Bioveiligheidsraad
Conseil de Biosécurité

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Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC/2015_0113

Title: Advice of the Belgian Biosafety Advisory Council on the notification B/BE/14/BVW1 of the company Amgen for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

Context

The notification B/BE/14/BVW1 has been submitted by Amgen to the Belgian Competent Authority in August 2014 for a request of deliberate release in the environment of genetically modified organisms other than higher plants for research and development according to Chapter II of the Royal Decree of 21 February 2005.

The planned activity concerns a clinical trial and the title of the notification is: **"A Phase 2, Multicenter, Open-label, Single-arm Trial to Evaluate the Correlation Between Objective Response Rate and Baseline Intratumoral CD8+ Cell Density in Subjects With Unresected Stage IIIB to IVM1c Melanoma Treated with Talimogene laherparepvec"**.
The purpose of the release is a clinical trial to investigate the safety and efficacy of Talimogene laherparepvec in subjects with previously untreated, unresected, stage IIIb-IV melanoma.
Talimogene laherparepvec is an investigational medicinal product (IMP) developed for oncolytic immunotherapy. It is a recombinant herpes simplex type 1 virus (HSV-1) disabled by the functional deletion of two genes (ICP34.5 and ICP47) of the viral genome and genetically modified to express the human granulocyte macrophage colony-stimulating factor (hGM-CSF). Talimogene laherparepvec induces viral lysis of tumour cells and the expression of hGM-CSF stimulates a tumour-specific immune response.

Talimogene laherparepvec is administered by intralesional injection into cutaneous, subcutaneous, and nodal tumours. Multiple injections are foreseen until the patient has achieved a complete response to the treatment. The injection site is covered with an occlusive dressing but shedding from the treated tumour cannot completely be excluded knowing that viral replication in tumour tissue is possible. HSV-1 is an enveloped virus which is sensitive to and rapidly inactivated by both physical inactivation (dehydration, heat, low pH) and disinfectants (lipid solvents and mild detergents). It is a globally endemic pathogen of humans and has no known other natural host.

As the trial centres are located in Brussels, Flanders and Wallonia the national territory is considered as the potential release area of the rHSV-1.

The dossier has been officially acknowledged by the Competent Authority on 1 September 2014 and forwarded to the Biosafety Advisory Council for advice.
Within the framework of the evaluation procedure, the Biosafety Advisory Council, under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the dossier. One experts from the common list of experts drawn up by the Biosafety Advisory Council (BAC) and the Biosafety and Biotechnology Unit (SBB) answered positively

to this request. The SBB also took part in the evaluation of the dossier while the Platform for Molecular Biology and Biotechnology of the Scientific Institute of Public Health evaluated the analytical procedure for the detection of rHSV-1 submitted by the notifier.
The experts and the SBB assessed whether the information provided in the notification was sufficient and accurate in order to state that the deliberate release of the genetically modified organism for its intended use, would not raise any problems for the environment, animal health or human health (people coming in contact with the treated patient and/or with the GMO). See Annex II for an overview of all the comments from the experts.

On 3 October 2014, based on a list of questions prepared by the BAC, the Competent Authority requested the notifier to provide additional information about the notification. The answers from the notifier to these questions, including updated instructions for the personnel and for the patient, were received by the Competent Authority on 11 February 2015 and transmitted to the secretariat of the BAC on the same day. This complementary information was reviewed by the coordinator and the experts.

The scientific evaluation has been performed considering following legislation:
- Annex II (principles for the risk assessment) and annex III (information required in notifications) of the Royal Decree of 21 February 2005.
- Commission Decision 2002/623/EC of 24 July 2002 establishing guidance notes supplementing Annex II to Directive 2001/18/EC.
The pure medical aspects concerning the efficacy of the medicinal product and its safety for the treated patient, as well as aspects related to social, economical or ethical considerations, are outside the scope of this evaluation.

