State Research Center of Virology and Biotechnology "Vector"
Koltsovo, Russia

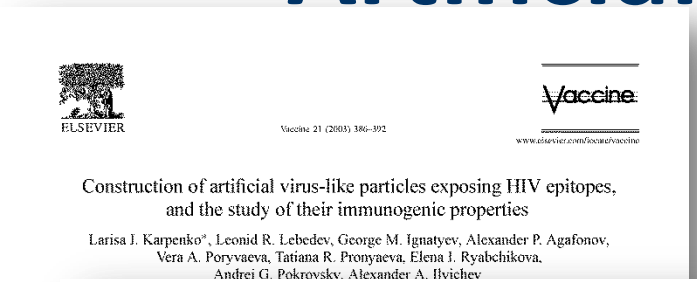
DNA vaccines against HIV-1 and other infectious and somatic diseases, developed in State Research Center of Virology and Biotechnology Vector

Larisa Karpenko

Toolkits for DNA vaccine design, an update
Moscow 17-21 November 2016

State Research Center of Virology and Biotechnology Vector has been designing DNA-vaccines against
a number of viral pathogens;
DNA-vaccines against cancer (melanoma and Breast Carcinoma);
DNA-vaccine against Spring Viraemia of Carp

Artificial polyepitope approach



ELSEVIER

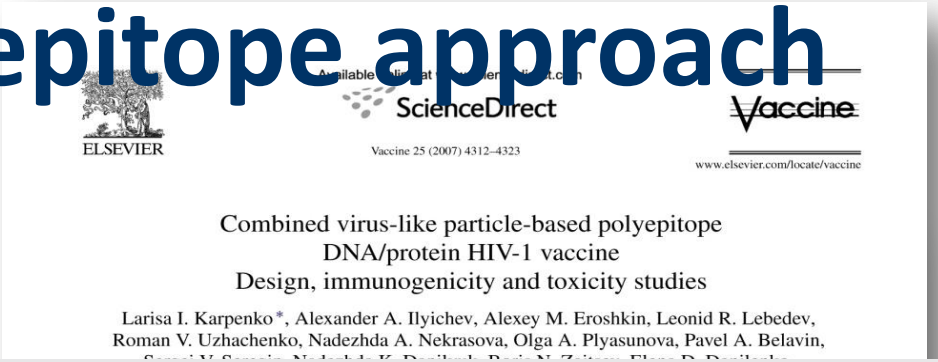
Vaccine 21 (2003) 386–392

Vaccine

www.elsevier.com/locate/vaccine

Construction of artificial virus-like particles exposing HIV epitopes, and the study of their immunogenic properties

Larisa I. Karpenko*, Leonid R. Lebedev, George M. Ignatyev, Alexander P. Agafonov, Vera A. Poryvaeva, Tatiana R. Pronyaeva, Elena I. Ryabchikova, Andrei G. Pokrovsky, Alexander A. Ilyichev



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ScienceDirect

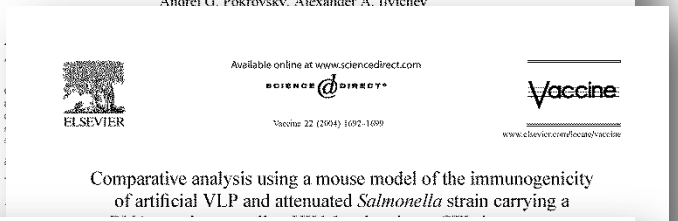
Vaccine 25 (2007) 4312–4323

Vaccine

www.elsevier.com/locate/vaccine

Combined virus-like particle-based polyepitope DNA/protein HIV-1 vaccine
Design, immunogenicity and toxicity studies

Larisa I. Karpenko*, Alexander A. Ilyichev, Alexey M. Eroshkin, Leonid R. Lebedev, Roman V. Uzhachenko, Nadezhda A. Nekrasova, Olga A. Plyasunova, Pavel A. Belavin,



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Available online at www.sciencedirect.com

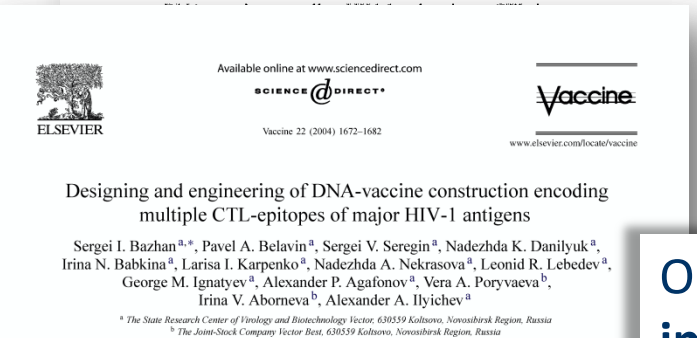
SCIENCE DIRECT

Vaccine 22 (2004) 1692–1699

Vaccine

www.elsevier.com/locate/vaccine

Comparative analysis using a mouse model of the immunogenicity of artificial VLP and attenuated *Salmonella* strain carrying a



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SCIENCE DIRECT

Vaccine 22 (2004) 1672–1682

Vaccine

www.elsevier.com/locate/vaccine

Designing and engineering of DNA-vaccine construction encoding multiple CTL-epitopes of major HIV-1 antigens

Sergei I. Bazhan[a,*], Pavel A. Belavin[a], Sergei V. Seregin[a], Nadezhda K. Danilyuk[a], Irina N. Babkina[a], Larisa I. Karpenko[a], Nadezhda A. Nekrasova[a], Leonid R. Lebedev[a], George M. Ignatyev[a], Alexander P. Agafonov[a], Vera A. Poryvaeva[b], Irina V. Aborneva[b], Alexander A. Ilyichev[a]

[a] *The State Research Center of Virology and Biotechnology Vector, 630559 Koltsovo, Novosibirsk Region, Russia*
[b] *The Joint-Stock Company Vector Best, 630559 Koltsovo, Novosibirsk Region, Russia*

Abstract

A synthetic T cell immunogen (TCI) has been designed as a candidate DNA-based vaccine against Human immunodeficiency virus (HIV)-1 using cytotoxic T lymphocytes ($CD8^+$ CTL) and T-helper lymphocytes ($CD4^+$ Th) epitopes retrieved from the *Los Alamos HIV Molecular Immunology Database*. The protein 392 amino acids in length contains about eighty CTL-epitopes, many of which are overlapping and are totally restricted by ten different HLA class I molecules. To be able to detect CTL responses induced by a DNA vaccine in experimental animals, additional epitopes, restricted by mouse and *Macaque rhesus* major histocompatibility complex (MHC) class I molecules, were included in the target immunogen. The gene encoding the TCI protein was assembled, cloned into vector plasmids and expressed in a prokaryotic and a eukaryotic system. The presence of HIV-1 protein fragments in the immunogen structure was ascertained by ELISA and immunoblotting using panels of HIV-1-positive sera and monoclonal antibodies to p24. It has been demonstrated that DNA vaccine can induce both specific T cell responses (CTL and blast transformation) and specific antibodies in mice immunized with pcDNA-TCI.

