GEOVAX MVA-VLP AND MVA PLATFORMS

EXECUTIVE SUMMARY

GeoVax utilizes Modified Vaccinia Ankara (MVA) as a recombinant viral vector to express vaccine antigens of interest in a format suitable for global use. Our MVA-Virus-Like Particle (GV-MVA-VLP™) platform combines the outstanding safety of MVA with the enhanced immunogenicity of vaccine antigens displayed on the surface of VLPs. The VLPs are generated *in vivo* within the vaccinated patients. Research in animal models has demonstrated vaccines based on the MVA-VLP platform to be safe, immunogenic and to induce immunity capable of protecting animals against a variety of disease-causing agents. For Ebola, Lassa Fever and Zika virus, single inoculations of GeoVax MVA-VLP based vaccines fully protected animals against lethal viral challenges. The MVA-VLP vaccines induce both humoral (antibody) and cellular (T-cell) immune responses characterized by high magnitude and durability. Our GOVX-B11 vaccine for HIV has demonstrated outstanding safety and immunogenicity in multiple clinical trials and is currently being tested in clinical trials as a component in preventive vaccine and as a therapeutic, working toward a "functional cure."

INTRODUCTION

MVA is a highly attenuated strain of the vaccinia virus (VV) that was developed specifically for use in humans as a vaccine against smallpox. This viral vaccine vector is unable to replicate in human cells which imparts exceptional vaccine safety, while readily replicating in cells of avian origin, such as duck and chicken cell lines, facilitating efficient, high volume manufacturing.

MVA is approved and licensed as a smallpox vaccine in Europe and the USA and is the preferred product for individuals that may not readily tolerate the VV vaccine, such as the elderly, immune compromised and those with various co-morbidities. In the United States the Biomedical Advanced Research and Development Authority (BARDA) has funded development of MVA for the strategic stockpile against bioterrorism and pandemic threats.

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MVA and VV were among the first viral vaccine vectors developed because of their large "coding capacity" for foreign genes. Unlike other vaccine vectors such as adenovirus, herpesvirus and Lymphocytic Choriomeningitis virus (LCMV), MVA can be engineered to carry large genetic inserts that express multiple viral proteins (as in our HIV vaccine, which express the Gag, Pol and Env proteins) and produced without the need for a helper virus/helper plasmid or engineered packaging/manufacturing cell lines. These properties coupled with the higher level of attenuation of MVA and documented safety profile, all contribute to the value of this vector system.

THE MVA-VLP PLATFORM

In the MVA-VLP platform, we take advantage of MVA's large "coding capacity" to insert genes that encode multiple proteins, the combination of which is adequate to support the generation of VLPs by the MVA infected cells. Utility has been demonstrated for multiple vaccine candidates wherein the MVA-encoded viral matrix proteins and glycoproteins assemble into VLPs. VLPs are highly effective vaccine immunogens for enveloped viruses because they mimic the native structure of the pathogenic virus and induce immune responses specific to natural forms of viral surface proteins, the envelope glycoproteins. These envelope glycoproteins are critical vaccine targets because they mediate viral entry into cells and protective antibody responses block the infection step, a process referred to as viral neutralization. The inclusion of matrix proteins (e.g. Gag, VP40 or Z) not only provides the structural elements for VLP formation but these proteins induce cellular immune responses that are critical for removal of virus infected cells, clearance of infection and the establishment of immunological memory.

Figure 1 shows examples of thin section electron micrographs of actual viruses and VLPs for these viruses expressed by GeoVax MVA-VLP vaccines.

