EMERGEX VACCINES

Zika Vaccine White Paper

In this White Paper we briefly review Zika virus epidemiology and the implications for foetal complications during pregnancy and investigate the scientific and business rationale for the development of EMX-001, a new cross-reactive vaccine for Zika, Dengue and Yellow fever.

What is the proposed scientific idea and business case?

The Zika outbreak can be defined as a foetal-maternal issue (3). Evidence has confirmed a link between Zika infections in pregnant mothers and birth defects (i.e. microcephaly ~ 1% incidence) (1, 2). It is also now proposed that in 20% of cases maternal Zika can lead to some form of neurologic damage to the foetus. Several animal models have shown the Zika virus has placental tropism and can cause birth defects, placental damage, foetal demise and is neurotoxic (4-7). In order to have an effective vaccination regime to combat the main foetal related pathological features of the Zika outbreak, a vaccine that is able to vaccinate both the mother and the foetus simultaneously is required to prevent descending transmission. In contrast vaccination of the male partner may be required to prevent ascending transmission. Most current vaccine technologies are not suited to in utero vaccination (19-28). Antibody vaccines are not suited since antibodies cannot cross the placenta until ~ 3rd trimester so Zika related pathology that occurs in the foetus in 1st/2nd trimester will not be diminished by maternal antibodies. A vaccine that promotes a T-cell response in the mother cannot protect the foetus, since maternal CD8+CTL cells are destroyed by the placenta via the HLA–G system (24,25). Any foetal or maternal microchimerism is also suppressed by foetal T Regs (26). An attenuated live virus would be able to pass to the foetus and provoke an immune response (the foetus is immunologically competent ~ 10 weeks), but it may not be appropriate from a safety perspective to expose the foetus to live virus (19-28). Furthermore, there will always be a brief viraemic phase (no vaccine is considered complete) even if the mother is pre-immunised against Zika, meaning the foetus will always be at risk of infection.

A lead pipeline product of Emergex is a cross-reactive vaccine against Zika, Dengue and Yellow fever (EMX-001). This vaccine construct is produced by attaching experimentally validated viral peptides (MHC-Class I) that are cross-reactive to all 3 viruses (all of the Flavivirus family share many sequences) to a gold nanoparticle carrier. This produces an immune active particle that can produce a T-cell response to all three viruses (29-35). Importantly each nanoparticle contains multiple epitopes and vaccine constructs will typically contain 6 different epitopes (3-4 copies of each). This allows for multiple CD8+CTL targets and if peptides are chosen correctly increases the ability of the vaccine to cover a large segment of an HLA diverse population (supertype vaccines). A vaccine of this nature has some important qualities that make it compatible with in utero vaccination. The vaccine is very small (~5nm) and therefore can pass placental or amnion/chorion (Zika virus is 50nm in diameter). The vaccine will be administered dermally (37, 38, 41, 42) to the mother in combination with micro sterile adjuvant technology to induce the required soluble mediator danger signal which should pass into the foetal circulation (33, 39). The vaccine could provide in utero protection from the Zika virus in the key window between foetal immune-competence (<10 weeks) and when protection can be transferred from the mother to the foetus (3rd trimester). The vaccine should exhibit a high safety profile; i) the vaccine is 100% synthetic (no biological components) and does not require a live virus for delivery ii) the vaccine does not require potentially toxic chemical adjuvants to be effective and iii) the gold nanoparticle carrier technology has already been shown to be safe in phase 1/2 trials.

Dengue (15-18) and Yellow fever are global infections priorities in their own right with Dengue infecting 390 million people per year, and Yellow fever having intermittent high profile outbreaks. Zika, Dengue

and yellow Fever are spread by the same type of mosquito in the same lower/middle income regions and therefore a vaccine able to provide triple protection against all three infections would provide a practical and logical benefit. Given the geographical regions where these infections occur it is important that a vaccine candidate is viable for delivery in low resource settings. The 100% synthetic nature of the vaccine means it does not require cold chain. The vaccine can be administered using dermal syringe free applications (microneedle patches) that support repeat dosing required (40) and better patient compliance. The production process is quick and cheap, potentially able to provide on demand vaccines at less than a dollar for an immunisation regime.