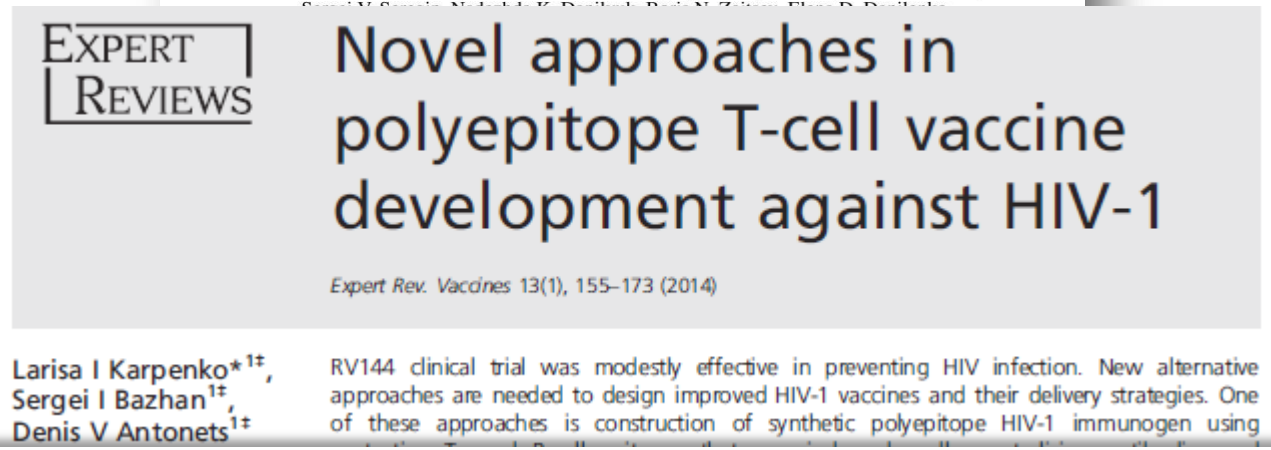
Keywords: Human immunodeficiency virus (HIV); Cytotoxic T lymphocytes (CTL); T-helper lymphocytes (Th); HIV CTL-epitopes; Designing a poly-CTL-epitope-based immunogen; Synthetic gene expression; DNA vaccine; Polymerase chain reaction (PCR); Immunogenicity

1. Introduction

One of the promising approaches to the development of a new generation of effective and safe vaccines is based on identification of T and B cell epitopes in virus proteins for use as a basis for synthetic polyepitope vaccines [1,2]. It is expected that these vaccines will have none of the many drawbacks that are inherent to the those based on native viral proteins or live attenuated or whole inactivated pathogens. In particular, synthetic polyepitope vaccines will have no regions that induce immunopathology or inhibit protective immunity.

To provide protection effectively, a vaccine should be able to induce both humoral and cell immune responses. Although new promising approaches to the induction of neutralizing antibodies are still being developed [3], the mainstream is the induction of cell immunity [4–8]. And that is for a reason, because convincing evidence exists that the responses of cytotoxic T lymphocytes ($CD8^+$ CTL) associated with HIV infection are important mediators of antiviral immunity and, therefore, induction of HIV-specific CTLs could be an important component of an effective vaccine against HIV-1 [9,10]. For example, a reliable negative correlation has been found between the frequency of HIV-specific CTLs and the amount of virus RNA in the blood of HIV-infected individuals [11]. It is hypothesized that CTLs are capable of protecting the host against HIV infection, because they would kill HIV-infected cells before they could produce new virions [12] and, furthermore, CTLs would release chemokines, which inhibited HIV infection [13,14].

This work describes the engineering of a synthetic poly-CTL-epitope T cell immunogen (TCI), which is con-



EXPERT REVIEWS

Novel approaches in polyepitope T-cell vaccine development against HIV-1

Expert Rev. Vaccines 13(1), 155–173 (2014)

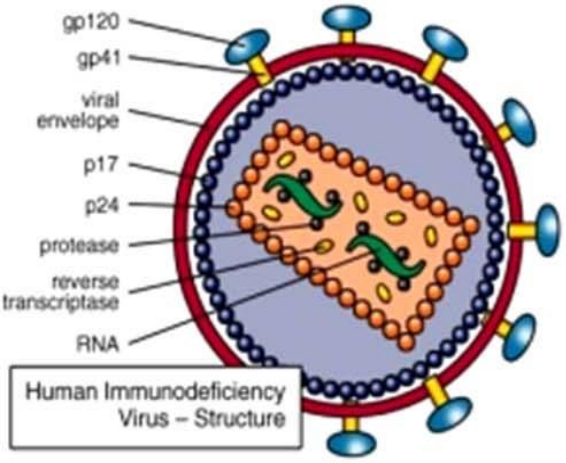
Larisa I Karpenko*[1‡], Sergei I Bazhan[1‡], Denis V Antonets[1‡]

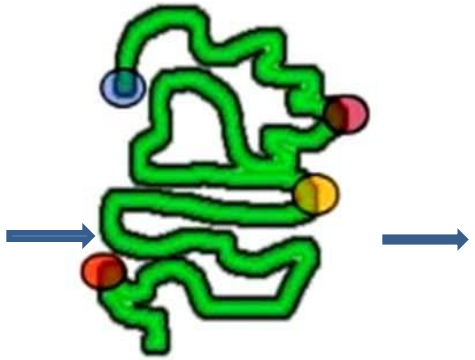
RV144 clinical trial was modestly effective in preventing HIV infection. New alternative approaches are needed to design improved HIV-1 vaccines and their delivery strategies. One of these approaches is construction of synthetic polyepitope HIV-1 immunogen using

Our approach is based on the design of synthetic **polyepitope immunogens using wide range of protective T- and B-cell epitopes of main virus antigens** that can induce neutralizing antibodies or $CD8^+$ and $CD4^+$ T-cell responses.

This approach potentially allows us to cope with antigenic variability of virus, focuses immune response on protective determinants and enables to exclude from the vaccine compound adverse regions of viral proteins that can induce autoantibodies or antibodies enhancing infectivity of virus.

