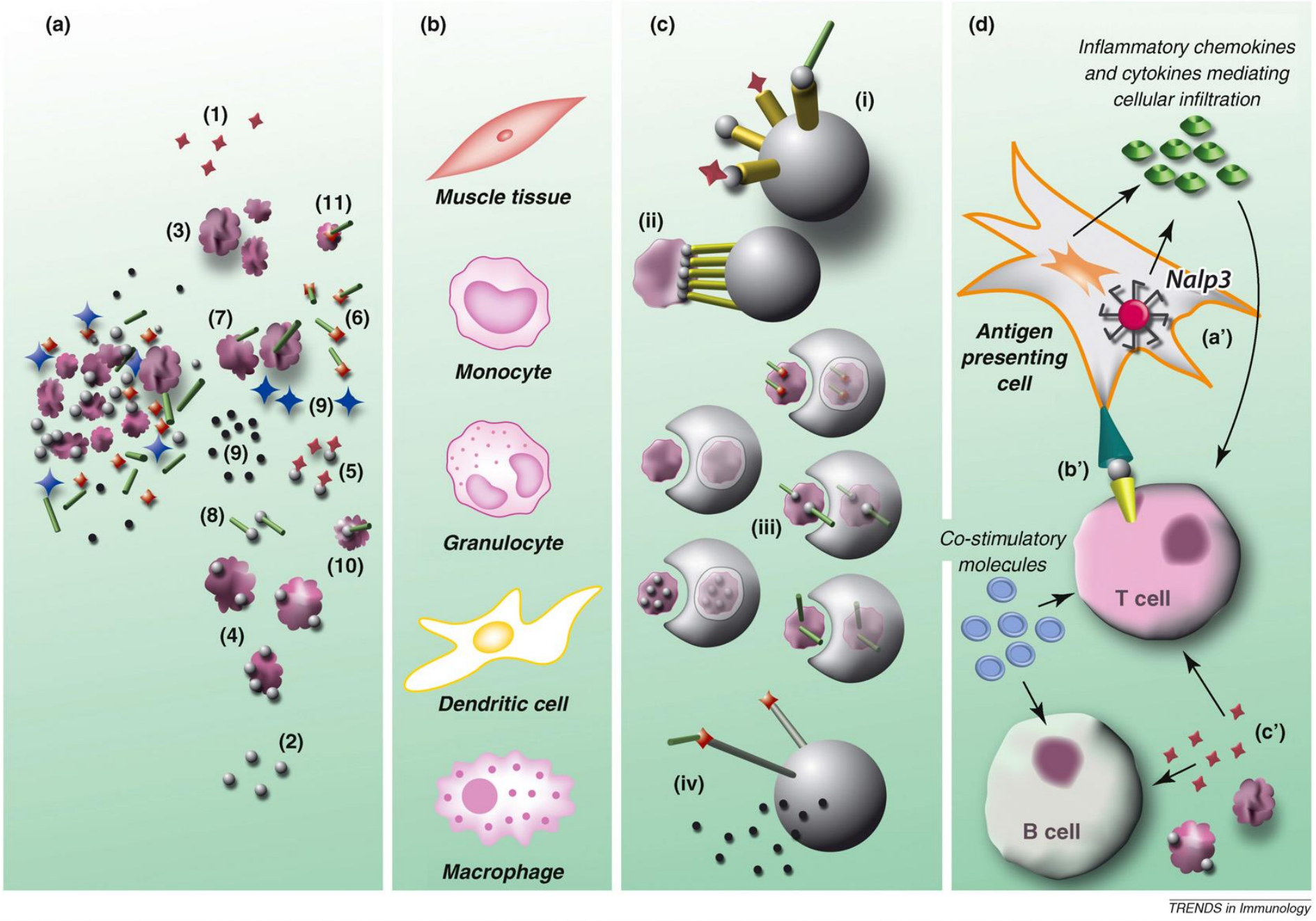
Exley *Allergy, Asthma & Clinical Immunology* 2014, **10**:4
http://www.aacijournal.com/content/10/1/4

