Meeting report

A small step closer to the Holy Grail of DNA vaccines: undisputed clinical benefit in humans

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Published: 23 January 2009

Genome Medicine 2009, **1**:15 (doi:10.1186/gm15)

The electronic version of this article is the complete one and can be found online at http://genomemedicine.com/content/1/1/15

Abstract

A report of the DNA Vaccines 2008 meeting, Las Vegas, Nevada, USA, 9-11 December 2008.

Introduction

The development of a prophylactic and/or therapeutic DNA vaccine for humans has been shown to be more difficult than anticipated. This has often been attributed to problems related to delivery. However, things are slowly changing in the DNA vaccine arena. Today, four DNA vaccines have been licensed for veterinary use. Importantly, at the DNA Vaccines 2008 meeting the first reports with early positive data from human studies using *in vivo* electroporation were presented. In parallel with this, new immunological approaches have highlighted the importance of studying the quantity and quality (polyfunctionality?) of DNA vaccine-activated T cells. These may allow us to better understand the relation between *in vitro*-determined immune responses and *in vivo* protection and functionality. With these cautiously encouraging data, we may hope to see rapid advances in the field of DNA vaccines over the coming years.

Aims and meeting facts

The DNA Vaccines 2008 meeting [http://www.bioconferences.com/CONFERENCES/DNA/] was held at the Tropicana Resort and Casino, Las Vegas, NV, USA, December 9-11, 2008. The main goals of the meeting were to gather as many scientists, clinicians, and academic and industrial investigators as possible working in the field of DNA vaccines to report and discuss their latest breakthroughs. Moreover, the meeting aimed for more intensive interactions between researchers in academia and biotechnology/pharmaceutical companies.

The meeting gathered approximately 150 attendees from academia, biotechnology and pharmaceutical companies, and media representatives. At the meeting, over 40 talks and around 60 posters were presented. In this report a few highlights regarding clinical studies have been selected.

The current status in the field of DNA vaccines

The meeting aim was to gather academic and industrial researchers interested in DNA vaccines. This aim was certainly fulfilled. A major obstacle in the DNA vaccine field has been the observation that although DNA vaccines work well in small animals, they do less well in larger animals and in humans. It was therefore no surprise that many of the presentations this year focused on optimizing delivery, particularly using *in vivo* electroporation. Many of the industrial attendees were from companies involved in developing this technique. One of the take-home messages from the meeting, as very well summarized in the panel debate, was a desire to get DNA vaccines to a stage where there is undisputed evidence of clinically beneficial effects in humans. This meeting showed that the field is now a step closer to reaching this goal. Several preclinical studies in non-human primates and clinical studies have shown encouraging results in the field of DNA vaccination.

Important evidence for success of the DNA vaccine field is, in particular, the progress in the animal health product portfolio. To date we have at least four licensed animal DNA-based products on the market, which indicates that the field is moving forward. Dr Steve Chu, from Fort Dodge Animal Health, Wyeth (Overland Park, KS, USA) presented results from the world's first licensed DNA vaccine against equine West Nile virus (EWNV) for horses. He showed that two intramuscular doses of the DNA vaccine provided 12-month immunity against EWNV. To maintain long-term protection against EWNV an annual revaccination was needed. The DNA vaccine was importantly shown to be safe and tolerable. Moreover, Ruxandra Draghia-Akli, MD, from VGX Pharmaceuticals Inc. (Blue Bell, PA, USA), presented results from the world's first licensed porcine growth hormone-releasing hormone (GHRH) supplementation product, encoded by a DNA vaccine given in combination with electroporation. A single dose of the GHRH-expressing DNA vaccine had visible effects in pigs for 12 to 18 months post vaccination.

Improved immunogenicity is needed for development of a successful DNA vaccine

So far no DNA vaccine is close to being licensed for human use and the biggest unmet goal today is the lack of proof-of-concept regarding efficacy in humans. This is somewhat surprising since it is a widely accepted view that DNA vaccines have several advantages over conventional vaccines. In particular, they are easy to produce and manufacture, the time from bench-to-clinic is short, and they have, so far, no problems related to vector immunity. During the past 15 years of DNA vaccine development, several unanticipated problems have arisen, where the failure of activating potent immune responses in humans has become a major issue.