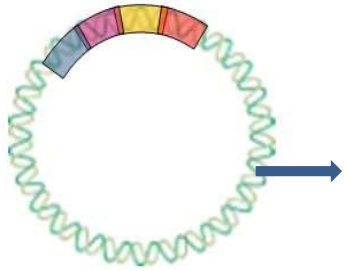
Design and engineering of artificial polyepitope immunogens



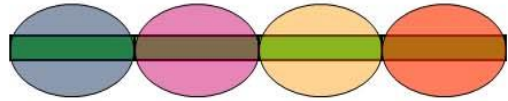


Selection of the most interesting T- and B- cell epitopes of viral proteins

DNA vaccine



Design and synthesis of artificial gene coding for selected epitopes

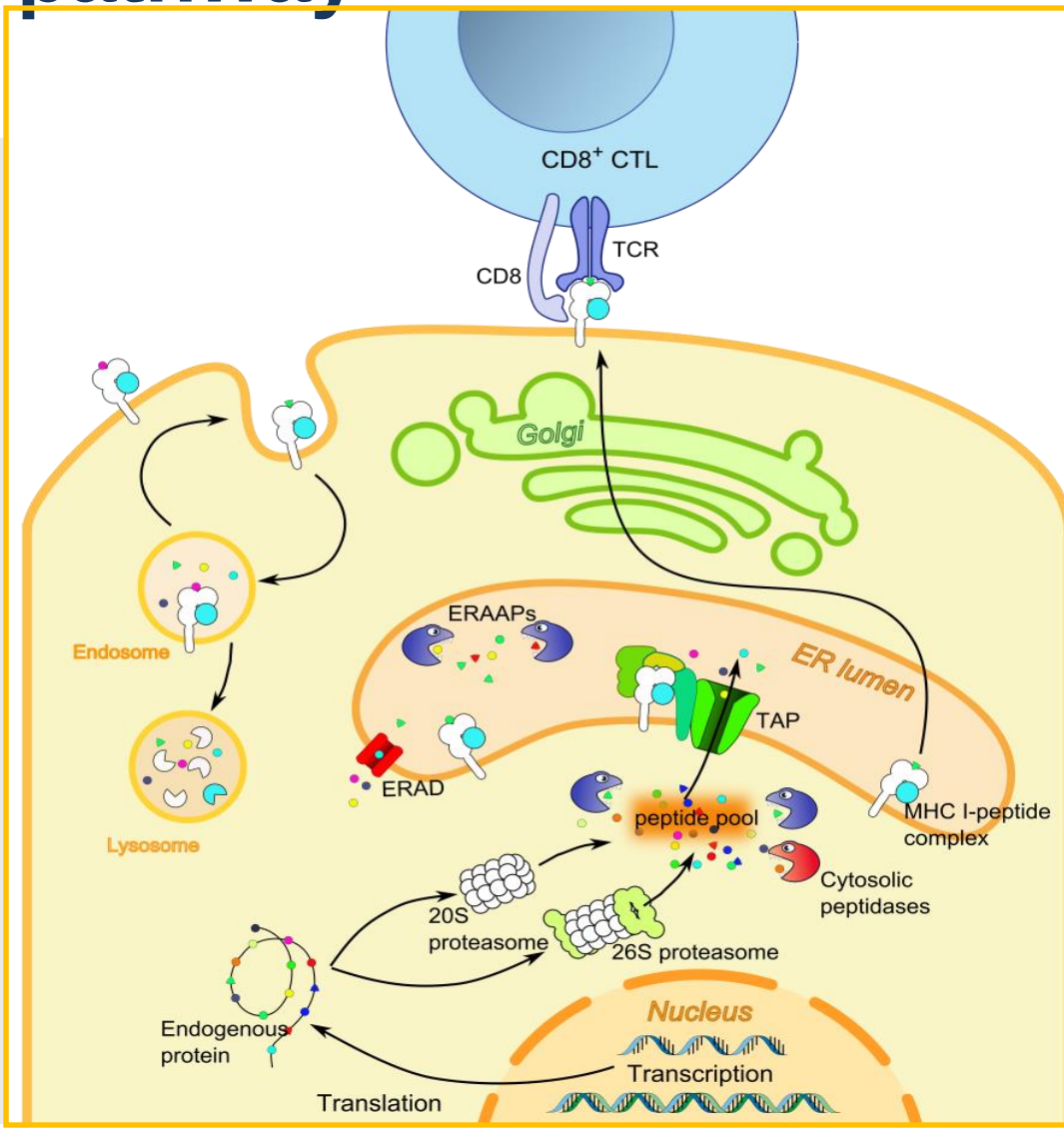


Gene expression in bacterial or eukaryotic cells

When designing artificial polyepitope immunogens, it is necessary to optimize the processing and presentation of contained epitopes taking into account major steps of MHC class I - dependent antigen processing.

MHC class I-dependent antigen presentation pathway

As is known, CD8+ CTLs recognize the viral protein antigens synthesized in the cell as short peptides (8–12 amino acid residues) associated with specific MHC class I molecules rather than full-sized proteins. These short antigenic epitopes are produced from endogenously expressed protein antigens by the proteasome-mediated processing with subsequent transportation to the ER lumen by TAP1/TAP2 heterodimers (TAP – Transporters Associated with antigen Processing) where they bind to the MHC class I molecules. Obtained complexes [peptides-MHC class I molecules] are transported through the trans-Golgi network to the cell surface where they are presented to CD8+ CTLs.



We compared a number of parameters including **different strategies for fusing ubiquitin to the polyepitope and including spacer sequences between epitopes to optimize proteasome liberation and TAP transport**. It was demonstrated that the vaccine construct that induced in vitro the largest number of [peptide–MHC class I] complexes was also the most immunogenic in the animal experiments. This most immunogenic vaccine construct contained the N-terminal ubiquitin for targeting the polyepitope to the proteasome and included both proteasome liberation and TAP transport optimized spacer sequences that flanked the epitopes within the polyepitope construct.

Bazhan et.al., Mol Immunol. 2010

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Bazhan et.al., Mol Immunol. 2010

The results were the basis for the development of original software TEpredict and PolyCTLDesigner, which we use as a universal platform for the rational design of polyepitope immunogens - candidate DNA vaccine for inducing T-cell immunity against infectious diseases and cancer.