ALLERGY, ASTHMA & CLINICAL IMMUNOLOGY

REVIEW **Open Access**

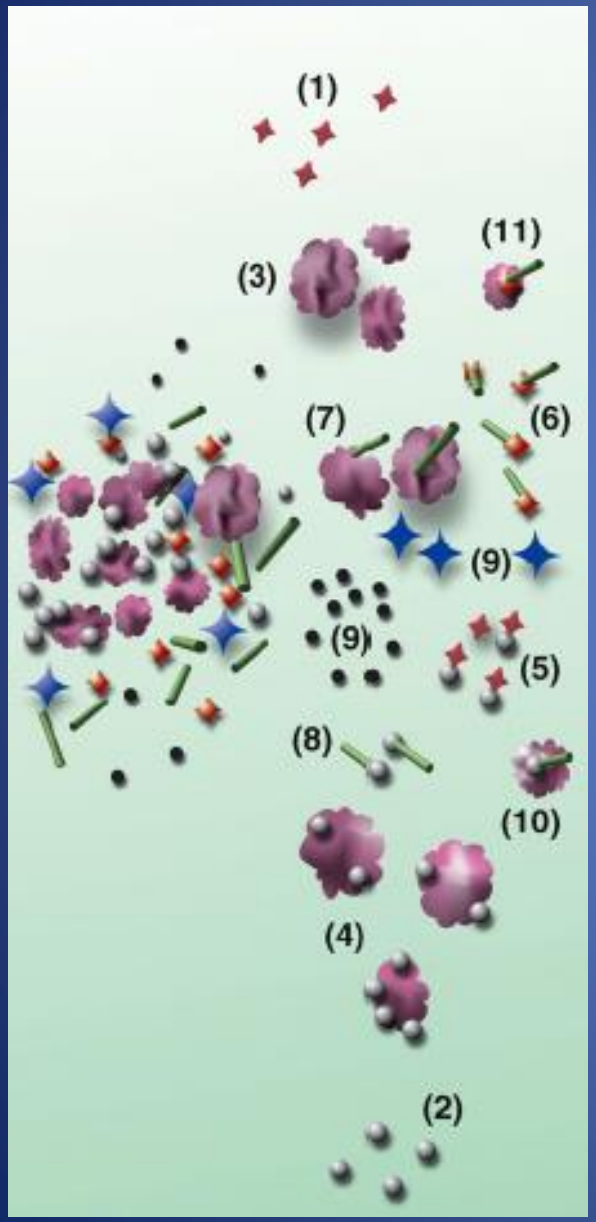
Aluminium adjuvants and adverse events in sub-cutaneous allergy immunotherapy

Christopher Exley



Exley et al.,(2010) The Immunobiology of aluminium adjuvants; how do they really work? Trends in Immunology, 31,103-109

Injection site chemistry: Kinetics versus thermodynamics



Dilution of the allergy therapy preparation at the injection site (IS) results in an array of potential agonists of the immune cascade, including:

(1) $Al^{3+}_{(aq)}$;
(2) free antigen (AG);
(3) particulate adjuvant (ADJ);
(4) ADJ with associated AG;
(5) AG-Al complex;
(6) IS ligand-Al complex;
(7) ADJ with associated IS ligand;
(8) IS ligand-AG complex;
(9) particulate iron (as contaminant of adjuvant) either free or with adsorbed Al/AG and resultant reactive oxygen species (ROS);
(10) ADJ with associated IS ligand-AG complex;
(11) ADJ with associated IS ligand-Al complex. IS ligands might include biomolecules such as; ATP, albumin, transferrin, citrate, fibrinogen.