A general consensus regarding HIV vaccines was that from now on they will be benchmarked with the Merck vaccine used in the recently terminated STEP (HIV Vaccine Trial Network, Study 502) trial. Michael Betts, assistant professor at University of Pennsylvania (PA, USA), gave a presentation where he discussed anti-vector immunity and different reasons for the failure of the STEP trial. The conference chairman, David Weiner, also a professor at University of Pennsylvania, (PA, USA), highlighted that in order to succeed in the development of prophylactic and/or therapeutic DNA vaccines for humans, several steps need to be taken into consideration. The DNA vaccine needs to be optimized in all possible ways, it needs to be delivered effectively, and, if required, molecular adjuvants such as interleukin-12 (IL-12) can be added. Dr Weiner showed data suggesting that all these factors combine and contribute in different ways to the immunogenicity and effect of the vaccine. Dr Michael Egan, of Profectus Biosciences, Baltimore (MD, USA), provided data along the same lines from testing HIV vaccines in non-human primates, showing that both *in vivo* electroporation and the co-delivery of an IL-12 plasmid have beneficial effects on the priming of immune responses. In particular, the polyfunctionality of the responses improved when using this combination. These differences may have been missed if the polyfunctionality had not been determined, highlighting the potential importance of this type of readout.

DNA vaccines starting to show some effects in humans

Results from several promising ongoing phase I and II clinical studies were presented at the meeting. In these trials many of the above-mentioned problems had been considered.

Professor Freda Stevenson, from the University of Southampton (UK), discussed the data from a phase I/II trial on an epitope-specific DNA vaccine for prostate cancer delivered by *in vivo* electroporation. She highlighted that although the cytotoxic T lymphocyte (CTL) responses were low when measured directly *ex vivo*, they could effectively expand memory CTLs by *in vitro* re-stimulation. The trial is still under way. Professor Richard Heller, from the Frank Reidy Research Center for Bioelectrics, Old Dominion University (VA, USA), presented results from a phase I study of a DNA vaccine encoding IL-12 administered in combination with electroporation as an immunotherapy against metastatic melanoma. Heller's results showed safety and tolerability as well as durable partial and complete regression of treated melanoma lesions. Ten out of 24 enrolled patients showed a therapeutic effect. Matti Sällberg, professor at Karolinska Institutet (Sweden), presented results from a phase I/II study, where a DNA vaccine against hepatitis C virus (HCV) was delivered via *in vivo* electroporation to treat naïve chronic HCV-infected patients. This study provided data supporting good safety and tolerability of the treatment. Importantly, the study showed an activation of HCV-specific immune responses, and transient reductions in the viral load of up to 2.4 $\log_{10}$ in four out of six patients in the two highest-dose groups. Dr Mart Ustav, from FIT Biotech (Tampere, Finland), presented early results of a phase II trial with a DNA vaccine against HIV-1 delivered by the biojector. The vaccine showed good safety and tolerability as well as effects on the viral load and increased CD4+ T-cell counts compared to placebo controls.

Concluding remarks

The above-mentioned studies demonstrate optimism that DNA vaccination may actually work in humans. Although there may be a long way to go, these initial data indicate that DNA vaccination in humans has a therapeutic effect on cancer and infectious diseases. The DNA Vaccines meeting of 2008 suggests that we may see more rapid advances in clinical trials, with the Holy Grail being a successful DNA vaccine in the not too distant future.

Abbreviations

CTL, cytotoxic T lymphocyte; EWNV, equine West Nile virus; GHRH, growth hormone-releasing hormone; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IL-12, interleukin-12.

Competing interests

LF and MS own shares in Tripep AB. MS is a founder, board member and consultant to Tripep AB.

Authors' contributions

LF and MS contributed equally in the preparation, writing and submission of this paper.

Authors' information

Both LF and MS have a PhD in virology from Karolinska Institutet (2004 and 1992, respectively). LF is a postdoctoral fellow at Karolinska Institutet. MS is a DDS and a full professor in biomedical analysis since 2000 at Karolinska Institutet. LF and MS have been involved in genetic vaccine development for viral hepatitis over more than 10-15 years.

Acknowledgements

The present paper was produced with financial support from The Swedish Science Council, The Cancer Foundation, the EC-funded VIRGIL network of excellence, and the Stockholm County Council to MS. LF was supported by grants from the Swedish Society for Medical Research, the Swedish Society of Medicine, the Swedish Foundation for Research and Development in Medical Microbiology, the Ruth and Richard Juhlin Foundation, Lars Hiertas Memorial fund, Goljes Memorial fund and Karolinska Institutet.