



INTERNATIONAL SYMPOSIUM ABOUT DNA VACCINES

July 21st, 2022

Ege University Vaccine Development Application and Research Center Bornova/İzmir, Turkiye



ABSTRACT BOOK

Organized by Ege University Vaccine Development Application and Research Center

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| I | nternational Symposium about DNA vaccines |
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| | Scientific Programme |
| 09:00-09:30 | Registration |
| | Opening Talks |
| 09:30-10:00 | Necdet BUDAK, Ph.D., Prof., Ege University, Rector |
| | Adnan Yüksel GÜRÜZ, M.D., Ph.D., Prof., President of Vaccinology Society of Turkey, Chairman of Ege University Vaccine |
| | Development Application and Research Center |
| 10:00 - 10:15 | Coffee Break |
| 10:15-11:15 | Moderators: Adnan Yüksel GÜRÜZ, M.D., Ph.D., Prof. |
| 10:15-10:35 | DNA vaccines from past to present |
| | Mert DÖŞKAYA, M.D., Ph.D., Assoc. Prof. |
| | Ege University Faculty of Medicine, Department of Parasitology, Vice President of the Board of Ege University Vaccine |
| | Development Application and Research , Turkey |
| 10:35-10:55 | Use of DNA vaccines in medicine |
| | Aysu DEGIRMENCI DOŞKAYA, M.D., Ph.D., Assoc. Prot. |
| | Ege University Faculty of Medicine, Department of Parasitology, Member of the Board of Ege University Vaccine |
| | Development application and research center, forkey |
| 10:55-11:15 | Designing DNA vaccines with immuno-informatics methods |
| | Huseyin CAN, Ph.D., Assoc. Prot. |
| | Ege University Faculty of Science Department of Biology Molecular Biology Section, Ege University Vaccine Development |
| 11.15 11.20 | Coffee Preak |
| 11.13-11.30 | |
| 11:30-12:10 | Moderator: Gülten KANTARCI Ph.D. Prof |
| 11:30-12:10 | Moderator: Gülten KANTARCI, Ph.D., Prof. |
| 11:30-12:10 | Moderator: Gülten KANTARCI, Ph.D., Prof. Nanoformulations in DNA vaccines Hasan Akbaba. Ph.D., Assoc. Prof. |
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ORAL PRESENTATIONS

OP-1 - DNA vaccines from past to present <u>Mert Döşkaya</u>

OP-2- Use of DNA Vaccines in Medicine <u>Aysu Değirmenci Döşkaya</u>

OP-3- Designing DNA vaccines with immuno-informatics tools <u>Hüseyin Can</u>

OP-4- Nanoformulations in DNA Vaccines <u>Hasan Akbaba</u>

OP-5-DNA Vaccine Production Technologies <u>Aytül Gül</u>

OP-6- DNA Vaccines for Veterinary Applications <u>Muhammet Karakavuk</u>

OP-7- DNA vaccine delivery systems <u>Tuğba Karakavuk</u>

OP-8- Disease-X and DNA Vaccine Technology <u>Ceren Gül</u>

ABSTRACTS

DNA Vaccines, from Past to Present

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Abstract

The scientific interest in DNA vaccines dates back to the 1990s. The most important starting point is that Ulmer et al. (1993) who showed that they stimulated a protective immune response in a pre-clinical study with a DNA vaccine expressing the influenza virus protein. Later, the efficacy and immunological mechanisms of DNA vaccines were demonstrated in pre-clinical models of many diseases such as cancer, autoimmunity and allergies as well as infectious diseases. The success of DNA vaccines in pre-clinical studies in the first years paved the way for clinical studies. In this context, DNA vaccine developed for HIV-1 is among the first phase I clinical studies conducted 25-30 years ago. Subsequently, trials were conducted in influenza, HPV, hepatitis and malaria. Although the results of these studies were disappointing in terms of the strength of the immune response induced by the DNA vaccine, clinical studies made important contributions to the safety of DNA vaccines. For example, DNA vaccines were non-living nucleic acids and self-replication property eliminated the risk of infection in the vaccinated individual. In addition, ease of GMP production for clinical studies, high resistance to room temperature were its important advantages. There were two important criticisms for DNA vaccines which are the integration of plasmid DNA into genomic DNA and the risk of developing an anti-DNA immune response (autoimmunity). In various clinical studies, it has been shown that the risk of mutation brought by integration into genomic DNA is less than the risk of normal mutation, and that the risk of autoimmune response does not increase. Ultimately, DNA vaccines have been shown to be extremely safe and well tolerated. DNA vaccines are being developed for many diseases. According to the clinicaltrials.gov database, DNA vaccines have been tested in more than 600 clinical trials. Lastly in COVID-19 pandemic, there were more than 15 candidate SARS-CoV-2 DNA vaccines in clinical trials that can combat the epidemic. Among these candidates, India's drug regulator has granted emergency use

approval for nCoV DNA vaccine to be used in humans. DNA vaccines have also been developed against veterinary diseases such as melanoma in dogs, West Nile virus, fish hematopoietic necrosis virus and approved for veterinary use.