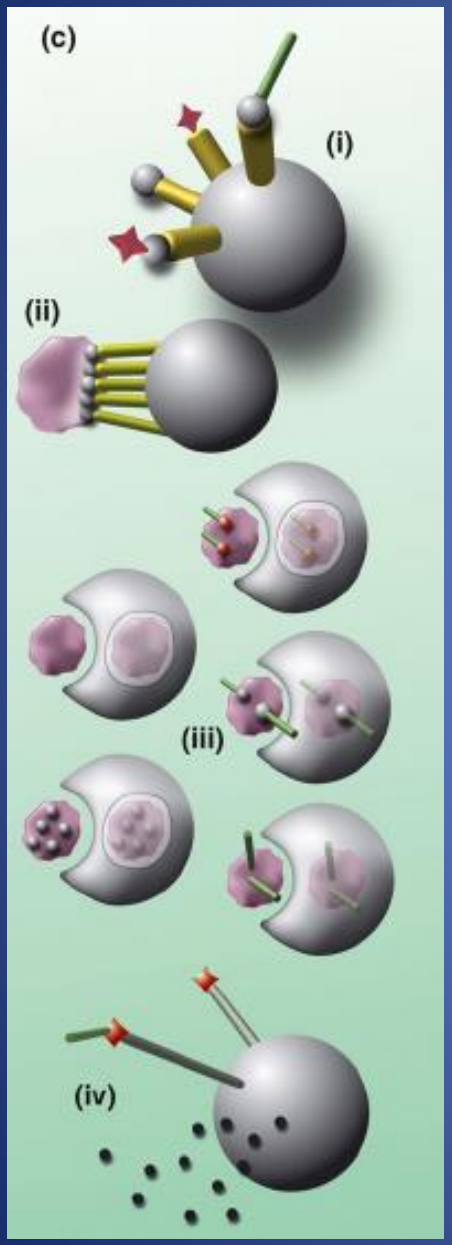
Cellular Targets of Adjuvant Activities

The array of agonists act upon a number of cell types including;

the resident **injection site tissue** (potentially causing necrotic and/or apoptotic cell death);

infiltrating innate cells such as, **monocytes** (potential for AlADJ-induced differentiation to dendritic cells), **granulocytes** (potential for AlADJ-induced eosinophilia acting directly on B cells), **macrophages** (are known to persist for long periods close to the injection site and may be characterised by inclusions of AlADJ) and **dendritic cells** (DC). The latter may be the major antigen presenting cell (APC)

Cellular Mechanisms of Antigen / Adjuvant Activities



There are myriad possible modes of interaction between agonists and innate cells including;

(i) toll-like receptor (TLR) binding of AG, AG-Al complex, IS ligand-AG complex, $Al^{3+}_{(aq)}$

(ii) multiple TLR binding of AG-ADJ;

(iii) phagocytosis of ADJ, AG-ADJ, IS ligand-ADJ, IS ligand-Al complex-ADJ, IS ligand-AG complex-ADJ;

(iv) direct or indirect binding of $Al^{3+}_{(aq)}$ by membrane receptors and extracellular (lipid membrane) or intracellular (nucleus) activity of ROS.

Adjuvant/Toxicant
Implications for Adverse Events

Reported adverse reactions in individuals receiving allergy immunotherapy;

foreign body granulomas, urticaria, sub-cutaneous sarcoidosis, progressive circumscribed sclerosis, sub-cutaneous nodules, cutaneous-sub-cutaneous pseudolymphoma.

The European Medicines Agency (EMA) lists as many as 32 adverse reactions to immunotherapy ranging from discolouration of the skin to encephalopathy.

Mechanisms of Adverse Events?

Aluminium body burden?

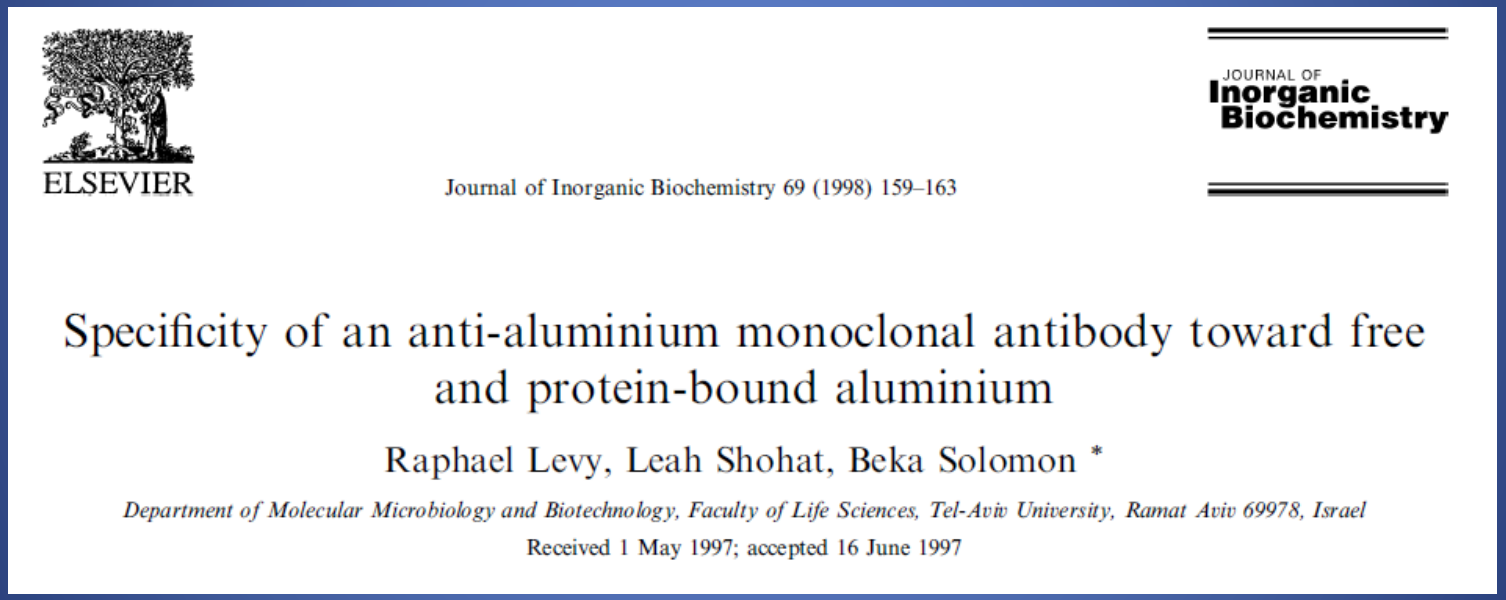
Table 1 Typical dosing regimens used in sub-cutaneous allergy immunotherapy