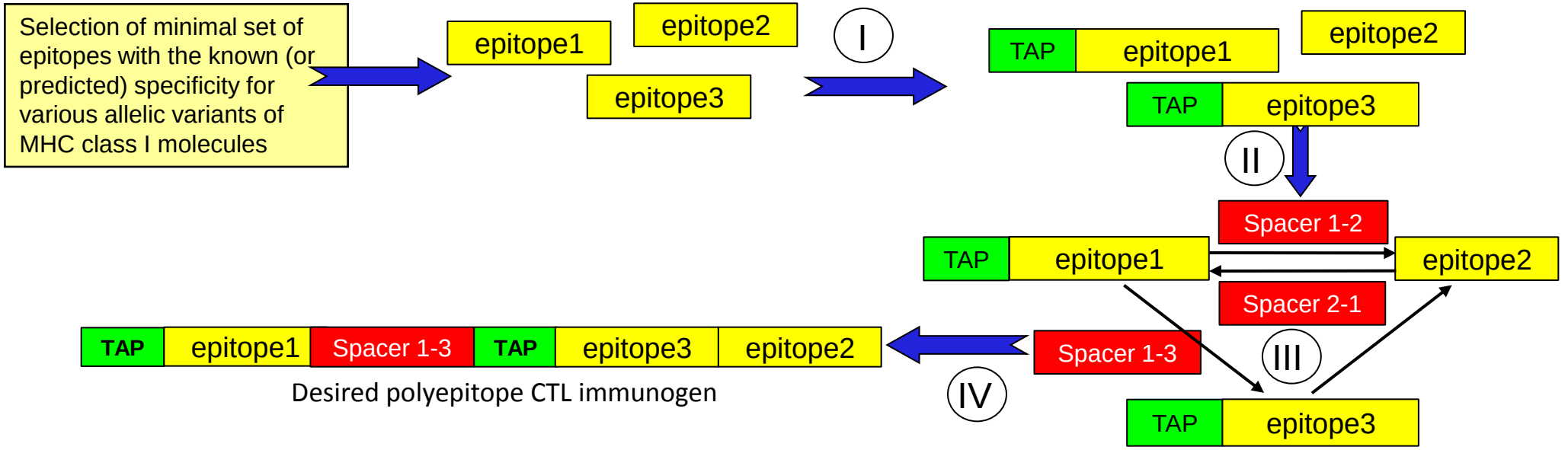
Author: Dr. Denis V. Antonets
antonec@yandex.ru

http://tepredict.sourceforge.net/PolyCTLDesigner.html.

PolyCTLDesigner software. A program for construction of polyepitope immunogens

(Author: Denis V. Antonets

http://tepredict.sourceforge.net/PolyCTLDesigner.html.



I – Prediction of binding affinity of peptides to TAP and, if necessary, the addition of N-terminal flanking residues to optimize this binding

II – Engineering the optimal spacer sequences for each pair of peptides

III – Creation of a directed weighted graph, where nodes represent target epitopes, and edges – possible variants of their combining. Each edge has the following attributes: the spacer sequence and the weight vector corresponding to

α(rank) + β(length) + ω(junk),

where *rank* corresponds to predicted efficiency of proteasomal cleavage; *length* is the spacer length and *junk* is the number of predicted non-target epitopes.

IV – design of the polyepitope immunogen sequence (the resulting sequence is defined as the longest simple path in a graph that has the least weight).

PolyCTLDesigner allows:

- To select the minimal set of CD8+ T cell epitopes with the known (or predicted) specificity towards various allelic variants of MHC class I molecules;

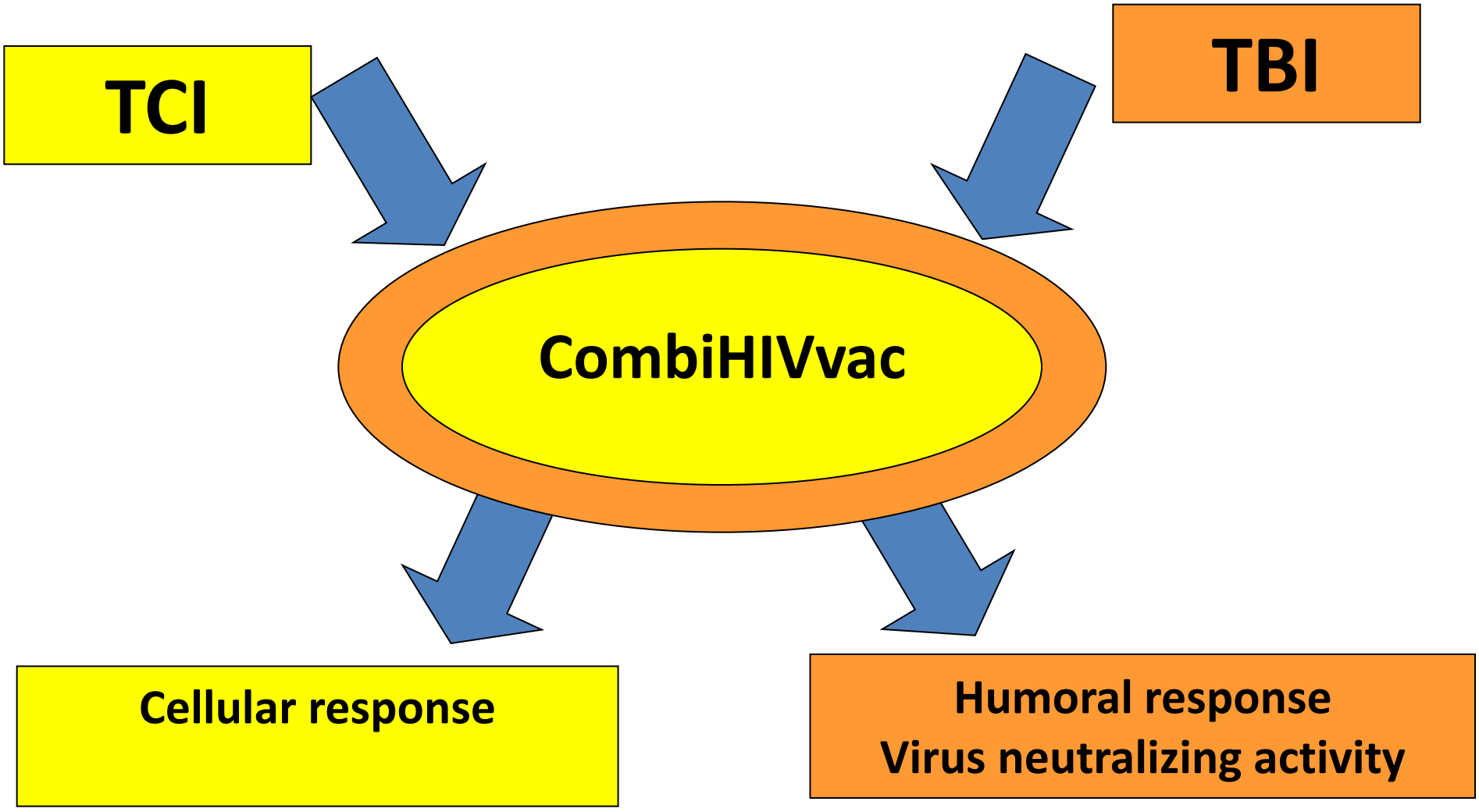
- To predict binding affinity of peptides to TAP and, if necessary, the addition of N-terminal flanking residues to optimize this binding;

- At the next stage PolyCTLDesigner provides engineering the optimal spacer sequences for each pair of peptides.

