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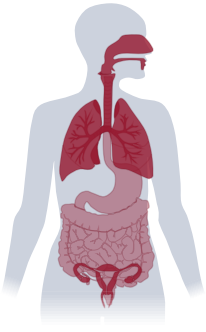
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Sublingual Vaccination by an Oro-Dispersible Patch made with Natural Polymers: Optimization for Vaginal and Rectal Protection

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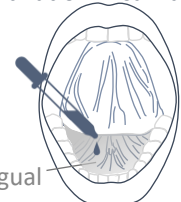
Context



Mucosae represent preferential entry sites for pathogens. Consequently, the mucosal immune system has been shaped to act as the first line of defense to prevent microorganisms' invasions. By sublingual vaccines administration, protection can be achieved with both systemic and local immune response induction, as well as rectal and vaginal protection.


Introduction

Sublingual liquid vaccines:
Heterogeneity due to partial dilution in saliva



Sublingual Floor
Floor of the mouth: 10 – 100 μm

Oro-dispersible membrane:

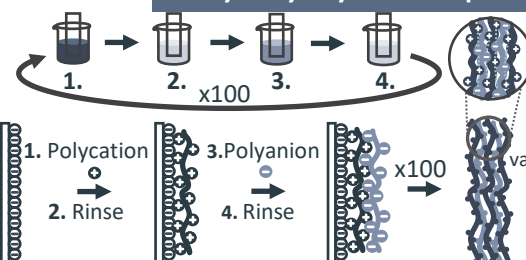


Bioactive vaccination patch containing subunit antigens and protein or nanoparticulate adjuvants

Sublingual vaccination patch

- Biocompatible**
Composed with polysaccharides which are not toxic for cells and mucosae
- Functionalizable & Biodegradable**
Protein antigen & adjuvant incorporation without bioactivity loss. Antigen released during patch degradation by salivary enzymes.
- Mucoadhesive**
Lengthen contact time between formulation and mucosa to induce a better response
- Bioactive**
Induce a systemic and mucosal immune response

Layer-by-Layer technique

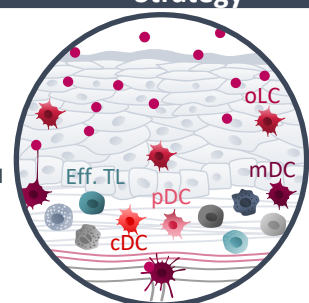


1. Polycation
2. Rinse
3. Polyanion
4. Rinse

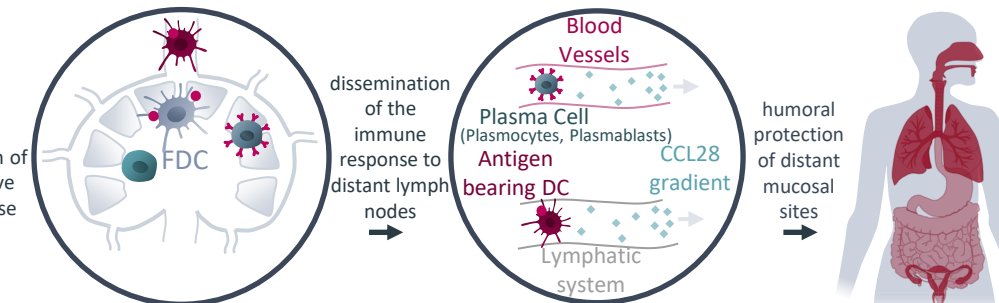
x100

pH variation
protein
& NP
pH variation
sublingual delivery

Strategy



initiation of adaptive response



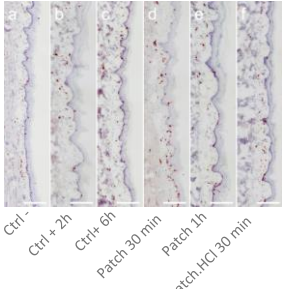
dissemination of the immune response to distant lymph nodes

humoral protection of distant mucosal sites

Blood Vessels
Lymphatic system
Plasma Cell (Plasmocytes, Plasmablasts)
Antigen bearing DC
CCL28 gradient

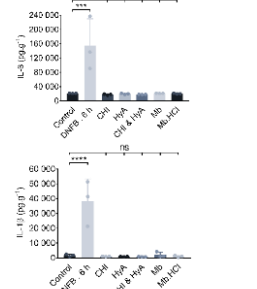
Biocompatible

MHC-II IHC at sublingual site after patch adm.



Ctrl -
Ctrl + 2h
Ctrl + 6h
Patch 30 min
Patch 1h
Patch HCl 30 min

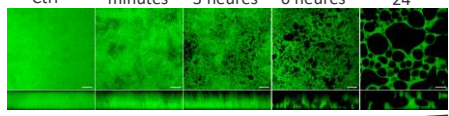
Cytokines quantification after patch adm.



Biodegradable & functionalizable

Fluorescent patch (in green) degradation in salivary enzymes

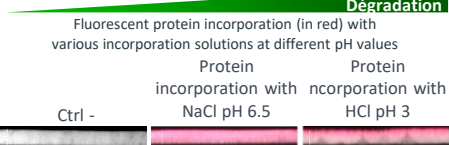
30 minutes 3 heures 6 heures 24



Dégradation

Fluorescent protein incorporation (in red) with various incorporation solutions at different pH values

Protein incorporation with NaCl pH 6.5
Protein incorporation with HCl pH 3

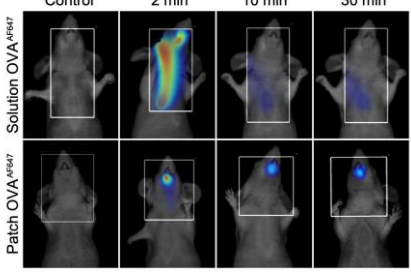


Results

Mucoadhesive

Fluorescent protein delivery *in vivo* with patch or as solution

Control 2 min 10 min 30 min

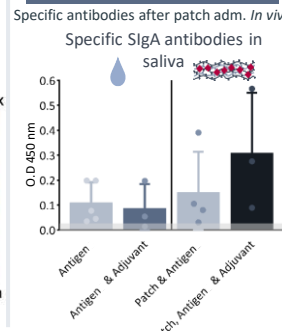


Solution OVA^{496/47}
Patch OVA^{496/47}

Bioactive

Specific antibodies after patch adm. *In vivo*

Specific IgA antibodies in saliva



Antigen
Antigen & Adjuvant
Patch & Antigen
Patch, Antigen & Adjuvant

Conclusion & Perspectives

Our results demonstrate this oro-dispersible patch biocompatibility through IHC and cytokines quantification after patch administration. This patch permits protein incorporation using various pH, allowing protein release once degraded by salivary enzymes. Its mucoadhesive properties permits a prolonged delivery at the sublingual site inducing a higher quantity of specific sIgA in saliva. For an enhanced mucosal response, especially at distant mucosal sites (such as rectal and vaginal mucosa), other mucosal adjuvants should be tested, especially through NP formulation for a better presentation to immune cells.