Context	Criteria	Range
First year	Range of number of injections for up dosing to a maintenance dose	4 to 16 injections [7-10]
	Range of number of injections for remaining first year maintenance course	4 to 12 injections [7-10]
Subsequent years	Range of number of injections for subsequent annual maintenance courses	6 to 12 injections [7-10]
	Recommended number of years of treatment	3 to 5 years [11,12]
Whole course	Range of number of injections for 3 years treatment for a single allergen	Up to 54 injections

Do individuals receiving immunotherapy have a higher than ‘usual’ body burden of aluminium?

Mechanisms of Adverse Events?

Aluminium as an antigen?



ELSEVIER

Journal of Inorganic Biochemistry 69 (1998) 159–163

JOURNAL OF Inorganic Biochemistry

Specificity of an anti-aluminium monoclonal antibody toward free and protein-bound aluminium

Raphael Levy, Leah Shohat, Beka Solomon *

Department of Molecular Microbiology and Biotechnology, Faculty of Life Sciences, Tel-Aviv University, Ramat Aviv 69978, Israel

Received 1 May 1997; accepted 16 June 1997

Do individuals receiving immunotherapy demonstrate a ‘memory’ of previous exposures to aluminium?

Mechanisms of Adverse Events?

Aluminium as an adjuvant?