In parallel to the scientific evaluation of the notification, the Competent Authority also made the dossier available on its website for the one-month public consultation foreseen in the abovementioned Royal Decree. The Competent Authority received one reaction of the public. The questions of the public tackling biosafety issues of the GMOs under consideration are taken in consideration in the opinion of the Biosafety Advisory Council. Answers to the questions of the public have been sent to the CA.

Summary of the Scientific evaluation

1. The characteristics of the donor, the recipient or parental organism

The donor, recipient and parental organisms have been correctly described in the dossier after additional information was requested and obtained from the notifier.

2. Information related to the characteristics of the GMO and the medication

It is theoretically possible that individual recombination virions containing DNA with one copy of ICP34.5 and one copy of hGM-CSF could be generated.
In answers to questions of the experts the notifier evaluated the probability of occurrence and the consequences of these recombinations and convincingly demonstrated that the likelihood of such an event is low because it is unlikely that a wild-type virus would be in the same tissue as Talimogene laherparepvec in subjects since the latter is directly injected in tumour cells and cannot spread effectively into normal tissue, while a pre-existing HSV-1 would be in the mucosal tissues or neuronal ganglia of the patient. Furthermore, these variants are unstable and their virulence would not be restored to the levels of the wild-type HSV-1.

Recombinations of hGM-CSF with DNA sequences of the treated patient (host) could also occur. But the risk of homologous recombination between hGM-CSF and host sequences is negligible because DNA exchanges would be contained entirely within the hGM-CSF coding

sequence and possible consequences of such an event are negligible and the likelihood is low.

Expression of the hGM-CSF in a non-target host could have adverse health consequences by hindering the immune response but the notifier adequately argumented that Talimogene laherparepvec is engineered to replicate selectively in tumour tissue and expression of GM-CSF is limited to the injected tumour tissue. Absence of GM-CSF in serum has been demonstrated in a previous clinical trial.

For the experts it was not clear if Talimogene laherparepvec is able to reactivate endogenous wild-type HSV-1 during the establishment of a latent infection and if, in the long term, Talimogene laherparepvec is able to alter neuronal function. But the notifier notes that in previous clinical trials with this IMP incidences of HSV-1 infection in the treated patient are lower than the background rate in the general population. Possible reactivation of wild-type HSV-1 during and after treatment with Talimogene laherparepvec continues however to be studied extensively in ongoing clinical trials. In addition in pre-clinical studies, no evidence of virally-associated neuropathy has been observed in any animal treated with Talimogene laherparepvec.

3. The condition of release

The BAC had several criticisms relating to the measures to prevent inadvertent release of the GM product and the instructions prepared for the personnel. It was advised to reduce aerosol producing operations during preparation and administration of the GMO and to instruct personal manipulating the GMO to wear a mask. In addition the medical staff has to wear closed shoes in order to be protected against sharp and syringes that fall. Finally the internal transport of the vials containing the GMO should be performed in a hermetic transport box containing absorbent paper towels.
These remarks were taken into account by the notifier who updated the investigational product instruction manual and the information for healthcare personnel.

4. The risks for the environment and human health

Immune-compromised individuals are at potential risk to develop an infection if coming inadvertently into contact with the GMO. This was not discussed in the initial dossier. On request of the BAC the notifier has updated the Environmental risk assessment and in the amended instructions for the patient it is clearly stated that if patient's close contact or family member is pregnant or has a weakened immune system, they should not help when the injection sites have to be cleaned and the dressings have to be changed.

Related to the above point in case an immune-compromised person is inadvertently infected with the GMO the possibility exist that no obvious direct link is done with a patient treated with the GMO and will therefore not benefit of an adequate treatment. On request of the BAC the notifier has addressed this point and has committed to make available to all investigators in clinical trials with Talimogene laherparepvec the qPCR-based validated test to identify DNA of Talimogene laherparepvec in biological samples, including in swabs from lesions suspected to be herpetic in origin. Swabbing of any lesions suspected being herpetic in origin in patients, patients' close contacts, health care providers and caregivers for testing of Talimogene laherparepvec DNA, is part of the monitoring activities foreseen for this clinical trial.