The gold nanoparticle carrier technology Emergex will use is well established and has previously been approved in the clinic for unrelated and vaccine indications. Experimental vaccine candidates can be produced quickly and the proposed proof-of-concept experiments are relatively fast and cheap.

Given the high sales potential of each individual indication (Dengue, Zika, Yellow Fever, peaks sales ($1.24B, $154M, $500M, respectively) and high priority interest from government/NGOs a clear route to market exists once the vaccine has completed Phase 1 trials. This could be in the form of licensing to pharma partners, marketing the vaccine, or providing vaccines to stockpile organisations such as Project Bioshield (US GOV) or GAVI as was seen recently for Ebola/smallpox.

What is the innovation of EMX-001 and what technical steps are required for development?

The innovation of this product is the synthesis and validation of a synthetic gold-nanoparticle based T-cell (CD8+CTL) triple vaccine against Zika, Dengue and Yellow Fever (EMX-001) that has the properties to be suitable for in utero immunisation against Zika if required. The vaccine derives from the combination of two existing technologies, one of which Emergex has acquired and the other for which Emergex has an exclusive license, these being a library of experimentally validated cross reactive viral peptides and a gold nanoparticle carrier system, respectively. Emergex has access to a library of experimentally validated cross-reactive viral MHC Class–I peptides that are involved in the T-cell response to Zika, Dengue and Yellow Fever. These peptides on their own are immunologically weak when administered in vivo and would not produce a T-cell response sufficient for an effective clinical vaccine. The gold nanoparticle technology, for which Emergex has a license, can overcome this problem. By attaching the viral peptides and various carbohydrates to gold nano central core (typically <1.6nm nanometre) a vaccine construct that is immunogenic and able to deliver the viral peptides to immune response generating cells (in both the mother and foetus) can be produced. If combined successfully, the peptide library and the gold nanoparticle carrier technology will produce a vaccine capable of delivering the right peptides, to the right place, in order to produce a strong T-cell vaccine response. This project will be the first time such a vaccine construct has been produced to be used for the purposes of vaccination in infectious disease. The following act as background validation for the potential success of the development of EMX-001: -

i) The gold nanoparticle technology has been shown to be safe and effective as a carrier for the delivery of insulin (a peptide itself) in humans. This indication is currently being tested in phase 2 clinical trials
ii) The library of Dengue viral peptides have been validated in vitro by illustrating the reactivity of the peptides with peripheral blood mononuclear cells (PMBCs) from seropositive post-infectious blood from Dengue patients
iii) Using the same gold nanoparticle technology, a peptide based cancer vaccine was able to induce a strong T-cell CD8+CTL response against lung cancer cells in humanised mice.

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What is the intellectual property position for EMX-001 and how does it compare to competitors?

Emergex has rights to broad two patent families as detailed below. It also holds an exclusive license to a nanoparticle carrier technology and has acquired a library of experimentally validated cross-reactive viral peptides that are involved in the T-cell response to Zika, Dengue and Yellow Fever.

1. Emergex has licensed five patents from Midatech Pharma Limited. This licence provides freedom to operate with respect to the use of Midatech's gold nanoparticle technology in the production of vaccines for infectious disease. The patents are granted and are not currently subject to any opposition. The patents are as follows: "Nanoparticles" (WO2002/32404), "Nanoparticles Comprising Antigens and Adjuvants, and Immunogenic Structures" (WO2006/037979), "Nanoparticles Comprising Antibacterial Ligands" (WO2007/122388), "Nanoparticles for Providing Immune Responses Against Infectious Agents" (WO2007/122388), "Nanoparticle Peptide Composition (WO2013/034726)".

2. Emergex has acquired 2 patents from Immunotope Ltd. This acquisition provides freedom to operate with respect to use of a particular library of viral peptides that are cross reactive for Zika, Dengue and Chikungunya. The patents are as follows: "Dengue virus specific multiple HLA binding T cell epitopes for the use of universal vaccine development" (WO/2015/175361), "Cytotoxic T-lymphocyte-inducing immunogens for prevention, treatment, and diagnosis of dengue virus infection" (WO/2013/003579).