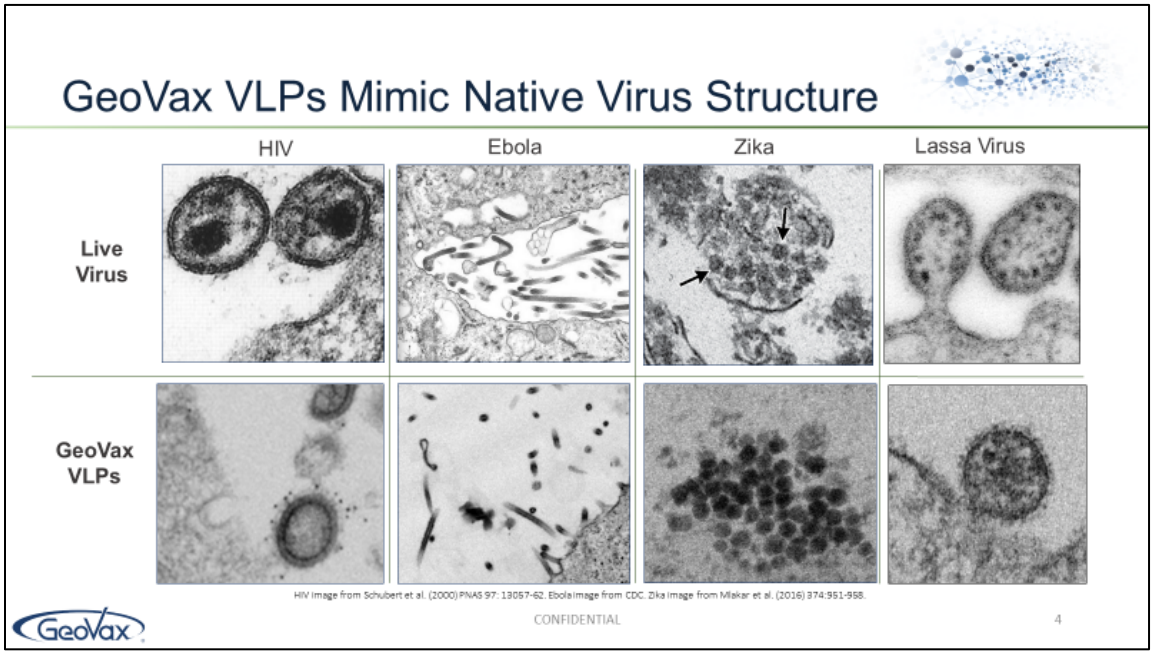

Figure 1. Comparisons of MVA-VLPs and native virus structures

We collaborated with the laboratory of Dr. Bernard Moss at NIH/NIAID on four different generations of MVA vectors, spanning over 15 years of collaboration, to effectively express vaccine proteins that assemble into VLPs. These efforts led to the development of different shuttle vectors and the identification of multiple insertion sites for introducing foreign genes encoding the vaccine target proteins into MVA in a manner that optimizes each product for manufacturing stability[1]. Each MVA-VLP vaccine has multiple

expression cassettes, each encoding one or more antigens selected from pathogens of interest. At a minimum, each vaccine expresses two antigens required for VLP formation; in the case of HIV and hemorrhagic fever vaccines, a viral matrix protein and an envelope glycoprotein. We use a synthetic early late promoter that provides high, yet not lethal, levels of insert expression, which is initiated immediately after infection in cells of the vaccinated individual[2,3].

Figure 2 illustrates the process by which MVA-VLP vaccines induce cellular (T-cell) and humoral (antibody) immune responses. The flow chart assumes intramuscular injection, but vaccines administered by other routes will function by the same mechanism.

