MAnufacturing process for Cold-chain Independent VIrosome-based VAccines

Sprawozdania

Informacje na temat projektu

MACIVIVA

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Periodic Reporting for period 3 - MACIVIVA (MAnufacturing process for Cold-chain Independent VIrosome-based VAccines)

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Podsumowanie kontekstu i ogólnych celów projektu

Virosomes are small lipid-based spherical particles acting as carrier for vaccinal antigens that are purified or recombinant proteins or synthetic pieces of proteins (peptides) derived from a pathogen for making the vaccine. These virosomal particles mimic the structure of enveloped viruses and after needle injection into the body (ex. intramuscular), they stimulate the immune system for producing protective antibodies toward the target proteins (ex. antibodies against the gp41 on human immunodeficiency virus (HIV)) and neutralize the invaders before the infection can spread.

Virosome-based vaccines are generally under liquid form and as any liquid vaccine they contain a lot of water. Consequently, such vaccines are susceptible to instability due to vulnerability to accidental freezing or exposure to high temperature (> 35oC) during storage or transportation, leading to irreversible damages to the virosomal vaccines. Furthermore, chemical modifications may take place in the liquid vaccine (ex. product oxidation), and increase the risk of unwanted side effects. These scenarios frequently happen during vaccine shipment to warm countries. Therefore, maintenance of the cold chain at the right temperature is fundamental for preserving the vaccine bioactivity. However, such infrastructures are absent or inadequate in many developing countries, and it increases the risk of losing vaccines or rendering them less efficacious.

To prevent or reduce chemical modifications and improve the vaccine thermostability in case of exposure to low and high temperatures, removing most of the water from the virosome-based vaccines to generate needle-free vaccines under various powder forms with low moisture content (< 5% water) was identified as a promising approach.

This led to the set-up of the MACIVIVA (Manufacturing process for cold-chain Independent Virosome-based Vaccines) consortium in 2015 supported by the EU Horizon 2020 and the Swiss government (grant agreement No 646122). For achieving the project objectives, MACIVIVA involved collaborators with expertise and manufacturing capabilities in heat spray-drying (Upperton Ltd) or freeze/freeze drying also known as lyophilisation (Catalent UK Swindon Zydis Ltd) that could be applied to virosomes as vaccinal antigen carrier (Mymetics SA/BV) for generating new solid vaccine dosages. Other collaborators joined the consortium for providing their expertise and manufacturing capabilities either for the vaccinal synthetic P1 peptide (Bachem AG) or the recombinant gp41 HIV-1 protein produced in bacteria (subcontracted to Px'Therapeutics). These new solid vaccine forms were used for vaccinating animals for confirming that that they have retained their ability to induce antibodies. For evaluating the vaccine-induced antibody responses in the blood and mucosal secretions from various tissues (genital, rectal, nasal and lungs), the detection of antibodies was performed by the partner

with the expertise in the development of innovative antibody quantification assays (Chimera Biotec GmbH). MACIVIVA project ended in early November 2018 after 42 months of outstanding collaborations between the six Consortium partners and a dozen of subcontractors, achieving all the objectives. Three new GMP Pilot Lines are now available in Europe for manufacturing virosomal vaccines as spray-dried nasal and oral powders and lyophilized sublingual tablets.

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

Over the last 42 months of MACIVIVA, through highly interactive discussions, information and expertise sharing, partners and collaborators conducted several investigations for: a) Optimizing the liquid virosomal HIV-1 vaccine formulation to allow its processing by the new Pilot Lines, and then liquid virosome manufacturing as non-GMP and GMP clinical lots that are provided to the partners: b) Identifying safe ingredients at adequate concentrations that can be mixed with the provided liquid virosomes and then used for generating solid vaccine forms; c) Identifying first the optimal non-GMP manufacturing conditions and then upscaling and GMP production for each Pilot Line (nasal, oral and sublingual) ; d) Optimizing the production and purification steps for both vaccinal antigens (P1 and rgp41); e) Developing numerous bioanalytical methods for characterizing the vaccinal antigens and the different vaccine forms; and f) Developing highly sensitive immuno-assays for detecting antibodies in blood and mucosal secretions.