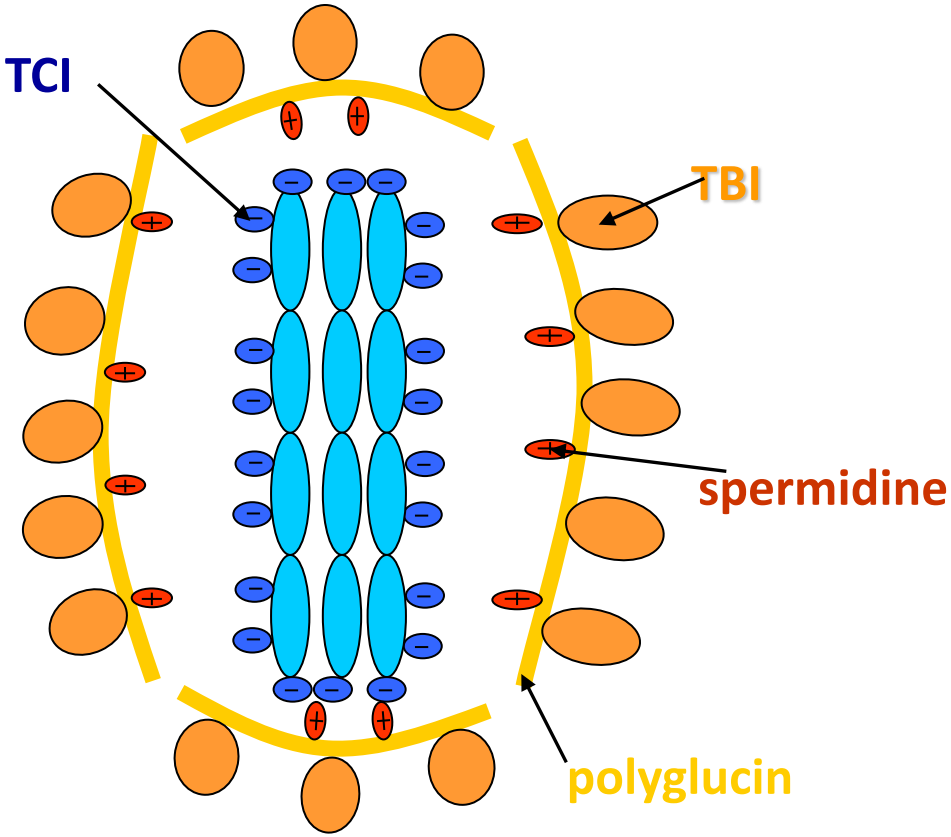
Phase I clinical trials CombiHIVvac - DNA-protein vaccine containing artificial polyepitope immunogens

Karpenko et.al., Vaccine 2007; Karpenko et al. Russian Journal of Bioorganic Chemistry, 2016

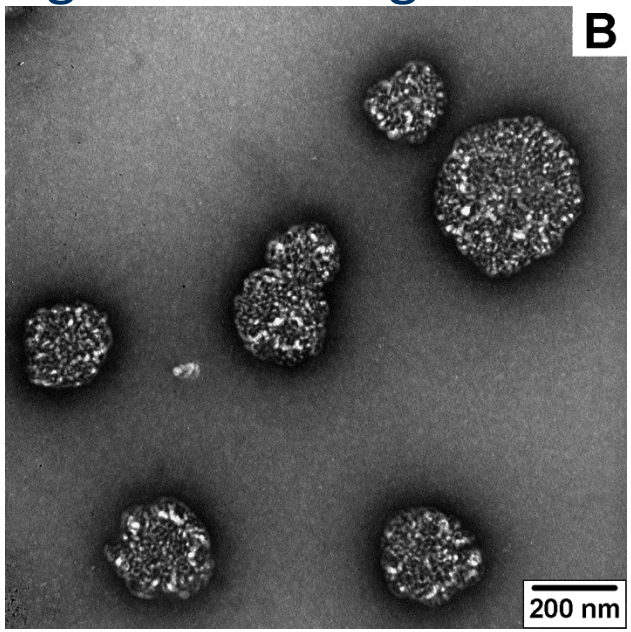
We have designed a vaccine named CombiHIVvac (Combined HIV-1 vaccine), which combines TBI and TCI immunogenes in one artificial particle.



The DNA vaccine pcDNA-TCI is encapsulated within a conjugate of TBI protein with polyglucin-spermidine. These components self-assemble into the artificial particle.

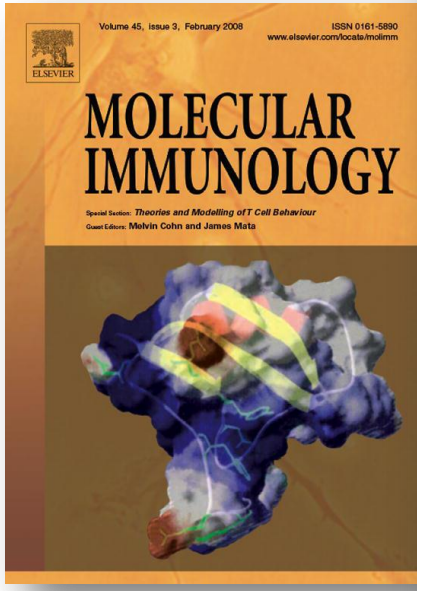


Transmission electron microscopy with negative staining



The CombiHIVvac particle dimensions are 40 -100 nm.
TBI protein is present in multiple copies on the particle surface, and this allow the immunogenicity of the TBI protein to be considerably enhanced. Additionally, the polyglucin coat protects the DNA vaccine against nucleases and contributes to the enhancement of the immunogenicity of the DNA vaccine by improving the chances of intake by antigen-presenting cells.

Combination of two B- and T-cell immunogens (TBI and TCI) in one construct results in a synergistic increase in the HIV specific antibody response



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ScienceDirect
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Molecular Immunology 45 (2008) 661–669
Molecular Immunology
www.elsevier.com/locate/molimm

A synergistic effect of a combined bivalent DNA–protein anti-HIV-1 vaccine containing multiple T- and B-cell epitopes of HIV-1 proteins

Sergei I. Bazhan *, Larisa I. Karpenko, Leonid R. Lebedev, Roman V. Uzhachenko, Pavel A. Belavin, Alexey M. Eroshkin, Alexander A. Ilyichev

Theoretical Department, State Research Center of Virology and Biotechnology "Vector", 630559 Koltsovo, Novosibirsk Region, Russia

Received 24 May 2007; received in revised form 9 July 2007; accepted 10 July 2007
Available online 14 September 2007

Abstract

Immunogenic properties of the combined vaccine CombiHIVvac, comprising polyepitope HIV-1 immunogens, one being the artificial polyepitope protein TBI, containing the T- and B-cell epitopes from Env and Gag proteins, and the DNA vaccine construct pcDNA-TCI coding for the artificial protein TCI, carrying over 80 T-cell epitopes (both CD4+ CTL and CD8+ Th) from Env, Gag, Pol, and Nef proteins, are studied in this work.