5. The monitoring, control, waste treatment and emergency plans proposed by the applicant

Even if the risks are low some uncertainty remains (see above paragraphs 2 and 4). This stresses the importance of biosafety precautions to avoid unintended dissemination of the GMO that could lead to unknown adverse effects.
On request of the BAC the notifier amended the Investigational product instruction manual to ensure waste materials are incinerated even after decontamination and added detailed instructions in case of accidental spills or breakage of a vial containing the GMO.
The Accidental Spill information for Health care personnel could be further improved as suggested in Annex 1

In the dossier submitted by the notifier a detailed PCR protocol for the identification and detection of the GMO was lacking. The requested detailed protocol was submitted by the notifier on 11 February 2012 and it was considered adequate and sufficient by the GMO laboratory of the Scientific Institute of Public Health.

Conclusion

Based on the scientific assessment of the notification made by the Belgian experts, the Biosafety Advisory Council concludes that it is unlikely that Talimogene laherparepvec developed for oncolytic immunotherapy, will have any adverse effects on human health or on the environment in the context of the intended clinical trial and provided that all the foreseen safety measures are followed.

Therefore, the Biosafety Advisory Council issues a **positive advice with the following conditions**:

- The notifier and the investigators must strictly apply the clinical trial protocol, and all the safety instructions as described in the dossier also taking into account the suggestions from the Biosafety Advisory Council for improvement of the personnel instructions.

- Any protocol amendment has to be previously approved by the Competent Authority.

- The notifier is responsible to verify that each study centre has qualified personnel experienced in handling infectious material and that the investigator has the required authorizations to perform the clinical trial activities inside the hospital (laboratory, pharmacy, hospital room, consultation room...) according to the Regional Decrees transposing Directive 2009/41/EC on Contained use of genetically modified micro-organisms.

- For the transport of the IMP the notifier should conform to the transportation rules regarding transport of GMO's.

- The Biosafety Advisory Council should be informed within 2 weeks when the first patient starts the treatment and the last patient receives the last treatment.

- At the latest six months after the last visit of the last patient included in the trial, the notifier must send to the competent authority at the attention of the Biosafety Council a report with details concerning the biosafety aspects of the project. This report will at least contain:
    - the total number of patients included in the trial and the number of patients included in Belgium;
    - a summary of all adverse events marked by the investigators as probably or definitely related to the study medication;
    - a report on the accidental releases, if any, of the recombinant HSV-1 .

Prof. M. De Proft
President of the Belgian Biosafety Advisory Council

Annex 1: Suggestions for improvement of the Accidental Spill information for Health care personnel
Annex 2: Compilation of comments of experts in charge of assessing the dossier B/BE/14/BVW1 (ref: BAC_2014_0647)

Annex 1
Suggestions for improvement of the Accidental Spill information for Health care personnel

Suggestion to improve the text after the third bullet:

In case you are involved in an accidental spill or breakage of a vial containing Talimogene Laherparepvec, please alert people in the area of the spill, remove all contaminated clothes and tell everybody to leave the area for 30 minutes.

As explanation for the 30 minutes between the spill and evacuation on one hand and the start of the clean-up it is suggested to add the following sentence in the text or as footnote:

In general, a 30-minute wait is sufficient for the droplets to settle and aerosols to be reduced by air changes but it depends on the number of air changes per hour. Longer waiting periods may be imposed depending on the situation.

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03 October 2014

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC_2014_0647
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Compilation of Comments of Experts in charge of assessing the dossier B/BE/14/BVW1

Mandate for the Group of Experts: mandate of the Biosafety Advisory Council (BAC) of 24 June 2014
Coordinator: Prof. Jozef Anné (KUL)
Experts: Anton Roebroek (KUL), Aline Baldo (WIV-ISP, SBB)
Domains of expertise of experts involved:
Secretariat (SBB): Didier Breyer, Fanny Collard, Martine Goossens, Katia Pauwels

INTRODUCTION

Dossier **B/BE/14/BVW1** concerns a notification of the company Amgen Ltd for deliberate release in the environment of genetically modified organisms other than higher plants according to Chapter II of the Royal Decree of 21 February 2005.
The notification has been officially acknowledged on 1 September 2014 and concerns a clinical trial with Talimogene laherparepvec a recombinant Herpes simplex virus 1. The herpes virus has been attenuated by the functional deletion of two genes (ICP34.5 and ICP47) of the HSV-1 genome and has been genetically modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF). This GM-medication is developed for use as an oncolytic immunotherapy in melanoma patients.