By the end of MACIVIVA in month 42 (November 3rd 2018), the consortium successfully achieved all the main objectives, with the 24 Deliverables initially planned that were completed and submitted to the European Commission. There were also eight Milestones that were successfully achieved, with the establishment and completion of the three GMP Pilot Lines with their corresponding GMP vaccine lots with a promising thermostable and immunogenic HIV-1 vaccine candidate as end-product. These new solid vaccine forms are making the virosome technology more attractive and competitive, and it opens the door to other future therapeutic and prophylactic vaccines based on virus-like particles, improving also the European competitiveness with this nanovaccine manufacturing technology.

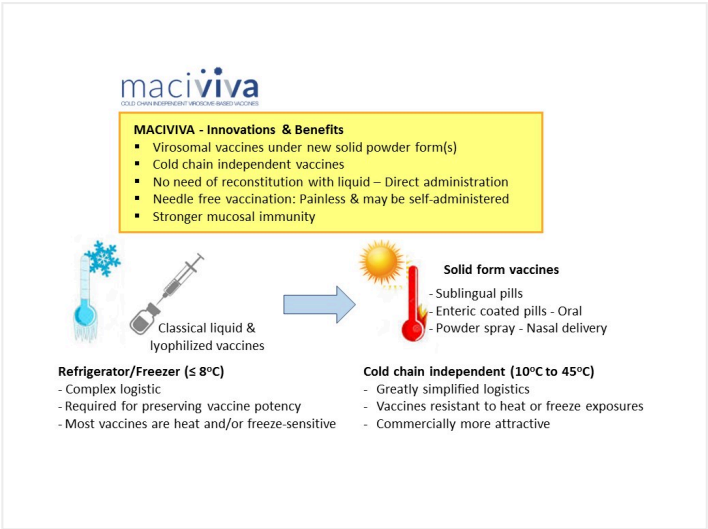
Innowacyjność oraz oczekiwany potencjalny wpływ (w tym dotychczasowe znaczenie społeczno-gospodarcze i szersze implikacje społeczne projektu)

The new solid forms of the HIV-1 candidate vaccine manufactured by the three Pilot Lines (nasal, oral and sublingual vaccine) are not damaged by accidental freezing conditions at < -15oC and they can also support long time exposure to 40oC (at least 2-3 months) without affecting their ability to induce relevant antibodies, representing major innovations. Therefore, short term cold-chain independent vaccine transportation at room temperature (25oC) or under warm and humid conditions (40oC/75% humidity) could be possible during shipment from the primary storage facilities to the distant doctor offices, local hospitals and clinical sites , with limited risk to reduce vaccine bioactivity during that period. MACIVIVA vaccines fully comply with the WHO recommendations, as a vaccine maintaining

its bioactivity at 40oC up to 1 month is already a major achievement and such vaccines will address an important issue in the vaccine industry.

Furthermore, with “ready-to use” vaccine solid dosage forms, there is no more need to provide needles and vials with diluents for vaccine reconstitution, rendering vaccine handling safer with a simplified logistics. Mucosal vaccinations are non-invasive and painless, favoring a broader population acceptance. They are expected to elicit mucosal immunity in the genital and rectal tract, the main entry doors of HIV-1 and many other pathogens, offering improved protection against sexually transmitted pathogens, as compared to vaccines inducing only blood immune responses for preventing mucosally transmitted pathogens.

Other existing virosomal vaccines or other vaccines obtained by different technologies could benefit from MACIVIVA Pilot Lines and acquired know-how. Due to the ease of mucosal administration of solid vaccine forms, gradual replacement of liquid and lyophilized/reconstituted vaccines by needle-free vaccines is expected, favoring higher immunization coverage for the great benefit of the overall health care system. MACIVIVA results may raise high interest from major stakeholders, increase the European attractiveness as location of choice to carry-out thermostable vaccine development, promise sustainability and creation of high tech jobs and leverage investments.



MACIVIVA project concept

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