The data reported demonstrate clearly that a combination of two B- and T-cell immunogens (TBI and TCI) in one construct results in a synergistic increase in the antibody response to both TBI protein and the proteins from HIV-1 lysate. The level of antibodies induced by immunization with the constructs containing either immunogen alone (TBI protein or the plasmid pcDNA-TCI) was significantly lower as compared to that induced by the combined vaccine. The analysis performed suggests that the presence of CD4+ T-helper epitopes, which can be presented by MHC class II, in the protein TCI may be the main reason underlying the increased synthesis of antibodies to TBI protein due to a CD4-mediated stimulation of B-cell proliferation and differentiation.

Keywords: HIV-1; T- and B-cell epitopes; Combined polyepitope DNA–protein vaccine; Virus-like particle; Immunogenicyty; Synergistic effect

1. Introduction

The demand for the vaccines against HIV and hepatitis C, the infections spreading quickly all over the world, on the background of the absence of any preventive vaccines, is exclusively high. It becomes ever more evident that the Pasteur principles, based on the use of attenuated or whole inactivated virus, do not work in this case. Thus, it is necessary to apply new approaches based on the state-of-the-art achievements in the field of immunology and molecular biology of these viruses.

One of the most promising approaches implies designing of synthetic polyepitope vaccines containing viral T- and B-cell epitopes (Bazhan et al., 2004; Firat et al., 2001; Hanke et al., 1998; Karpenko et al., 2004; Lorin et al., 2005; Woodberry et al., 1999). Such vaccines will be free of numerous shortcomings characteristic of the vaccines involving live attenuated or whole inactivated pathogen as well as the vaccines based on individual virus proteins.

Earlier we constructed two polyepitope proteins. The protein TBI (T- and B-cell epitopes containing immunogen) was designed for stimulation of the humoral immune response (Eroshkin et al., 1995; Loktev et al., 1996). This protein contains four T-cell epitopes and five B-cell neutralizing epitopes from HIV-1 proteins Env and Gag. It has been demonstrated that TBI induces the antibodies displaying a HIV-neutralizing activity in various species of laboratory animals (Loktev et al., 1996). The poly-CTL-epitope T-cell immunogen (TCI), with a length of 392 amino acid residues comprising about 80 optimally selected CTL epitopes, was designed to stimulate the HIV-specific cytotoxic response. TCI includes fragments from the main virus proteins Env, Gag, Pol, and Nef, which contains the epitopes inducing both $CD8^+$ CTL and $CD4^+$ Th (Bazhan et al., 2004; Karpenko et al., 2004). The DNA vaccine pcDNA-TCI, providing the synthesis of TCI protein in eukaryotic cells, was produced.

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doi:10.1016/j.molimm.2007.07.016

Phase I Clinical trials

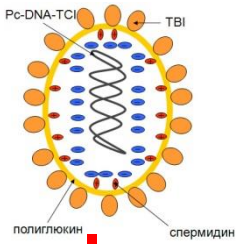
- First of all **we have got regulatory, ethical, and governance approvals.**
- This study was approved by the Russian Ministry of Health and Ethical Committee.
- All volunteers gave fully informed written consent, and the trial was conducted according to the Russian Clinical Trials Regulations and Good Clinical Practice guidelines. The trial was conducted at Hospital 163, Novosibirsk, Russia.

- **Participants**
- Healthy men and women (20–50 years old) were suitable for participation if they were not at high risk for HIV-1.
- Group 1 (5 men and 10 women) received one intramuscular injection of 1 dose of vaccine
- Group 2 (5 men and 10 women) received two intramuscular injections of 1 dose of vaccine

Study Design

1 dose of vaccine :
50 mkg TBI protein;
75 mkg DNA vaccine pcDNA-TCI

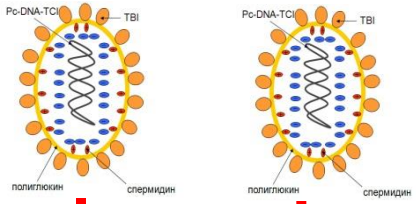
Group 1 (n=15)



month

-3 0 14 28 day 3 month 6 month 9 month 12 month

Group 2 (n=15)



month

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Protocol for the evaluation of the safety of vaccination with CombiHIVvac in human volunteers

Local reactogenicity (including pain, tenderness, erythema, edema)

Systemic reactogenicity (including fever, chills, headache, nausea, vomiting, malaise)

Hematological parameters, including red and white blood cell counts, platelets, HCT, WBC, hemoglobin concentration)

Biochemical Parameters Including:

Kidney function tests which are composed urea, createinen and uric acid.

Liver function tests which are composed of ALT , AST, Alkaline Phosphates and total protein.

Urine analysis: visual, dipstick and microscopic exam; concentration of protein, sugar and urea)

Immune status: CD3, CD4, CD8, CD16, CD 14, CD 72 T -lymphocytes, IgG, IgA, IgM , hypersensitivity of the slowed-down type , immunoregulatory index (IRI), NST-reduction of monocytes, EA- **phagocytosis** of the monocytes

Subjects were controlled for adverse events, general health and clinical laboratory parameters at each study visit.

Safety data

- Single and double CombiHIVvac injections were well-tolerated without local and systemic reactogenicity.
- Neither single nor double intramuscular injection of vaccine had persistent effects on the immunological, hematological or biochemical parameters in the individuals.
- No pathological signs were observed at the site of the vaccine injection.
- CombiHIVvac is safe and well tolerated

Cellular and humoral immunogenicity of CombiHIVvac
Methods

Humoral immunogenicity:

Western Blot Kit (New Lav blot, Bio-Rad)

ELISA

Pseudovirus neutralization assay using HIV-1 Env clones SF162.LS and PVO.4 (clade B) and Env clones SP-2010 and SP-392 (clade A)

Cell immune response

INF-γ ELISpot (BD)

Blasttransformation

MHC-pentamers (Proimmune)

Humoral immunogenicity:

Maximum immune response was detected on the 14-th day after the second vaccine injection.

In the **singly vaccinated group** presence of antibodies was detected in **60% of volunteers**.

In the **doubly vaccinated group** antibodies at least to one HIV-1 protein were detected in **100% of volunteers**. The second immunization stimulated immune response resulted in increase of detected positive sera.

Virus neutralizing activity of sera were tested using pseudovirus neutralization assay

- Maximum neutralizing antibodies were detected on the 14 day after the second vaccine injection. The level of neutralizing anbodies (>1:100) is formed in **80% of vaccinated volunteers (Group 2).**
- 12 months later (at the and of clinical trials) level of antibodies in sera 1:100 is observed in **25% of vaccinated volunteers**.

