Polysaccharide-based membrane for sublingual vaccination

Sprawozdania

Informacje na temat projektu

PolyVac

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Periodic Reporting for period 1 - PolyVac (Polysaccharide-based membrane for sublingual vaccination)

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Podsumowanie kontekstu i ogólnych celów projektu

Vaccination is one of the most effective methods against life threatening diseases. Vaccines administered by the mucosal route (oral, vaginal...) present the advantage to be needle-free and reduce the risk of pathogen transmission. Among the existing mucosal vaccines, the sublingual ones are an interesting way of immunisation since the sublingual mucosa is particularly thin and would allow easy penetration of antigens. Also, this administration allows to bypass the gastrointestinal tract, has better safety record than intranasal vaccines and have better compliance for vaccinating infants and children. They have a fast removal by body fluids and enzymes. PolyVac introduces a pioneering system for controlled targeted delivery of bioactive molecules and, for the proof of concept envisages the development of a sublingual vaccine for HIV.
HIV contamination is mainly transmitted via the mucous membrane. Protecting these pathways by directly producing antibodies to the mucosa would be an innovative strategy for preventive treatment. In immunology, it is known that the different mucosal tissues of the body are connected and that, therefore, the immune protection provided by a vaccine could spread through the mucosal tissue. Thus, it has been established that the activation of antibody production by the sublingual route also allows for the production of antibodies in the vaginal mucosa. In PolyVac, we propose an innovative approach to vaccination using a patch to be used under the tongue that would provide mucosal protection at remote sites. This patch will be composed of natural polymers, completely biodegradable and produced by green chemistry. This patch will include an HIV antigen and a biological adjuvant that will stimulate the immune response. Sublingual immunisation tests are planned in vivo to check for the presence of so-called neutralising antibodies in both vaginal and rectal mucosa, unknown information to date. As outcomes it is expected to obtain mucosal protection at remote sites after sublingual administration of the vaccine. If successful, this mode of administration would allow prophylactic treatment against HIV and could also be applied to other infectious diseases. PolyVac envisages, as final product, an innovative sublingual patch for human immunotherapy that among the advantages presented above will also overcome one of the main drawbacks of injected vaccines that

is the storage at around 4°C. Overcoming this issue they could be widely used for immunotherapy in the developing countries.

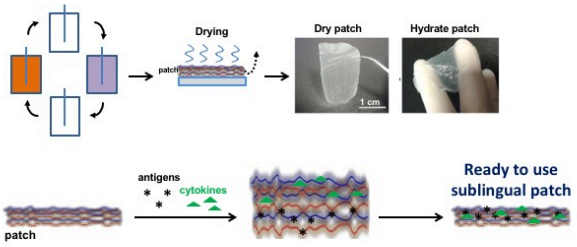
Prace wykonane od początku projektu do końca okresu sprawozdawczego oraz najważniejsze dotychczasowe rezultaty

PolyVac proposed a pioneering approach that was never been addressed to date for sublingual vaccination. Such new technology involved the development of a biocompatible, biodegradable, biomimetic and mucoadhesive multilayered free-standing membrane (patch) for the creation of a novel and pioneering vaccination mode. For that, patch composed of natural polymers were fabricated via the Layer-by-Layer. Once the final product will be administered orally to humans, the developed patches were produced in order to valorise and exploit the use of polymers from natural sources. A controlled delivery of the antigen and adjuvant was envisaged as well. The developed patches were loaded with a model protein, where the protein incorporation/release abilities of the patch were assessed. As in vitro models often fail in predicting living tissue behavior, the investigation of mucoadhesion, inflammation and antigen transport was evaluated in vivo through a mouse model. The persistence of bioactivity of a model cytokine was measured by a chemotaxis experiment to confirm the protective effect of our protein carrier. The HIV antigen delivered through the patch was adsorbed on the surface of a nanoparticle (NP). Immunisation of mice with a model antigen from HIV-1 adsorbed on a NP and administered either as a solution under the tongue or at the surface of the patch was performed. The NP formulation was either administered alone or with the cytokine as a biological adjuvant. The presence of cytokine in NP/patch led to significantly increase both the secretion of salivary IgA and the formation of germinal centers in the submandibular lymph nodes.

Innowacyjność oraz oczekiwany potencjalny wpływ (w tym dotychczasowe znaczenie społeczno-gospodarcze i szersze implikacje społeczne projektu)

Until now, there were technological barriers that impeded the development of an effective sublingual immunotherapy such as increasing its retention at delivery sites and reducing antigen degradation. These challenges, that were two major bottlenecks in the field, were the main objectives of PolyVac with the final purpose of providing an efficient system to induce a mucosal immune response. Increase the retention time of antigen at the mucosal site: As the final product will be administered orally to humans, the produced patch was composed of polymers from natural sources. The fluorescent model protein OVA, labelled with Alexa647, was incorporated in the core of the patch and the tracking of the fluorescence was performed. The patch allows a retention of the antigen in the buccal cavity during at least 1h, while it is rapidly dispersed when administered in solution. The patch was proven to be mucoadhesive and allow a more controlled and sustained delivery of the antigen than the liquid formulation. The detection of a moderate inflammation induced an interesting recruitment of immune cells at the immunisation site, possibly accelerating the antigen uptake. Reduce antigen degradation and maintain its bioactivity: The model antigen used was from a mucosal transmitted pathogen, namely HIV-1. Targeting of dendritic cells was achieved by incorporating a

cytokine as chemoattractant into the patch. The dissolution of the patch was assessed by playing with the protonation/deprotonation process and in combination with an artificial saliva. After the production and loading of the patch, it became a bioactive patch, ready for vaccination purpose. In order to assess if the bioactivity of the carried proteins was maintained once incorporated, a chemiotaxis experiment highlighted the protective effect of the natural polymers chosen. The polysaccharidic nature of the polymers could protect the cargo proteins against degradation as they have a natural affinity towards proteins.
Induce an efficient mucosal response after immunisation by the patch: The patch stability and bioactivity were assessed in vivo. After protein release characterisation, the sublingual vaccination patch was administrated to mice to evaluate the efficiency of the immunotherapy. For that, immunisation of mice with the antigen adsorbed on a NP and administered either as a solution under the tongue or at the surface of the patch was performed. The NP formulation was either administered alone or with the cytokine as a biological adjuvant. The presence of cytokine in NP/patch led to significantly activation of the local mucosal immunity by increase both the secretion of salivary IgA and the formation of germinal centers in the submandibular lymph nodes.
Impacts of the project: Under the scope of this project, a new and innovative sublingual patch composed of natural polymers with an antigen and an adjuvant is being developed.
One product patent is being prepared. Due its preparation one publication is submitted. The dissemination of the results were achieved through participation in scientific conferences.
A Press Release of PolyVac was made through Sidaction entitled: “Concevoir et tester une vaccination anti-VIH à l’aide d’un patch placé sous la langue”.



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