Use of DNA Vaccines in Medicine

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Abstract

DNA vaccines consist of bacterial plasmids containing the gene encoding the immunogen for which the immune response is sought. Since plasmids have a prokaryotic origin of replication, replication occurs only in the bacterial cell. After vaccination, plasmid DNA containing the target antigen enters the nucleus of somatic cells or dendritic cells, initiating gene transcription and protein expression in their cytoplasm. For this reason, there is a concern about the integration of plasmid DNA into the host chromosome, but such a result has not been observed in the studies carried out to date. Despite this disadvantage, DNA vaccines have advantages such as stimulating both B and T cell responses, being stable, not requiring a cold chain, rapid production and cost-effectiveness. Due to these advantages, clinical studies have been conducted with the DNA vaccine approach against autoimmune and allergic diseases such as cancer and peanut allergy, especially communicable diseases. There are currently 235 DNA vaccines that have completed clinical studies. In order to address the urgent need for vaccinations that arose with the COVID-19 pandemic, candidate vaccines, including DNA vaccines, have been developed. There are currently 16 DNA vaccines in clinical studies. One of these vaccines, the ZyCoV-D DNA vaccine created by Zydus Cadila, vaccine efficacy was found to be 66.6%. In addition, the vaccine has been granted an emergency use authorization, proving that DNA vaccines can be used on people.

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Designing DNA Vaccines with Immuno-informatics Tools

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Abstract

DNA vaccines are one of the next-generation vaccine platforms such as mRNA vaccines and viral vector-based vaccines. DNA vaccines are considered inherently safe because vectors do not replicate, only encode and express the target antigen, and are not live. DNA vaccines are plasmids that contain the sequences necessary for replication and selection in Escherichia coli (bacterial region) with the sequences to express the target gene encoded in vertebrate cells (eukaryotic region) after delivery to an organism and transfection into target tissue cells. In this vaccine platform, after the plasmid carrying target gene enters the nucleus of the cell, the target gene is transcribed and the mRNA is exported to the cytoplasm and subsequently translated. The antigen expressed by the host is presented to the immune system by the major histocompatibility complex (MHC) class I or II. Transfected plasmid also activates innate immunity, which is critical for promoting an immune response against the antigen presented by the MHC. In a plasmid design, there are two significant regions including the bacterial region and eukaryotic region. The bacterial region is necessary for replication (pUC origin) and selection (kanamycin resistance gene as a selectable marker) in E. coli. In the eukaryotic region, a promoter, ORF encoding the targeted antigen and a polyadenylation region are located. The promoter mediates the transcription of the target gene whereas the polyadenylation region mediates mRNA cleavage and polyadenylation. Cytomegalovirus (CMV) promoter is frequently used in DNA vaccine studies because of transcribing higher levels of mRNA than other cellular promoters. The polyadenylation sequences from Rabbit β globin or bovine growth hormone genes also are used as PolyA signals. The promoter region is followed by a Kozak sequence containing ATG start codon. The Kozak sequence is critical to start the translation of the mRNA in cytoplasm. pVAX1 (Invitrogen) and gWIZ (Genlantis) backbones can be used in vaccine studies. Also, the gWIZ vector has been reported to cause 5-fold improved expression compared to pVAX1. For the designing of plasmid, many user friendly plasmid tools are available such as GenSmart Design, VectorBuilder and SnapGene. These tools represent different plasmid backbones carrying bacterial and eukaryotic regions and researchers can easily insert the gene encoding target antigen to the plasmid using these tools. As a result, a plasmid design as a DNA vaccine vector can be easily conducted by the consideration of necessary sequences and the use of plasmid tools.