Cellular Immunogenicity

INF-γ ELISpot

More effective immune response was detected in group 2 (two weeks after second vaccination)

The singly vaccinated volunteers HIV-specific INFγ- ELISpot response was registered already two weeks after vaccination in 86%, after 3 and 6 months – in 33%, and after 12 months response was registered just in one volunteer.

- In the doubly vaccinated persons T-cell response was registered 14 days after the second vaccination in all (100%) vaccinated volunteers. Six months after the second vaccination response of CD8+ T-lymphocytes remains rather high and is registered in 69% of volunteers.
- There were no positive responses to any peptide pool in volunteers before vaccination (-3 days).

Cellular Immunogenicity
MHC-pentamers

MHC- pentamers

*A*0201 SLYNTVATL - PE and A*0201 KLTPLCVTL- PE* (Proimmune)

- Since we used MHC-pentamers specific to HLA-A*02 of locus of HLA I class, at first instance genotyping of volunteers was carried out.
- In the group of singly vaccinated volunteers seven people have HLA-A*02 genotype. In the group of doubly vaccinated persons five people have HLA-A*02 genotype.

- Background level before vaccination by CD8+/*A*0201 SLYNTVATL-PE and* CD8+/*KLTPLCVTL- PE* was ≤ 0.1 % of the total number of CD8+ lymphocytes.

MHC-pentamers
Results

- Maximum level was observed **on 14th day both in singly, and in doubly vaccinated volunteers** (at average 1.1 and 1.8%, correspondingly, of the total number of CD8+ cells) and was **11 and 20 times higher than background level before vaccination** (C.I. $p < 0.01$).

- HIV-specific CD8+ T-lymphocytes detected in vaccinated volunteers using MHC-tetramers method are functional, as confirmed by IFN-γ production in response to their stimulation by HIV-specific peptides in ELISpot test.

Phase I clinical trials
Conclusion

- **CombiHIVvac is safe and well tolerated.**
- **The vaccine eliciting both cellular and humoral anti-HIV responses.**
- **In the group of doubly vaccinated volunteers both humoral, and cell responses were higher and more prolonged compared to the group of singly vaccinates. After the second vaccination HIV-specific antibodies and CD8+ were detected in 100% of volunteers; 80% of subjects had neutralizing antibodies.**

Phase II clinical trials was approved but not stated yet

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ
РОССИЙСКОЙ ФЕДЕРАЦИИ

РАЗРЕШЕНИЕ № 621

на проведение клинических исследований

от 1 октября 2013 г.

Настоящим разрешается проведение клинических исследований
КомбиВИЧвак (Вакцина против ВИЧ-1/СПИД)
(наименование лекарственного препарата)

Организация, осуществляющая организацию проведения клинического исследования лекарственного препарата для медицинского применения:
разработчик лекарственного препарата Федеральное бюджетное учреждение науки «Государственный научный центр вирусологии и биотехнологии «Вектор», Россия, 630559, Новосибирская обл., Новосибирский район, рабочий поселок Кольцово.

Лекарственная форма и дозировка лекарственного препарата для медицинского применения: **лиофилизат для приготовления раствора для внутримышечного введения, 50 мкг/0,2 мл/доза (ампулы 0,5 мл).**

Наименование протокола клинического исследования лекарственного препарата для медицинского применения: **№ ВК 003/13: «Ограниченные клинические исследования вакцины «КомбиВИЧвак» (вакцина против ВИЧ-1/СПИД, лиофилизат для приготовления раствора для внутримышечного введения)».**

Цель клинического исследования лекарственного препарата для медицинского применения: **оценка иммуногенной активности, реактогенности, безопасности вакцины «КомбиВИЧвак», выбор оптимальной схемы иммунизации.**

Сроки проведения клинического исследования лекарственного препарата для медицинского применения: **с 01.10.2013 по 31.12.2015 г.**

Количество пациентов, принимающих участие в клиническом исследовании лекарственного препарата для медицинского применения: **240 пациентов (из них рандомизированных 120 человек).**

Перечень медицинских организаций, в которых будет проводиться клиническое исследование лекарственного препарата для медицинского применения: **согласно приложению № 1 на 1 л.**

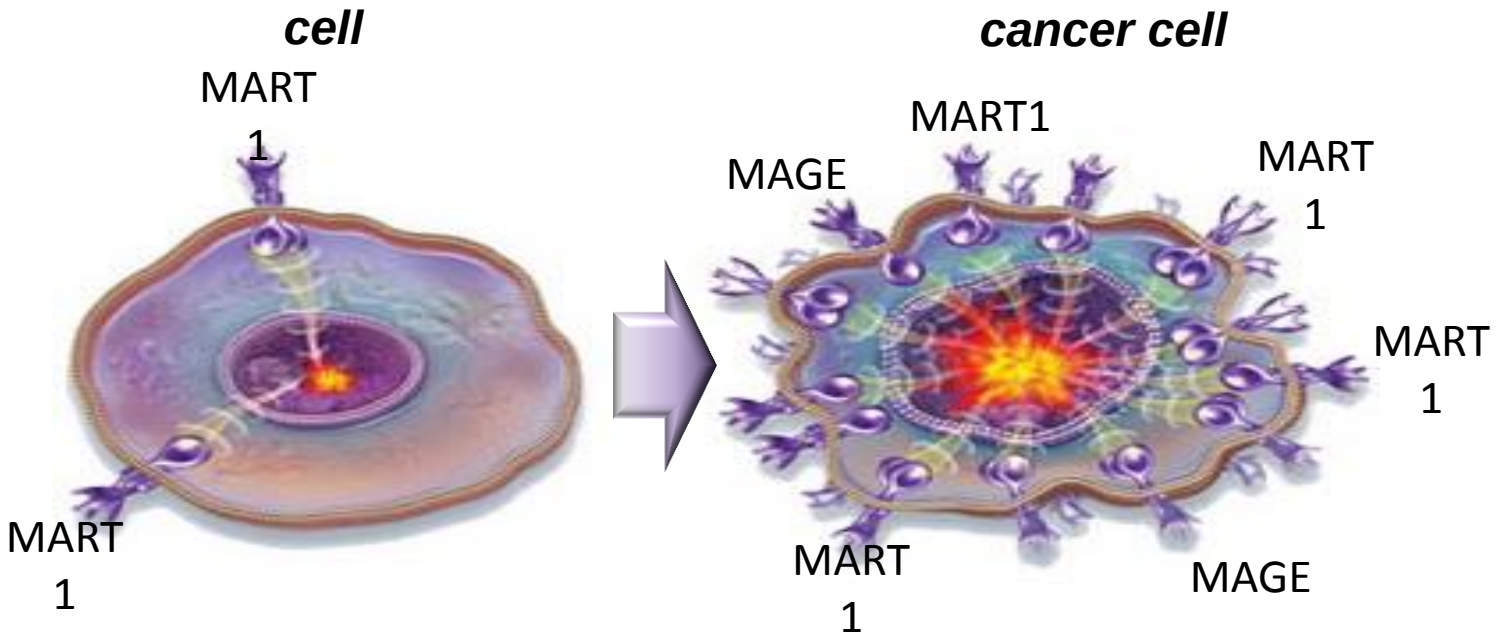
Данное разрешение действительно в течение всего срока проведения клинических исследований.

