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COMMUNICATION

Abiotic sequence-coded oligomers as efficient *in vivo* taggants for identification of implanted materials.

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Abstract: Sequence-defined oligourethanes were tested as *in vivo* taggants for implants identification. The oligomers were prepared *via* an orthogonal solid-phase iterative approach and thus contained a coded monomer sequence that can be unequivocally identified by tandem mass spectrometry (MS/MS). In order to simplify the use of these taggants, automated synthesis and sequencing protocols were developped in this work. Before testing them *in vivo*, cytotoxicity assays were performed and indicated an excellent cytocompatibility. The oligomers were then included in small amount (1 wt%) in square centimeter crosslinked poly(vinyl alcohol) (PVA) model films, which were intramuscularly- and subcutaneously-implanted in the abdomen of rats. After one week, one month and three months of *in vivo* implantation, the PVA films were explanted. The rat tissues exposed to the implants did not exhibit any adverse reactions, thus suggesting that the taggants are not harmful and probably not leaching out from the films; the latter aspect being confirmed by *in vitro* studies in physiological conditions. Furthermore, the explanted films were immersed in methanol, as a solvent for oligourethanes, and the liquid extract was analyzed by mass spectrometry. In all cases, the oligourethane taggant was detected and its sequence was identified by MS/MS.

The certification of biomedical and pharmaceutical products is a major health and economical challenge. Currently, the World Health Organization estimates that more than 8% of the medical devices in circulation are counterfeits. The widespread circulation of these products, which do not meet international safety regulations, may greatly put at risk the health and life of consumers.[1] This is particularly true in the case of *in vivo* materials such as plastic implants, which shall be safe, biocompatible and traceable. In the last few years, the US food and drug administration and the EU Commission have defined the requirements for the implementation of a Unique Device Identification (UDI) to avoid counterfeits and ensure medical device traceability. Labelling requirements include the UDI information on the label and/or the packages of medical devices. Nevertheless, this strategy does not completely eliminate the risk of counterfeit. Strategies to incorporate the UDI directly inside the medical device shall reduce considerably the risks, making also possible to identify a device after implantation. However, although a wide variety of anti-counterfeiting technologies are available,[2] only a few of them can be applied *in vivo*. Indeed, a valid anti-counterfeiting solution for long *in vivo* use shall be biocompatible and bio-stable. Therefore, relatively simple technologies, such as colored markers, are currently used to label implants.

Among all anti-counterfeiting technologies that have been reported in the literature, sequence-controlled polymers represent a new and interesting option.[3] In particular, uniform polymers containing a perfectly-defined monomer sequence can be used as a molecular barcode.[4] For instance, DNA, which contains specific sequences of the four nucleotide monomers A, T, G and C, has been extensively studied for practical anti-counterfeiting and traceability applications.[4c, 5] It can be sprayed on or included in a host material and decoded using a next-generation sequencing technology.[6] Furthermore, DNA taggants can be employed in trace amounts because they can be amplified by the polymerase chain reaction. However, DNA molecules are sensitive to chemical and thermal degradation and therefore cannot be employed in all processing conditions.[7] Similarly, bare DNA is far from being ideal for being applied as taggant *in vivo*. Indeed, genetic polymers are not bio-inert and may interfere with the biology of a host organism and *vice versa*, the genetic material of the host may contaminate the taggant and lead to false identification results. Thus, as demonstrated by Grass and coworkers, DNA taggants have to be encapsulated in silica nanoparticles for efficient anti-counterfeiting use.[8]

