PUBLISHABLE SUMMARY

Summary of the project objectives.

The BIOMUC project aimed at exploiting the natural properties of mucins, the biopolymer that composes our mucus, for the generation of new biomaterials for biomedical applications, and especially for drug delivery. The project was divided into three distinct goals.

1. Characterize the interactions between mucins and therapeutic molecules such as small drugs and exploit them to design drug delivery device for both hydrophilic and hydrophobic therapeutic molecules.

2. Develop thin films made of mucins and explore their potential for biomedical applications. Nano-thin films are assembled through the layer-by-layer deposition of two interacting components.

3. Develop three-dimensional mucin hydrogels for biomedical applications. We exploit the natural binding capacity of mucins to create long lasting drug delivery devices.

Main results.

Mucins were successfully deposited on surfaces, where they spontaneously adsorb to form coatings. We found that mucin coatings could very effectively prevent the adhesion of most mammalian cells, and of some bacteria. The mucin coatings were patterned on the surfaces, and used to precisely localize mammalian and bacterial cells on surfaces.

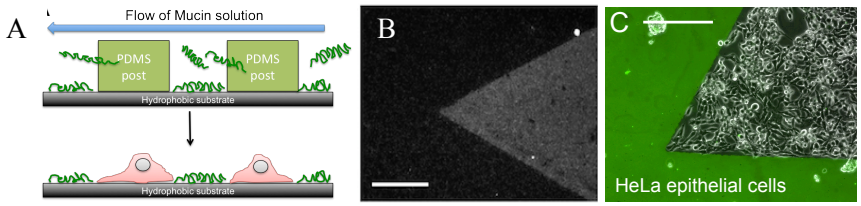

Figure 1. *(A) Mucin coatings were patterned on surfaces, preventing bacteria (B) and mammalian cells (C) to adhere. The green area in C is covered by the mucins*

These coatings, in addition to being used for cell patterning and to reduce bacterial attachment, were used to better understand the molecular origins of mucins' ability to hold water and to lubricate surfaces. Our study showed that the sugar molecules attached to the mucin protein core are essential for these properties to be maintained.

Mucins could also be assembled into thicker films, by associating them with other polymers or with sugar-binding proteins called lectins. These films were assembled by alternatively covering the surface with thin layers of mucin and lectins. The bonds formed between lectin and the sugars of the mucin molecules drove the auto-assembly and showed remarkable stability in various pH and ionic strength, however they could be disassembled by exposure to sugar solutions. This system was used to trigger the release of small polymer patches, which could be used as a drug delivery vehicle

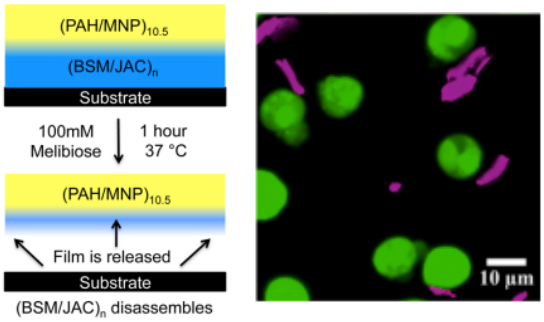

Figure 2. Nanometer-thick films were formed by alternatively depositing mucins and lectins on surfaces (BSM/JAC). The sensitivity of the films to sugar solutions was used as released mechanism for small polymer patches (PAH/MNP). The patches are then designed to attach to cells and can be used for drug delivery purposes.

In order to characterize and exploit mucins' interactions with small drug molecules, we designed three-dimensional mucin hydrogels. This was achieved by linking the mucin molecules together through covalent bonds (see Figure 6A). These robust hydrogels were used to deliver an antibiotic and an anticancer drug. We showed that the natural binding capacity of mucins for these drugs delayed their diffusion out of the gel and allowed their sustained release over days. Antibiotic-loaded mucin gels could be charged with sufficient amounts of antibiotic to effectively suppress bacterial growth for a month. These results could lead to the broader use of mucin for biomedical applications.

Other ways to assemble mucins in hydrogels were explored, in particular through their complexation with small sugar molecules called oligochitosans. These assembled with the mucins to form spherical objects (see Figure 6B). Depending o the oligochitosans chosen, the resulting permeability of the mucin gel was changed. This could lead to new strategies to modify our mucus properties in vivo. In that line of work, we developed lectin-PEG conjugates, which are able to bind altered mucin molecules, and restore some of their original properties. In particular we demonstrated their ability to restore mucin hydration and lubrication.

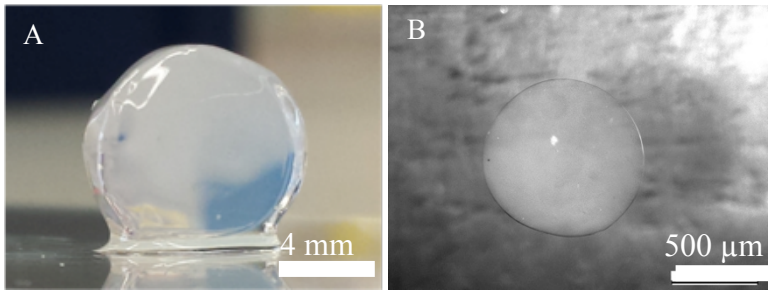

Figure 6. *(A) Bovine submaxillary mucin hydrogel formed by covalently crosslinking the mucin molecules together. (B) Image obtained with a stereo macroscope of a mucin drop complexed to oligochitosans.*

Impact.

Our work has demonstrated that the multiple functionalities of mucins can find useful applications, in particular in the biomedical fields. We established new methods to assemble mucins into biomaterials, and have characterized the resulting materials. We also contributed to the increase in knowledge of the mucin molecule properties by highlighting the importance of mucin-associated glycans in mucin coating structure and functionalities. The Marie Curie fellowship has also lead to dissemination work through 9 articles (2 under review) and 8 presentations at international conferences, as well as an infographic presenting interesting facts about mucus (http://dx.doi.org/10.6084/m9.figshare.1277545).