♦ INSTRUCTIONS FOR EVALUATION

Depending on their expertise, the experts were invited to evaluate the genetically modified organism considered in the notification as regards its molecular characteristics and its potential impact on human health and the environment. The pure medical aspects concerning the efficacy of the medicinal product and its safety for the treated patient are outside the scope of this evaluation.
The comments of the experts are roughly structured as in
- Annex II (principles for the risk assessment) of the Royal Decree of 21 February 2005
- Annex III (information required in notifications) of the Royal Decree of 21 February 2005
- Commission Decision 2002/623/EC of 24 July 2002 establishing guidance notes supplementing Annex II to Directive 2001/18/EC.

List of comments received from the experts

Remark: The comments below have served as basis for a list of questions that the Competent authority forwarded on 03-10-2014 to the notifier with a request to provide additional information. The comments or remarks highlighted in grey correspond to the questions addressed to the notifier.

1. INFORMATION RELATED TO THE CHARACTERISTICS OF THE DONOR, THE RECIPIENT OR PARENTAL ORGANISM

(e.g. possibility of natural transfer of genetic material to other organisms, pathological, ecological and physiological characteristics, indigenous vectors ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

2. INFORMATION RELATED TO THE VECTOR

(e.g. description, sequence, mobilisation ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

3. INFORMATION RELATED TO THE CHARACTERISTICS OF THE GMO

3.1. Information related to the genetic modification

(e.g. methods used for the modification, description of the insert/vector construction ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

In the “Technical and Scientific information on GMO”, fig 2 p 28, fig 4 p34 and fig 5 p35 : the figures do not correspond to the legend of fig 2, could the applicant indicate in these figures if the repeat sequences (R_L and R_S) are internal (IR_L and IR_S) or terminal (TR_L and TR_S)?
Could the applicant provide the studies 4647-00041 and 1182-00009?

Could the applicant explain why fragments of 17*syn*+ viral DNA were transferred into talimogene laherparepvec?

Additional comments from the coordinator

- The reference Mohr and Gluzman, 1996 does not describe what is mentioned in the figure (legend)
- The strain HSV-1 17syn+ is very well characterized (Bolovan et al, 1994) this clarifies why it has been used for the construction of talimogene laherparepvec.

3.2. Information on the molecular characteristics of the final GMO

(e.g. number of copies of the transgenes, phenotypic and genetic stability of the transgenes, expression of the new genetic material, re-arrangements in the genome, inclusion or suppression of genetic material ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Could the fragments of 17syn+ viral DNA and fragments of plasmid DNA have any consequences for the genetic stability of the final GMO?
Figure 6 page 41 is unreadable, could the applicant provide a larger version?
Could the applicant evaluate the consequences of recombinations of hGM-CSF with host sequences?
The applicant says p43 that “it is theoretically possible that individual recombination virions containing DNA with one copy of ICP34.5 and one copy of GM-CSF could be generated”. Even if these recombinants are not stable, could the applicant evaluate the consequences of this recombination and the probability of occurrence?

3.3. Considerations for human, animal or plant health

(e.g. invasiveness and virulence, toxic or allergenic effects, possibility of survival outside of receiving host, other product hazards ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

What are the consequences of expression of the hGM-CSF in a non target host? In the article of Harzstark and Small (2009), the authors say that “It is theorized that high doses of hGM-CSF may activate myeloid suppressor cells, create a counterproductive immune response. It is critical that the use of GM-CSF be optimized, in order to improve, rather than hinder, the immune response” Could hGM-CSF expressed in a non target host hinder the immune response?
Is talimogene laherparepvec able to reactivate endogenous wild-type HSV-1 during the establishment of a latent infection? Is talimogene laherparepvec able to alter neuronal function (long-term effect)?