doi: 10.1111/j.1365-2222.2010.03468.x

Clinical & Experimental Allergy, 40, 1091–1098

ORIGINAL ARTICLE Experimental Models of Allergic Disease

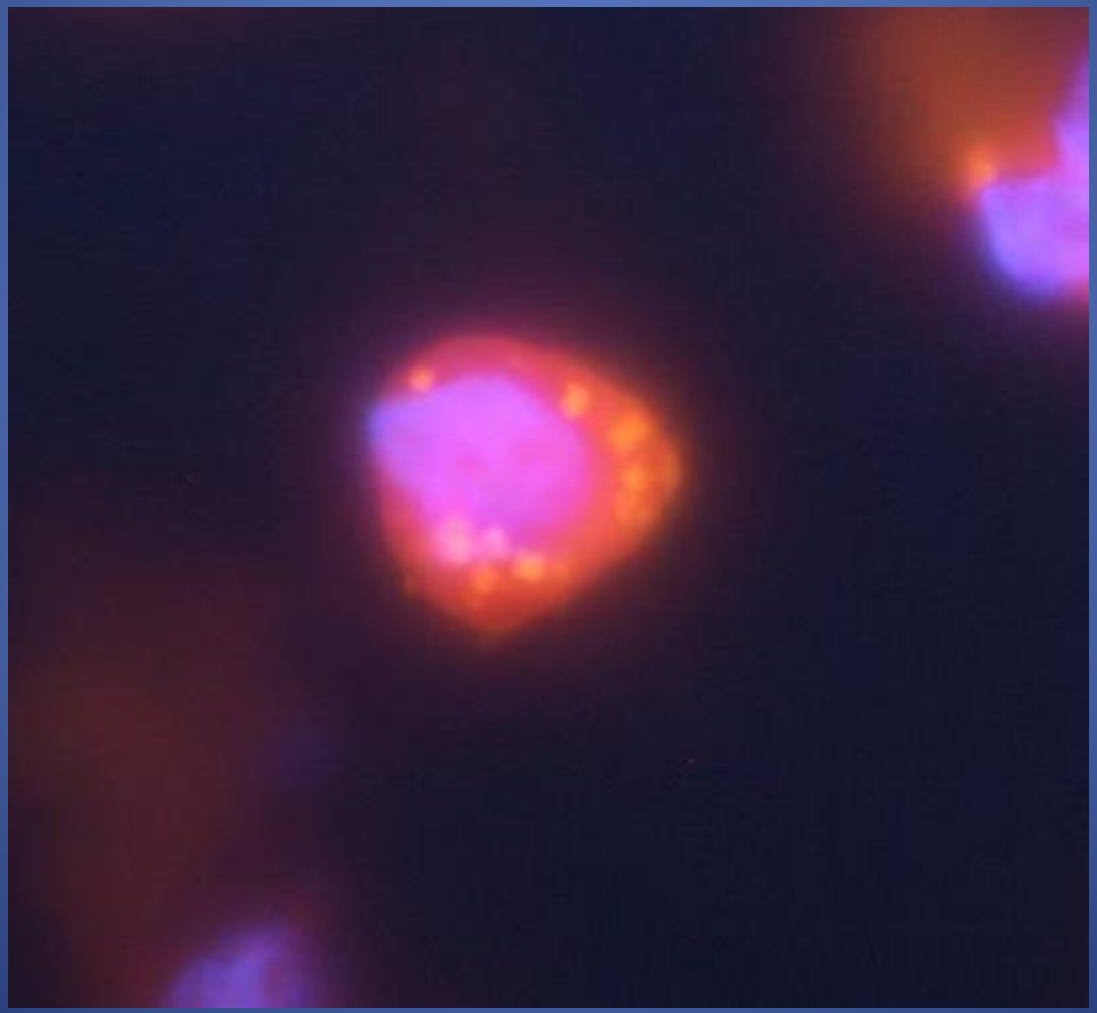
Antacids and dietary supplements with an influence on the gastric pH increase the risk for food sensitization

I. Pali-Schöll[1], R. Herzog[1], J. Wallmann[1], K. Szalai[1], R. Brunner[1], A. Lukschal[1], P. Karagiannis[1], S. C. Diesner[2] and E. Jensen-Jarolim[1]

[1]*IPP-Department of Pathophysiology, Centre of Physiology, Pathophysiology and Immunology* and [2]*Department of Paediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria*

Do individuals receiving immunotherapy become sensitised to other environmental/dietary factors (in addition to the allergen)?

Adjuvants in Immunotherapy
A Cause for Concern?



République Française

THE OSTA OF THE FRENCH PARLIAMENT

Public hearing
about
« THE VACCINE ADJUVANTS : A DISPUTED ISSUE »

For many decades, in particular aluminium salts have been sometimes added in vaccines. The adjuvants' role is to stimulate an immune response.

According to some scientists, the safety profile of these adjuvants is excellent, notably because they help to reduce the frequency and severity of local inflammation reactions. On the other hand, for more than 15 years, some studies have been insisting on the existence of links between these adjuvants and some diseases and considered that the long term effects from aluminium salts should be analyzed.

The present public hearing will aim at organizing discussions between the main stakeholders about te different aspects of these controversies.

organized by

Jean-Louis TOURAINE,
Member opf the National Assembly,
Member of the OSTA

Bruno SIDO,
Member of the Senate
Chairman of the OSTA

Jean-Yves LE DEAUT,
Member of the National Assembly,
First Vice-chairman of the OSTA

Corinne BOUCHOUX
Member of the Senate
Member of the OSTA

Thursday 22nd May 2014
2 pm - 7 pm

National Assembly
Salle Lamartine
101 rue de l'Université - Paris 7ème

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The Natural History of Aluminium
Past, Present and Future

Saturday, February 28 to Wednesday, March 4, 2015
Hôtel couvent des minimes, Lille

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