We have recently shown that abiotic sequence-coded polymers constitute an interesting alternative to DNA for anti-counterfeiting applications.[4b, 9] Indeed, using solid-phase iterative strategies, it is possible to write monomer-coded information on non-natural polymer chains.[10] Moreover, this information can be easily and very rapidly decoded by tandem mass spectrometry (MS/MS).[10b, 11] Among the different types of non-natural sequence-defined polymers that have been described,[12] oligocarbamates[13] (i.e. short polyurethanes) appear to be very interesting candidates for materials labeling.[14] Indeed, these oligomers are chemically- and thermally-robust and can therefore be dispersed in a wide variety of materials, including 3-D printed resins,[14] casted plastic films[9b, 14] and intraocular lenses.[9a] In all these examples, it was demonstrated that oligourethane taggants can be homogeneously included and stored in the host materials but can also be selectively extracted and decoded by tandem mass spectrometry. Moreover, standard polydisperse polyurethanes are usually biocompatible and

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therefore used in numerous biomedical applications.[15] Although some isocyanate monomers used in conventional step-growth polymerizations can be carcinogenic, polyurethanes by themselves were never evidenced to be harmful to living hosts.[16] In this context, it was tempting to evaluate the *in vivo* potential of sequence-coded oligourethane taggants. Figure 1a shows the general strategy that was investigated in this work. A sequence-defined oligourethane, containing a monomer-coded binary sequence, was synthesized and used as taggant for the labeling of poly(vinyl alcohol) (PVA) model implants. PVA has been used for over four decades for numerous medical applications, such as surgical sponges, contact lenses, as well as implantable materials such as cartilage substitutes, meniscus tissues and vascular grafts.[17] For instance, the PVA crosslinked sponge Ivalon® was one of the first PVA products marketed for duct replacement, articular cartilage replacement and pharmaceutical release. Hence, oligourethane-tagged crosslinked PVA films were implanted *in vivo* in eight rats for three months. Some films were explanted at different time intervals and their authentication was tested by mass spectrometry.

The sequence-defined oligourethane taggant was synthesized *via* an orthogonal solid-phase procedure that has been previously reported.[14] It is performed on an OH-functional resin and involves two successive steps: the reaction of the OH group with *N,N'*-disuccinimidyl carbonate (DSC) in the presence of triethylamine and then the reaction of the resulting succinimide-carbonate with the amine group of a coded amino-alcohol. The repetition of this two-steps cycle allows synthesis of oligourethanes. Here, a model taggant, containing a coded sequence of eight monomer units was prepared (Figure S1). In the present study, a binary language was used to encode the oligomers. As described in earlier works,[9, 14] monomer synthons containing either a butyl or a 2-methylbutyl linker are detected in MS/MS sequencing as 0 or 1 units, respectively. In addition, the hexanoic acid chain-end resulting from solid-phase cleavage is denoted as α, following previously established conventions.[14] It shall be remarked that binary coding is only used here as a proof-of-concept. For real anti-counterfeiting applications, more complex monomer codes are developped.[4a, 18] In the present work, the coded taggant was synthesized by both manual and automated synthesis. Figure S1a shows a typical electrospray (ESI) mass spectrum measured for an oligourethane synthesized by manual synthesis. Although near-uniform, the oligomer contains minor impurities. For instance, a species with a mass that is 56 Da heavier than the targeted oligomer, which probably results from a base-catalyzed insertion-mechanism occurring during the DSC/Et_3N step, is often detected in these syntheses.[9b] This problem was solved through the use of a weaker base, i.e. pyridine, which enables manual synthesis of perfectly-uniform oligomers. These conditions were then tested on a Chemspeed automated synthesis platform (Figure S2).[19] In this case, microwave irradiation, which is in general used during the DSC step was replaced by a simpler heating procedure. Nevertheless, the robotic instrument allowed succesful automated synthesis of uniform taggants (Figure S1b).