4. INFORMATION RELATING TO THE CONDITION OF RELEASE

(e.g. description of the activity, quantities of GMO to be released, workers protection measures, elimination of any contaminating material in the preparation of the GMO stock, elimination of the GMO at the end of the experiment ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Infection by HSV-1 virions occurs mainly by direct contact with the skin or mucous membranes, although transmission can also occur by inhalation of aerosols such as respiratory droplets (Lim et al., 2013). Aerosol producing operations should be reduced during preparation and administration of the GMO and personal manipulating the GMO should wear a mask because the puncture of a contained holding vector may produce aerosols. The medical staff should also wear closed shoes in order to be protected against sharp and syringes that fall.
The internal transport of the vials containing the GMO should be performed in an hermetic transport box containing absorbent paper towels.
Transportation (p. 74 of the technical dossier): The medicinal product containing GMO should be considered as a "Miscellanous dangerous Goods", Class 9 for the International Air Transport Association (IATA): "Miscellaneous dangerous goods are substances and articles which during transport present a danger or hazard not covered by other classes. This class encompasses, but is not limited to, environmentally hazardous substances, substances that are transported at elevated temperatures, miscellaneous articles and substances, **genetically modified organisms** and micro-organisms and (depending on the method of transport) magnetized materials and aviation regulated substances.

Additional comments SBB
When multiple lesions are treated it is not clear in the dossier if its needed to put each time a new needle on the syringe.

5. INFORMATION RELATED TO THE RISKS FOR THE ENVIRONMENT AND HUMAN HEALTH

5.1. Information on spread ("shedding") of the GMO from the treated patient/animal to other persons/animals or to the environment (including indirect/delayed effects due to vertical transmission to offspring).

(e.g. genetic transfer capability, routes of biological dispersal, target organisms ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

5.2. Information on possible effects on human health resulting from interactions of the GMO and persons working with, coming into contact with or in the vicinity of the GMO release (carekeepers, patient relatives, immunocompromised people ...).

Comment 1

ERA, 2.1.2.5.2 Effects in Immune-compromised Individuals (page 30-31)
In case an immunocompromised person will be infected with Talimogene Laherparepvec there is the possibility that there is no obvious direct link with a treatment with or a patient treated with Talimogene Laherparepvec. So specific testing for Talimogene Laherparepvec is not considered. Are the normal tests for HSV-1 diagnosis suitable to identify a Talimogene Laherparepvec infection as an HSV-1 infection resulting in treatment with e.g. acyclovir or is there any danger that in such a case a Talimogene Laherparepvec infection will be missed and no acyclovir treatment will be started.

Comment 2

Could the applicant evaluate the possible effects if an immunocompromised person comes into contact with the GMO?

Additional comment SBB
In the instructions for the patient it should be clearly stated that he should avoid ANY contact with immunocompromised persons.

5.3. Information on possible effects on animal health or on the environment.

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

5.4. Information on selective advantages or disadvantages conferred to the GMO compared to the parental organism.

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

5.5. Information on the possibility of the GMO to reconvert to his wild type form and possible consequences for human health or the environment.

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

5.6. Information on the possibility of the GMO to exchange genetic material with other micro-organisms and possible consequences for human health or the environment.

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

5.7. Information on the possibility of gene transfer to other organisms and about the selective advantages or disadvantages conferred to those resulting organisms (possible consequences for human health or the environment).

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

6. INFORMATION RELATED TO THE MONITORING, SURVEILLANCE AND CONTROL, WASTE TREATMENT AND EMERGENCY PLANS PROPOSED BY THE APPLICANT

6.1. Monitoring plan proposed by the notifier and possibility to identify the occurrence of non-anticipated adverse effects.

