

## **Annotation of Powerpoint Presentation**

### **Slide 1**

A Mechanism of Toxicity of Aluminium-based Adjuvants?

### **Slide 2**

One purpose of this presentation is to outline a possible mechanism whereby exposure to Al not only in adjuvants in vaccination but also in our everyday lives might predispose us to possible vaccine-related disease.

### **Slide 3**

I am a biologist by first degree and my research goal is to understand the myriad ways that Al impacts upon life and life processes.

### **Slide 4**

The biogeochemical cycle of Al describes why it is important to research the biological activity of Al (Exley, 2003). Though non-essential, the arrival of the 'Aluminium Age' at the end of the 19th Century, heralded an era of biological availability for Al. The question is how will living things respond to a burgeoning exposure to biologically-reactive Al?

### **Slide 5**

Darwin's 'natural selection' is as appropriate to the evolution of biochemistry as it is to the evolution of species.

### **Slide 6**

This 'Darwin-like' biochemical tree of life asserts that it is only very recently that Al has played an active role in biochemical evolution (Exley, 2009). Could it be that present evidence of Al playing an active role in such includes a number of chronic diseases of unknown aetiology?

### **Slide 7**

So what does Al have to do with vaccination? Clearly Jenner and all after him have provided a possible solution to many human diseases. However, what happens when the mechanism of action of such a solution is only incompletely understood?

### **Slide 8**

Probably 80% of all vaccinations given to all ages use an Al-based adjuvant without the mechanism of action of such adjuvants being understood and the safety of such products ever being tested (Exley et al., 2010).

### **Slide 9**

Breaking down the individual components which constitute the potential adjuvant activity of Al demonstrates the potential complexity beginning with the biological chemistry at the site of injection.

### **Slide 10**

Here the potentially wide number of cell types which could respond to adjuvant activity are recognised in their generic groups.

### **Slide 11**

There are numerous ways in which a cell can then be influenced by adjuvant activity including both extracellular and intracellular signalling mechanisms.

### **Slide 12**

There are similarly both direct and indirect ways that adjuvant activity actually stimulates immunity. In this paper I contend that a lack of appreciation of the bioinorganic chemistry of Al means that we are far from identifying the mechanism of action and potential toxicity of Al-based adjuvants (Exley et al., 2010).

### **Slide 13**

So what are the potential mechanisms of action of Al-based adjuvants?

### **Slide 14**

While it has been suggested that endocytosis of Al adjuvant could lead to disruption of the internalised endosome the mechanism whereby such might take place is not likely to be similar to that of uric acid crystals or silica (Marrack et al., 2009). While there is clearly the potential for cytotoxicity of Al-based adjuvant both at and far from the injection site the mechanism of cell death remains to be elucidated.

### **Slide 15**

The adjuvant activity of Al may not actually require cell death.

### **Slide 16**

There are a number of recent studies which implicate reactive oxygen and nitrogen species (ROS / RNS) in adjuvant activity. Since Al is a powerful pro-oxidant (Exley, 2004) and most vaccine preparations are contaminated with significant amounts of iron then Al adjuvants are likely to significantly stimulate the signalling and biological activities of these species in immunopotentialiation.

### **Slide 17**

ATP is the most important extracellular signalling molecule in the body and we are beginning to understand its role in the immune response, having both stimulatory and inhibitory effects (Di Virgilio et al., 2009). Since Al is known to potentiate the signalling activity of ATP (Korchazhkina et al., 1998) it is likely that Al adjuvants also contribute towards such mechanisms.

### **Slide 18**

Perhaps most unusual are the recent observations that Al salts can 'sensitise' the body to the presence of other substances which might not normally elicit any response (Palli-Schöll et al., 2010). Effectively this suggests that the persistence of Al in any particular environment could sensitise the immune system to other usually non-immune-reactive substances co-localised with the Al.

### **Slide 19**

The observation that Al can be both adjuvant and antigen appears to have been ignored (Levy et al., 1998). The possibility that Al added as an adjuvant as well as other sources and sinks of Al could induce the formation of antibodies against itself is intriguing and such would definitely contribute towards the mode of action of Al adjuvants.