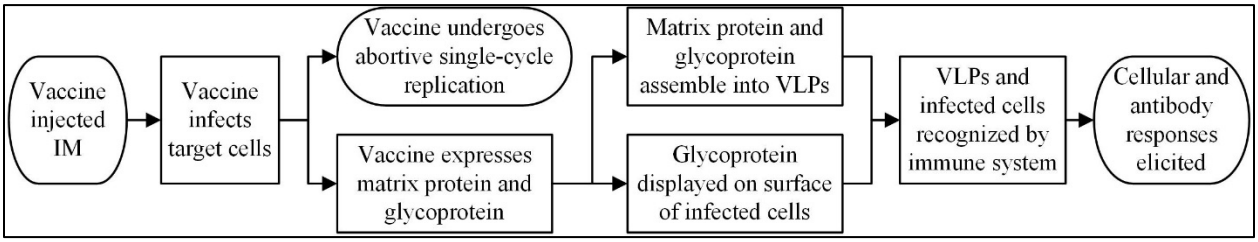

Figure 2. Induction of immune responses by MVA-VLP vaccine

COMPETITIVE ADVANTAGE OF MVA-VLPs VS OTHER MVAs AND VACCINIA VIRUSes

Figure 3 compares MVA-VLP vaccines with MVA vaccines that do not express VLPs and vaccines based on the vaccinia virus parent of MVA. This figure highlights the increased potency of VLP expression compared to expression of soluble proteins that do not have the advantage of presenting immunogenic proteins to the immune system in a concentrated and native form; specifically, on a particulate with multiple copies that mimic the natural viral pathogen.

Vector	VLP Formation	Potential for single-dose	Non-Replicating	Immunogenicity	Limited Preexisting Immunity	Transgene Stability	Thermal Stability	Self Adjuvanted
MVA-VLP	++	++	++	++	++	++	++	++
MVA	-	-	++	+	++	?	++	++
Vaccinia	-	++	-	++	++	?	++	++

++ High + Medium - Low

Figure 3. Advantages of MVA-VLP over other MVAs and its vaccinia virus parent

FEATURES AND ADVANTAGES OF THE MVA-VLP PLATFORM.

The unique features of the MVA-VLP platform and the corresponding advantages are summarized in Table 1.

Table 1. Features and Advantages of the MVA-VLP Platform

Features and Advantages of the GV-MVA-VLP™ Platform	
Feature	**Advantage**
Safety in all target populations including elderly and immunocompromised individuals	MVA-VLP vaccines are expected to be safe in all target populations including the immunocompromised. Safety for the MVA vector was demonstrated in more than 120,000 subjects in Europe, including immunocompromised individuals during the initial development of MVA[4] and more recently with the development of MVA as a safer vaccine against smallpox[5,6,7,8]. Safety for an MVA-VLP vaccine was documented for GeoVax MVA-VLP HIV vaccines in ~500 humans in clinical trials[9-11].
Rapid elicitation of protective immunity after a single dose	MVA-VLP vaccines can elicit protective immunity after a single dose, based on model animal studies completed by GeoVax against Ebola or Lassa virus challenges in rodent or macaques. In the Ebola study, antibody responses reached levels generally considered to be protective in under two weeks.
High efficacy in heterologous prime/boost regimens	MVA vaccines are highly effective at boosting immune responses that are primed by DNA, protein or other viral vector vaccines. It can also be used simultaneously with a protein or peptide vaccine.
Induction of both humoral and cellular immune responses	Extensive experience with MVA vectors has demonstrated their ability to raise humoral and cellular immune responses, including neutralizing antibodies, and has provided strong precedent for safe and effective use against multiple indications[8,12,13].
Durability of immune responses	MVA-VLP vaccines raise highly durable antibody and T cell responses, the most durable in the field of vectored HIV vaccines[14]. We hypothesize that induction of durable vaccine responses is conferred in part by the vector; the parent VV induce durable responses for smallpox[15,16].
Rapid production of prototype vaccines	GeoVax is skilled in the construction of MVA vectors and vaccines can be constructed quickly and easily using proprietary techniques.
High "coding capacity" to express multiple viral antigens	GeoVax has had success expressing multiple HIV-1 proteins with a single MVA vector. Immunogenicity and safety have been demonstrated for other MVA vaccines expressing up to four antigens from a single construct[17].
Thermostable formulation	MVA is stable in both liquid and lyophilized dosage forms. Precedent for lyophilization of MVA-vectored vaccines[18] suggests that a lyophilized MVA-VLP vaccine would be highly thermostable and suitable for long-term storage at refrigerator temperature.
No need for adjuvants	MVA stimulates strong innate immune responses and does not require the use of adjuvants[12].
Limited pre-existing immunity to vector; suitability for repeated use	Following the eradication of smallpox in 1980, smallpox vaccinations subsequently ended, leaving all but those born before 1980 and selected populations (such as vaccinated laboratory workers, first responders) unvaccinated and without pre-existing immunity. Repeated immunizations with MVA has been shown to boost antibody responses including neutralizing antibody[19].
Can be used for sequential immunizations against different pathogens	MVA-Ebola vaccine was used in animals vaccinated with MVA-Zika vaccine without any reduction of immunogenicity[20].
Robust, flexible, and scalable manufacturing processes	A scalable, cell culture-based process, which employs single-use bioreactor technology, for robust flexible and scalable upstream manufacturing combined with a defined downstream process, leveraging disposables-based approach for flexible manufacturing.
Genetic stability in manufacturing	If appropriately engineered, MVA can reliably be manufactured in Chicken Embryo Fibroblasts (CEFs) or novel continuous cell lines that support scalability as well as greater process consistency and efficiency.