A competitor analysis suggests there are currently 15 companies/organisations publically working on a Zika vaccine. As some groups have several programs in development this equates to 17 potential Zika vaccine products. Of these products: 7 are live attenuated vaccines, 3 are virus based recombinant vaccines (Zika surface protein epitopes added to a viral vector such as adenovirus), 3 are recombinant protein based, 3 are DNA vaccines and 1 is an RNA vaccine. Many of these vaccines, would in theory, be suitable for the vaccination of the general population against Zika, but to assess Emergex's competitive position relative to these products the suitability for in utero vaccination needs to be considered. The 7 attenuated Zika virus vaccines would not be suitable due to safety concerns using a live virus. The protein based recombinant vaccines are not suitable because these vaccines could only produce an antibody immune response. DNA and RNA vaccines are not suitable because viral proteins produced by transfection, in contrast to infection, do not give the same MHC-I target epitopes (different processing), so the T cell response for DNA and RNA based vaccines will be "off-target" (36). Furthermore, safety concerns associated with injecting DNA/RNA to the foetus would act as a regulatory barrier to vaccines of this type. An antibody based Zika vaccine could also induce DHF in Dengue sero-positive individuals (8). In summary, it appears Emergex is a developing the only product that could potentially be viable for in utero vaccination. There are no other groups working on a triple vaccine construct against all Zika, Dengue and Yellow Fever.

How is EMX-001 suited to low/middle income countries?

When delivering a vaccine to low/middle income countries, it is not sufficient to only have a product that is safe and effective, that product must also be suited to a low resource environment. The product must be able to be deployed to the right place, at the right time in the right conditions. In order to achieve this, vaccines should be temperature stable, have an accessible price and have a high ease of use.

The EMX-001 vaccine consists of a highly stable gold central core, encapsulated by simple carbohydrate linkers, to which are attached short linear peptide sequences that have no secondary or tertiary structure. Given the stability of each individual component of the vaccine construct, and the

stability of the bonds between each component, the vaccine will by definition be stable at a high range of ambient temperatures. Thermogravimetric analysis has shown that thermal decomposition does not occur on a peptide based gold nanoparticle construct below 100C. EMX-001 therefore would not require a cold chain, reducing the cost and risk of getting the vaccine to the user base in a functional condition.

The small size of EMX-001 means it would be suited to delivery via the dermis using microneedle patches. The simplicity of this method of administration means specialist skills are not required for immunisation. Emergex envisions that this would allow the users to have an initial dose from a local vaccine provider/distributor, but any booster doses could be provided to take home by the user for self-administration. This method may well improve compliance as the need to travel is reduced. Another advantage of this method is that since the vaccine is presented directly to antigen presenting cells within the dermis/epidermis, a much lower dose is required compared to other methods of administration which is favourable from both a safety and health economic perspective.

The production process of EMX-001 would be fast, cheap and highly scalable. A cost analysis shows that a particle such as EMX-001, that consists of 6 viral peptides, a gold core and others components such as spacers/ligands has a cost of goods of $72114 for 1 million doses. This equates to $.072 per dose. Midatech Pharma have agreed a manufacturing mark-up of 28%, and therefore Emergex could be provided with vaccines at $.092 per dose. Given this, an immunisation regime, including distribution, packaging and associated administration products (i.e. microneedle technology) at <$1 per user is realistic. In comparison, Sanofi is offering its newly developed Dengue vaccine at $23 a dose in a program aiming to immunise 1 million children in the Philippines.

There are in principle no limitations on production capacity, nor any known bottlenecks in the supply of raw materials, as all components can be synthesized using widely available equipment. The production process is modular, and can be scaled up without further process development. It would be feasible to produce 100g of vaccine in a single day; at 20ug a dose this would produce 5 million doses a day. This is in stark contrast to live attenuated vaccines, where the slow lead time and inefficient production have historically resulted in supply and cost issues for vaccines. With the unpredictably of epidemics/pandemics in low/middle income countries it is essential a vaccine technology should be available on demand in unforeseen circumstances.

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