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DNA Vaccines: Crossing a line in the Sand Introduction to Special Issue

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The initial reports, more than a decade and a half ago. that genetically engineered DNA can be directly delivered into animals resulting in the induction of immune responses served to create the field of DNA vaccines. Since that time, there has been a great deal of progress in our understanding of the basic biology of this important platform. Interest in the platform for clinical applications has been strong. Many infectious disease and cancer targets have been studied pre-clinically and have progressed into clinical trials. Interestingly, DNA vectors make up about 19% (246 out of 1311 total trials) of all gene therapy vector platforms studied in phase I to III trials in 2007. These data support the overall preclinical success and phase I safety of the platform, When we look at all open enrolling DNA vaccine/therapy trials, 68% are trials testing DNA therapies for cancer, while 11% are for treatment of cardiovascular diseases. Surprisingly, while some of the more attention getting DNA trials are in the area of infectious diseases, infectious disease trials make up roughly just 5% of the current open human clinical trials testing this platform. These include vaccines to treat or prevent HIV-1, cytomegalovirus, and Influenza, malaria and HCV among others. The majority of open clinical trials for the DNA platform are being tested in the United States (68%) with the United Kingdom (15%) and Germany following (8%) as additional important areas for clinical evaluation. It is clear that the clinical acceptance of this platform is growing rapidly as regulatory agency's become more and more comfortable with the enviable safety profile of this platform.

In theory, this conceptually safe vaccine approach represents an important non-live platform for the induction of both cellular and humoral immune responses. The DNA vaccine platform is unique in that its straight forward use of molecular design seems particularly amenable to scale up and manufacturing. Furthermore, the ability to drive cellular immune responses in a non live platform is an extremely compelling aspect of DNA vaccine technology, suggesting that a critical shift has occurred in vaccine development. Before these studies, live infection was believed to be required to induce strong cellular immunity and in particular, the elusive induction of killer Cytotoxic T Cells (CTL). The use of the DNA approach promised to overcome the safety concerns associated with live vaccines. Furthermore through manipulation of the plasmid encoded antigens, a DNA vaccine could

obviate any potential side effects of vaccination, yet in theory produce a similar immune response resulting in protective immunity. Unfortunately, this early optimism did not last. Based on immune responses observed in the first clinical trials of DNA vaccines in the areas of HIV, Influenza, Malaria, and Cancer among others, concerns were raised about the low levels of immunogenicity induced by this platform in humans. Furthermore, the immune responses in large animals and important primate model systems were much lower than expected based on the responses observed to be induced in small animal models. For more than the last 7 years DNA vaccines became relegated to a supporting role in vaccine development, as they were primarily being examined clinically for their ability to prime the immune response in prime boost vaccine trials. Even more worrisome was that in this more limited arena, concerns about the immunogenicity of the platform in the clinic and in larger animals lingered. It was under this cloud of controversy that last summer leading researchers in the DNA vaccine field gathered in Malaga, Spain to debate and discuss the latest results in advancing the DNA vaccine platform.

The mood at the opening of the conference was sober. In the past decade and a half, the DNA vaccine concept has been tested and applied against a variety of pathogens and tumor antigens. Many of the vaccines developed in through these studies are among the most creative ever designed for any vaccine application. There was a great deal of interest in improving DNA vaccine potency in a safe manner. Many technical improvements were discussed at the meeting including strategies for gene optimization, improved RNA structural design, novel formulations, immune adjuvants and improved delivery devices, regulatory T cell manipulations and cytokine modulations among others. Combination studies were also described. Consensus antigens based vaccine strategies were presented that suggest that such designs may allow specific vaccine prototypes to drive cross reactive immune responses to changing pathogens to some extent. Studies were presented using novel delivery devices to improve transfection efficiencies including the Gene Gun and electroporation technologies. Novel formulations or adjuvants were also presented including results using vaxfectin, or with cytokine adjuvants showing improved effects on the resulting immune responses in different models of host induced immunity. As the conference progressed the results presented using improved DNA vaccine combination approaches that were able to drive improved levels of cellular immune responses in many important animal model systems started to lift the mood of the participants. In human studies, prime boost approaches appeared to generate improved and consistent levels of IFNγ responses than had previously been reported with other platforms. This data suggested that through continued modifications of the technology, further improved responses can be generated. Exciting data was generated using the electroporation platforms where T cell responses in non human primates were driven to levels previously not observed with other DNA vaccine approachs. In some of these studies the levels of T cell immunity induced were similar to or superior to those induced by live viral vectors. All of these results were very encouraging for investigators in the field. The safety record of DNA vaccines in humans remained with out blemish, which was also encouraging. However, the field has been craving a true clinical success. Unfortunately, for this meeting this year a true clinical success was still elusive. However, it was progress in the veterinary market that served to further improve the energy and optimism of the conference. It was reported at the meeting

that four different veterinary use plasmid encoded products were licensed over the past few years. One approval was for a vaccine for protecting Salmon against Hematopoietic Necrosis Virus. This interesting vaccine is directly injected into hatchlings and results in the generation of protective immunity in farm-raised fish. A second impressive story was the report of a DNA vaccine that targets West Nile Virus infection by driving vaccine-induced anti-WNV antibodies and protects horses from this emerging pathogen. This interesting result was in the large animal arena which is a surprising but encouraging story. An exciting development was the presentation of a DNA vaccine used to treat canine melanoma that was conditionally licensed and shows extreme promise to alter the outcome of this fatal disease in dogs. This exciting development represents the first license for any immune therapy approach in this arena. A fourth product was described that delivers plasmid encoding GHRH to treat fetal loss in pigs using electroporation as its delivery platform for a plasmid product was also presented, shortly after the conference this product was also approved for animal health use. This represents the first such delivery platform success. These commercial successes for several groups including Merial, Novartis, Vical, Wyeth and VGX, have helped to demonstrate the commercial potential of this technology. These developments together with the clinical responses, helped to energize the conference attendees. This issue brings together many important research studies that were presented at the meeting. The many articles from diverse investigators from around the globe serve to underscore the important progress in this area and the continued vitality of the field. Advances in basic research, formulations, manufacturing advances, plasmid design, delivery schemes, clinical investigation into human and animal health are reported. The Malaga meeting appears to have been a true turning point for the field, both commercially and clinically. As this collection of papers underscores, field appears to be more determined, more focused and more productive than ever. The positive energy gathered from this meeting is providing significant momentum for further growth and collaboration with in the field. The next few years will be critical for DNA vaccine technology and the collaborative nature of the field will be central to the field’s success. We are actively looking forward to the next meeting and seeing the continued expansion and progress in the DNA vaccine arena and crossing the next threshold of progress together.