COMPETITIVE LANDSCAPE

GeoVax is unique in focusing on the development of MVA vaccines expressing VLPs. Two major companies also use MVA as a vaccine vector; Bavarian Nordic and Transgene. The Jenner Institute of Oxford University has recently formed Vaccitech Limited which uses Adeno and MVA vectors in a heterologous prime boost regimen (Table 2).

Table 2. Competitive Landscape for MVA-vectored Vaccines

Competitive Landscape for MVA-vectored Vaccines					
Developer	**Target Diseases**	**Antigens**	**VLP**	**Comment**	**Commercial Rights**
GeoVax (GOVX)	HIV	Native Env, Gag, Pol	Yes	*Ph 2.* Most durable Ab responses in field of HIV clinical trials. Protective immunity in non-human primates.	GOVX
	Hemorrhagic fever viruses	Native GP and VP40 for Ebola, Sudan and Marburg viruses. GPC and Z for Lassa fever virus	Yes	*Preclinical.* Single dose protection for Ebola and Lassa. Full efficacy for Marburg in Guinea pig model	GOVX
	Zika virus	NS1	No	*Preclinical.* Single dose protection with no risk of antibody dependent enhancement	GOVX
	MUC1-positive cancers (lung, breast, prostate, pancreatic and more)	Portion of MUC1, Marburg VP40	Yes	*Preclinical*. Efficacy in prophylactic and therapeutic murine-human MUC1 transgenic models. Synergy with peptide and immune checkpoint inhibitors	GOVX
	Chronic hepatitis B	S, core, truncated X	Yes	*Preclinical.* Testing for therapeutic use	GOVX
	Malaria	Full and modified CSP	Yes	*Preclinical.* Testing for prophylactic use	GOVX
	Head and Neck cancers	E2, E6 and E7 of HPV16	No	*Preclinical.* Testing for therapeutic use	GOVX
Bavarian Nordic (BN)	Smallpox vaccine	MVA	MVA parent	*JYNNEOS*, Approved in EU and USA for strategic stockpiling	BN
	Hemorrhagic fever viruses	Native GP from Ebola, Sudan, Marburg in one vector	No	*Ph 2*. most effective as boost in a heterologous prime/boost regimen	Janssen
	Respiratory syncytial virus	F and G glycoproteins	No	*Ph 2*	BN
	Yellow fever	PrM and E	?	*Ph 1: Vaccine efficacy was shown in hamsters after 2 doses*[21]	BN
	Chronic human papilloma virus infection	Modified E6 and E7	No	*Preclinical*	Janssen
	Prostate cancer	PSA	No	*PROSTVAC,* Ph 3	BMS
	Lung cancer	HER-2	No	*CV301*	BN
	Solid tumors	Brachury	No	*MVA-BN Brachyury*	BN
Transgene	Prostate	MUC-1, IL2		*TG4010, failed in Ph 3*	
	NSCLC	MUC-1, IL2		*TG4010, Ph 2b*	BMS
	HPV-positive cancers	Modified E6 and E7		*TG4001*	Pfizer
Jenner Institute, Oxford University	Malaria Tuberculosis	Multiple different genes	No	*Research and Ph 1/ 2*. MVA primarily being used to boost protein or adeno vector-primed responses	Jenner
Vaccitech Ltd	Influenza, prostate cancer, MERS, HPV, HBV, Zoster	Multiple different genes	No	Flu*, Ph 2b,* Prostate *Ph 2,* others preclinical	Vaccitech

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