### **Slide 20**

We recently suggested that in one individual a higher than usual body burden of Al contributed towards vaccine-related injuries (Exley et al., 2009).

### **Slide 21**

This suggestion that the body burden of Al might contribute towards vaccine-related disease asks the question if Al, not just when administered as an adjuvant, but when present throughout the body could also act as an adjuvant?

### **Slide 22**

How do we define the body burden of Al?

### **Slide 23**

The body burden of Al is simply the balance between our exposure to Al and its excretion from the body. So how are we exposed (Exley, 2009)?

### **Slide 24**

We are exposed to Al in water (and drinks), primarily through its absorption across the gut (Yokel et al., 2001), but other potential sites of exposure would include the lung, the nose and the skin.

### **Slide 25**

Al is a major contaminant of food (Saiyed & Yokel, 2005) It is also a known contaminant of parenteral solutions.

### **Slide 26**

It is perhaps less well known that tobacco and cannabis are significant sources of biologically available Al (Exley et al., 2006). For example, when you smoke a cigarette you excrete Al in your urine.

### **Slide 27**

Recreational drugs including heroin and cocaine can also be significant routes of exposure to Al (Exley et al., 2007).

### **Slide 28**

It is becoming of increasing interest that the skin is not a complete barrier to Al. For example, it has been shown that Al applied as an antiperspirant does cross the skin and enter the systemic circulation, albeit in relatively small amounts (Flarend et al., 2001). Aerosol antiperspirants could result in the uptake of Al into the body through the lung and, worryingly, directly to the brain via the nose and olfactory system.

### **Slide 29**

Medicines both include Al as active ingredients and are also 'contaminated' by significant amounts of Al (Reinke et al., 2003).

### **Slide 30**

It was recently demonstrated that sunscreens and sunblocks may contain significant amounts of Al such that one might apply up to 5 g of Al onto the skin surface during an average day on the beach. Little is known about the biological availability of Al in

such products but it has to be asked if they could contribute towards the high rate of melanoma found in populations using large amounts of sunscreens/sunblocks regularly (Nicholson & Exley, 2007)?

### **Slide 31**

Worryingly we are still exposing the most vulnerable members of society, pre and post-term infants, to very high levels of Al in infant formulas (Burrell & Exley, 2010).

### **Slide 32**

When we consider the myriad ways in which we are exposed to Al in our everyday lives it must be a concern that in addition we are also exposing ourselves to Al in vaccines. We know that this Al both elicits a strong immune response and is transported away from the injection site to the other organs and tissues of the body (Flarend et al., 1997).

### **Slide 33**

Thus living in 'The Aluminium Age' means that a body burden of Al is inevitable for all of us.

### **Slide 34**

There will be differences between individuals both in the overall size of the Al body burden and in where in the body the majority of the Al is found. These differences could have profound effects upon the potential toxicity of Al and even on how our body responds to an Al adjuvant in one or more vaccines (Exley, 2009).

### **Slide 35**

Al works effectively as an adjuvant as the relatively large dose which is administered at the injection site exceeds an 'activity' threshold which then initiates a cascade of following reactions (Exley et al., 2009; Exley et al., 2010). This 'threshold effect' is also probably relevant to Al's activity as an antigen (Levy et al., 1998). A pertinent question to ask would be whether this 'threshold effect' and the resulting cascade of biological reactions would also apply to other body stores of Al, for example, following stimulation by single or multiple Al-adjuvant containing vaccinations?

### **Slides 36-38**

The brain is one organ where Al is known to accumulate (Exley & House, 2011) and there are numerous possible compartments for Al including the very long-lived neurones (Exley, 1999). What might be the consequence of these stores of Al being 'activated' by an Al challenge through, for example, a vaccination (Exley et al., 2009)?

### **Slide 39**

The good news is that the majority of Al that enters the body by any route of exposure will eventually be excreted (Exley, 2009).

### **Slide 40 & 41**

We have developed a non-invasive method whereby the excretion of Al from the body via the urine can be facilitated (Exley et al., 2006). Ongoing research with both healthy individuals and individuals with disease is showing that regular drinking of a silicon-rich mineral water is helping to reduce the body burden of Al. The next

question which follows is whether a reduced body burden of Al will result in less Al-related disease including possible vaccine-related disease?

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