001437

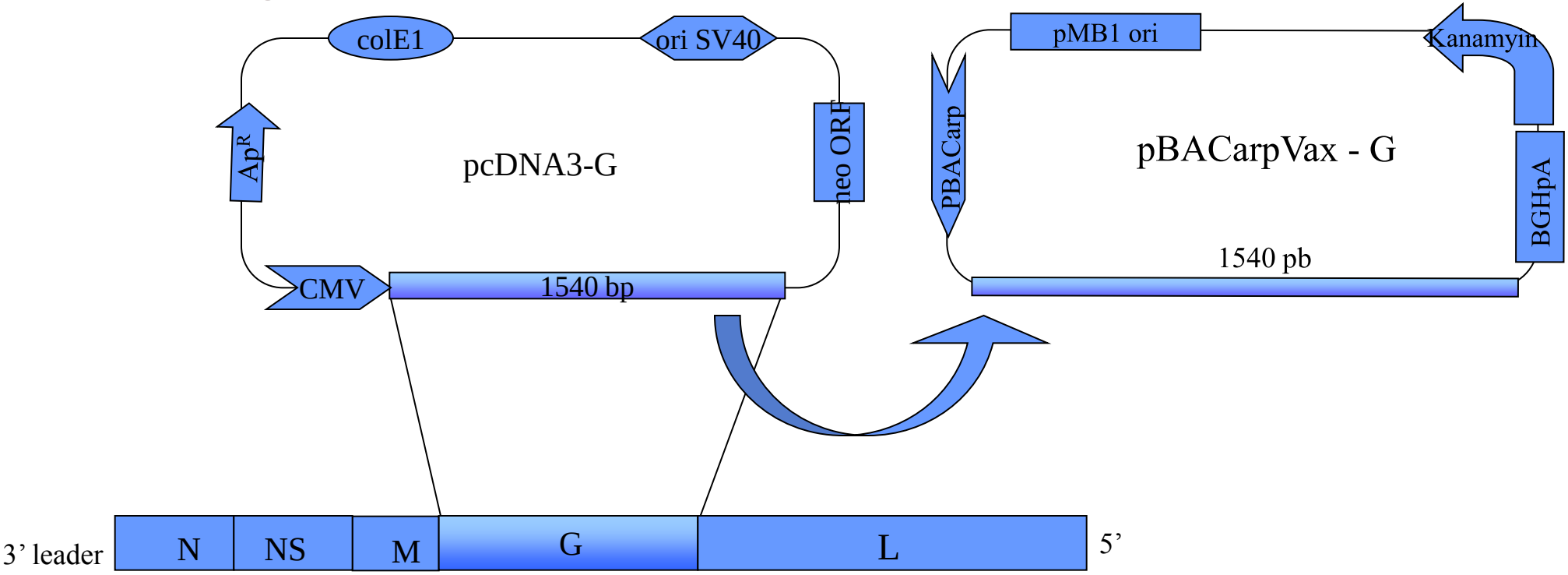
Therapeutic vaccine

Polyepitope DNA-vaccines against cancer:

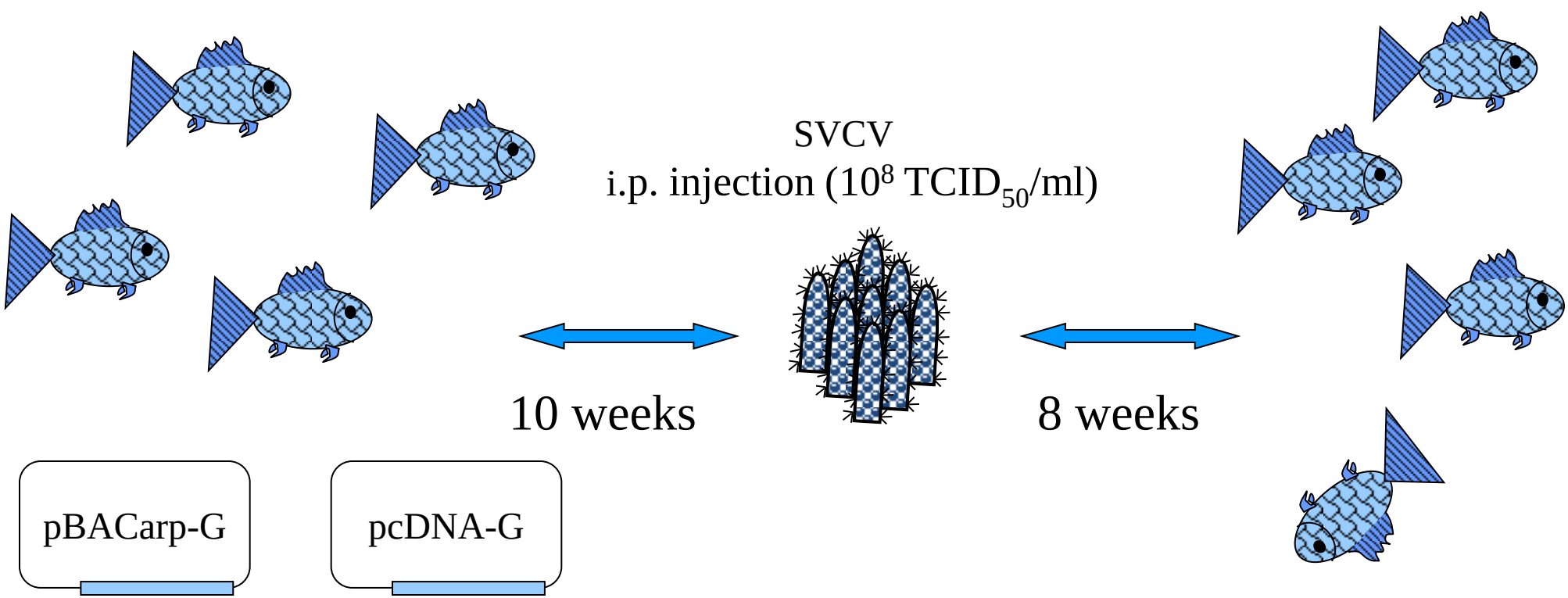
- DNA melanoma vaccine
- DNA vaccine against Breast Carcinoma



DNA-vaccine against Spring Viremia of Carp



Scheme of constructs pcDNA-G based on the full-length SVCV glycoprotein gene of the Russian reference isolate ZL4



Carp yearlings (*Cyprinus carpio*) with the average body weight 27g.

Schematic representation of immunization experiment

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