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- https://www.genscript.com/gene-and-plasmid-construct-design.html (Erişim Tarihi: 15.07.2022)
- 4. https://en.vectorbuilder.com/ (Erişim Tarihi: 15.07.2022)
- 5. https://www.snapgene.com/ (Erişim Tarihi: 15.07.2022)

Nanoformulations in DNA Vaccines

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Abstract

Emerging as an innovative technology against infectious diseases, including COVID-19 caused by SARS-CoV-2, mRNA vaccines have recently increased interest in the field of vaccinology. Lipid nanoparticles, which are non-viral gene delivery systems used in these mRNA vaccines approved by legal authorities, are a breakthrough development and the first of its kind in markets. Moreover, these nanoformulations, which do not have the disadvantages of viral gene delivery systems, are also promising candidates for DNA vaccine delivery.

Based on existing literature, there have been only a few nanomaterial-based DNA vaccine delivery systems that have successfully progressed to clinical trials, and none have been approved for human use so far. In order for DNA vaccines to repeat the success of mRNA vaccines, they need to increase their effectiveness. The most important factor in this challenge is the efficient delivery of DNA to the relevant tissue or cells where the viral and non-viral vectors are involved.

The current dilemma for DNA and RNA vaccines also applies to viral and non-viral vectors. Both systems have advantages and disadvantages. However, formulation of vaccines with nanoformulations have been shown to improve antigen and nucleic acid stability, availability and adjuvanticity as well as immunostimulatory capacity, target delivery and specific release. In this context, besides current literature studies, gene delivery efficiency of nanoformulations will be discussed by giving information about lipid nanoparticular delivery systems developed by our laboratory as well.

DNA Vaccine Production Technologies

<u>Aytül GÜL^{1,2}</u>

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Abstract

The unprecedented emergence of new outbreaks over the past two decades has made the development of vaccines that are fast and effective enough to immunize large populations a biomedical priority. DNA vaccines, next-generation vaccine platforms, have the greatest potential to accelerate the production of effective vaccines when urgently needed due to their ability to elicit both humoral and cellular immune responses, as well as demonstrating advantages related to easy manufacturability, high stability, long-term storability and does not require a strict cold chain for distribution. The production of DNA vaccines involves three general stages including upstream process (master cell bank preparation), a production process (bacterial fermentation) and a downstream process (plasmid DNA isolation and purification). Master and working cell banks are created by selecting bacterial strains capable of high-level replicating of plasmid DNA. During the fermentation process, the growth medium, bioreactor operating parameters, and cultivation methods are optimized to produce the high volumetric yield of super-coiled plasmid DNA. Genomic DNA, RNA, proteins, and other cell contaminants are removed in the downstream process to acquire DNA of an acceptable purity that meets pharmaceutical standards. The volumetric yield of DNA vaccines can be increased from 0.1 g/L to 2 g/L by optimizing these three basic stages.

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DNA Vaccines for Veterinary Applications

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Abstract

DNA vaccines, which are defined as new generation vaccines and a rapidly developing technology, offer new methods for the prevention and treatment of many illnesses. Successful *in vivo* transfection of mammalian cells following injection of purified DNA was first achieved 40 years ago. Its potential wasn't mainly understood until 1990, when it was showed that a reporter gene encoding an enzyme protein could be expressed in mouse skeletal muscle *in vivo* by Wolf and colleagues.

Veterinary vaccines, in addition to preventive medicine, are of great importance for the prevention of zoonotic diseases and for economic production. Most of the vaccines applied in the world and in our country are veterinary vaccines. Therefore, the importance of biotechnological vaccines is increasing in veterinary vaccine development.

Plasmid named Pvax-1, one of the DNA vaccine vectors, has been approved by the FDA (U.S. Food and Drug Administration) for human and animals suitable for human consumption The first commercial DNA vaccine, the H5N1 avian influenza DNA vaccine for chickens, entered the market in 2017. In addition, DNA vaccines developed against West Nile virus of horses, infectious hemopoietic necrosis disease and pancreatic disease of salmon, and melanoma diseases in dogs are licensed.

DNA Vaccine Delivery Systems

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Abstract

DNA vaccines are vaccines that are easy to produce, do not deteriorate in a cold chain-free environment, and elicit strong immune responses by mimicking natural infections. This vaccine platform is extremely interesting. The main goal of vaccination is to stimulate immune cells and ensure that the vaccine is delivered to the body in the correct conformation. The route of administration plays a critical role for successful vaccination. Generally, IM (intramuscular), ID (intradermal) and SC (subcutan) methods are widely used and easily applied. However, low protein expression levels in the cell and poor uptake of vaccine plasmids by antigen presenting cells (APC) can be observed in these methods. Therefore, new administration routes have been tried recently, which will provide a high immune response and less vaccine material usage. Electroporation creates a temporary change in the cell membrane and allows the entry of DNA into the cells. The tattoo method involves applying the vaccine directly to the skin surface and using a rotary tattoo device to introduce the plasmid immunogen into the dermis. Microneedles (MN) are another effective way to target the immunological APC network under the skin. The gene gun is a method that uses a gun to bombard the target DNA, allowing the DNA to enter the cell directly. On the other hand, jet injector method is used to deliver the vaccine with a high-pressure narrow-flow liquid to break through the skin barrier. There is also a focus on developing routes of administration for direct application to mucosal surfaces such as the mouth, nose, vagina, and rectum.