(adequation between the monitoring plan and risks identified during the risk assessment, when appropriate measures to minimize the potential risks to offspring ...)

Comment 1

Has evaluated this item and has no questions/comments.

6.2. Surveillance and control of the release

(adequation between the procedures to avoid and/or minimise the spread of the GMO and risks identified during the risk assessment...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

6.3. Information on the waste generated by the activity and its treatment.

(e.g. type of waste, amount ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

The applicant says that "**If possible**, materials deriving from healthcare activities should not be discarded in landfills even after decontamination." They should **never been discarded in landfills**, they should be incinerated even after decontamination.

6.4. If applicable, information on the emergency plan(s) proposed by the notifier.

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Strict procedures should be provided for medical staff and persons in contact with the patient during the release of the viral vector. These procedures should be posted in the hospital room where the treatment should take place.
A spill kit should be available in the facility, this spill kit should contain appropriate disinfectant, personal protective equipment (PPE, i.e. gloves, safety glasses, laboratory coat, mask), tongs or forceps in order to take broken vials, absorbent paper towels, biohazard waste bags.
In case of accidental spills or breakage of a vial containing the GMO, the medical staff should alert people in the area of the spill, remove contaminated clothes and leave the area for 30 min. He should close the area and post "DO NOT ENTER". After 30 min, he must wear a clean lab coat and wear gloves, glasses and a mask. He must cover the spill with towels and other absorbent material starting from the edge toward the centre. He must carefully pour the appropriate disinfectant over the absorbent material starting from the edge to the centre. It must allow a sufficient contact time for the

disinfectant to inactivate the GMO. After that, he must remove the paper towels and broken vials with tongs or forceps and discard in a biohazard waste bag. The PPE should be discard in the biohazard bag. The lab coat should be decontaminated before disposal. The medical staff should report the incident to the responsible of the site.

6.5 Information related to the identification of the GMO and the detection techniques

(e.g. identification methods and detection techniques, sensitivity, reliability and specificity of the proposed tests ..)

Comment 1

See also 5.2.
Technical and Scientific information on the GMO (page 48-50)
f) Description of identification and detection techniques including techniques for the identification and detection of the inserted sequence and vector
g) Sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques

Is there any risk, that a Talimogene Laherparepvec infection is not recognized as a HSV-1-like infection in standard HSV-1 diagnosis tests?

Additional comment SBB:
According to the Royal Decree of 21 February 2005, the notifier is requested to provide in the notification a description of identification and detection techniques, including information on sensitivity, reliability and specificity of these techniques. The submitted dossier lacks a detailed PCR protocol for the identification and detection of the GMO.

7. OTHER INFORMATION

7.1 Do you have any other questions/comments concerning this notification that are not covered under the previous items?

Comment 1

ERA 2.1.2.4.2 Clinical Safety Data Obtained with Talimogene Laherparepvec (page 29-30)
Several clinical trials using Talimogene Laherparepvec are already conducted. The most commonly reported treatment-related adverse events in patients are listed and apparently considered not to be prohibitive objections against the use of Talimogene Laherparepvec. As the dose of Talimogene Laherparepvec used in these previous studies is not mentioned nor compared with the proposed dose in the present study the suggested conclusions are not justified unless the additional information is provided stating that the doses are similar/comparable.

Additional comment SBB:
The aspects concerning the safety of the medicinal product for the treated patient are outside the scope of this evaluation

References

Bolovan CA, Sawtell NM, Thompson RL. ICP34.5 mutants of herpes simplex virus type 1 strain 17syn+ are attenuated for neurovirulence in mice and for replication in confluent primary mouse embryo cell cultures. *Journal of virology*. 1994;68:48-55.

Harzstark AL, Small EJ. Immunotherapeutics in development for prostate cancer. *Oncologist*, 2009, 4, 391-8.

Lim F., Khalique H, Ventosa M, Baldo A. Biosafety of gene therapy vectors derived from Herpes simplex virus type 1. *Curr Gene Ther*, 2013, 13, 478-91.