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Disease-X and DNA Vaccine Technology

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Abstract

Vaccination is an efficient approach because of its preventative nature and low cost compared to treatment, which can help to reduce healthcare costs. In the last two decades, new and reemerging epidemics, especially those caused by zoonotic viruses, have shown that vaccines need to be developed extremely rapidly. Continuous surveillance is not possible for all emerging potential zoonotic diseases. Therefore, vaccine platform technologies must be optimized for quick response to disease-X in a short time. DNA vaccines consist of plasmids containing a targeted antigen of the pathogen. The DNA vaccine platform has advantages such as no risk of conversion to infective form as it does not contain the pathogen itself, stimulating both B and T cell responses, simpler production processes, physical stability and storage without cold chain. In addition to these advantages, DNA vaccines provide a safe platform in the face of an epidemic or pandemic due to the lack of anti-vector immunity or non-target acquired immunity against DNA in the vaccine recipient. There are 32 DNA vaccines in total so far, 16 of which are in preclinical and 16 in clinical stages, developed against the COVID-19 pandemic that started in Wuhan, China on December 1, 2019. The ZyCoV-D DNA vaccine, developed by Zydus Cadila, has passed the phase studies in humans one by one and received emergency use authorization, demonstrating the applicability of DNA vaccines to humans.

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| | July 21, 2022 - Ege University Vaccine Development Application and Research Center, Bornova / |
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| | Ocientific D nagytumine Z ALL REGISTRATIONS ARE |
| 09:00-09:30 | Registration |
| 09:30-10:00 | Opening Talks Necdet BUDAK, Ph.D., Prof., Ege University, Rector Adnan Yüksel CÜRÜZ, M.D., Ph.D., Prof. President of Vaccinology Society of Turkey, Chairman of Ege University Vaccine Development Application and Research Center |
| 10:00-10:15 | Coffee Break |
| 10:15-11:15 10:15-10:35 | Moderator: Adnan Yüksel GÜRÜZ, M.D., Ph.D., DNA Vaccines from Past to Present Mert DÖŞKAYA, M.D., Ph.D., Assoc. Prof. Ege University Faculty of Medicine, Department of Parasitology, Vice President of the Board of Ege University Vaccine Development Application and Research , Turkey |
| 10:35-10:55 | Use of DNA Vaccines in Medicine Aysu DEČIRMENCI DÕŞKAYA, M.D., Ph.D., Assoc. Prof. Ege University Faculty of Medicine, Department of Parasitology, Member of the Board of Ege University Vaccine Development Application and Research Center , Turkey |
| 10:55-11:15 | Designing DNA Vaccines with Immuno-informatics Methods Hüseyln CAN, Ph.D., Assoc. Prof. Ege University Faculty of Science Department of Biology Molecular Biology Section, Ege University Vaccine Development Application and Research Center |
| 11:15 - 11:30 | Coffee Break |
| 11:30-12:10 | Moderator: Gülten KANTARCI, Ph.D., Prof., |
| 11:30-11:50 | Nanoformulations in DNA Vaccines Hasan Akbaba, Ph.D., Assoc. Prof. Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Ege University |
| 11:50-12:10 | DNA Vaccine Production Technologies Aytûl CÛL, MsC Ege University Faculty of Engineering Department of Bioengineering, Ege University Vaccine Development Application and Research Center |
| 12:10 - 12:45 | Lunch Break |
| 12:45-13:55 | Moderator: Cemal ÜN, Ph.D., Prof., |
| 12:45-13:05 | DNA Vaccines for Veterinary Applications Muhammet KARAKAVUK, Ph.D., DVM. Ege University Odemis Vocational School, Department of Parasitology, Member of the Board of Ege University Vaccine Development Application and Research Center, Turkey |
| 13:05-13:25 | DNA Vaccine Delivery Systems Tugba KARAKAVUK Ege University, Institute of Science, Department of Biotechnology, Ege University Vaccine Development Application and Research Center |
| 13:25-13:55 | Disease-X and DNA Vaccine Technology Ceren GOL Ege University, Institute of Science, Department of Biotechnology, Ege University Vaccine Development Application and Research Center |