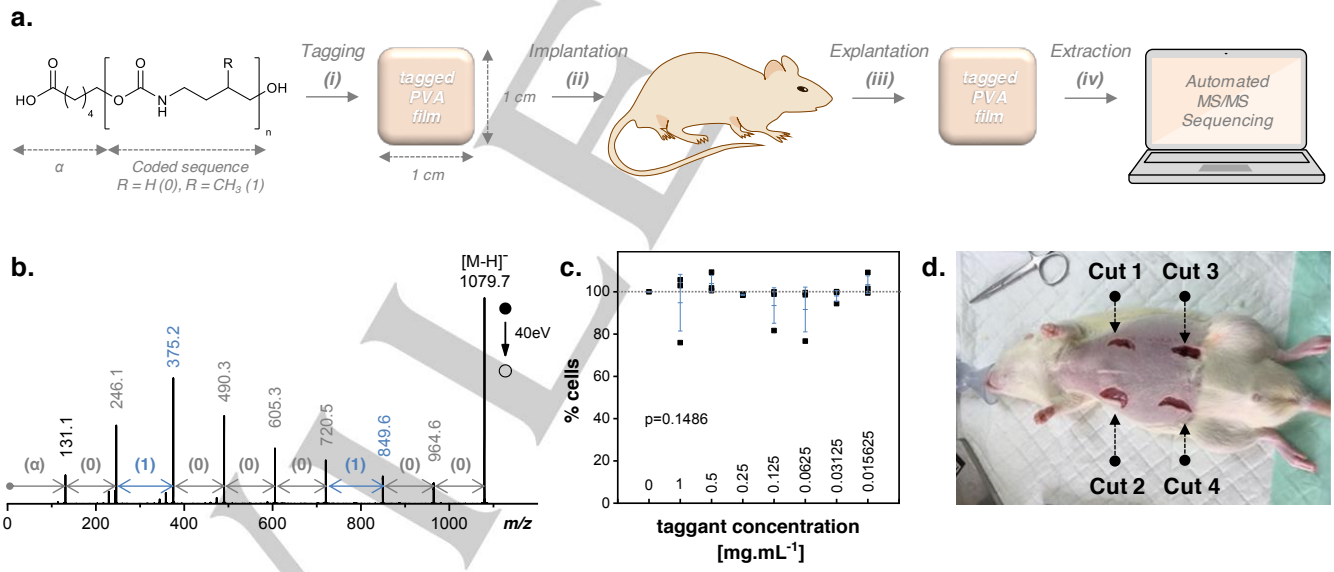

Figure 1. (**a**) General strategy studied in this work. Experimental conditions: *(i) In situ* tagging during PVA crosslinking: Taggant, PVA, sodium trimetaphosphate, NaOH, H_2O/DMF 90°C; *(ii)* Implantation: UV-sterilization, invasive surgery; *(iii)* Explantation: surgery, H_2O swelling, drying; *(iv)* Taggant-extraction: MeOH, ammonium acetate. (**b**) ESI-HR-MS/MS spectrum obtained in negative mode for the pure oligourethane-taggant, containing the coded sequence α-01000100, obtained after its synthesis. (**c**) Cytotoxicity assay obtained for endothelial cells incubated for 48h in the presence of the oligourethane taggant at different concentrations. These results were obtained with three independent experiments. Bars correspond to the standard error of the mean. (**d**). Photography of an anesthetized rat during surgery. The arrows show the four incisions, two intramuscular (cuts 1-2) and two subcutaneous (cuts 3-4), in which the model PVA implants were placed.

Figure 1b shows the MS/MS spectrum obtained for the oligourethane taggant after its synthesis. In the negative ion mode,[20] the sequence of the oligomer α-01000100 can be easily decoded. It can be obtained by manual sequencing, i.e. by measuring the fragment-to-fragment distance corresponding to the mass of either 0 or 1 synthons that are successively found in

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the sequence, as shown in Figure 1b; but it can also be deciphered in a few milliseconds using the shareware MS-DECODER.[11b] Moreover, the cytotoxicity of the oligourethanes was tested using two cell lines, namely human umbilical vein endothelial cells and NIH3T3 fibroblasts (Figure S3). These cell lines were chosen according to potential PVA applications, e.g. vascular grafts and surgical sponges. The doses studied in the cytotoxic assay were selected assuming that the tagged implants tested *in vivo* (see below) contain about 0.5 mg of oligourethane taggant. The studied concentrations were comprised between 0.01 and 1 mg·mL^{-1}, which is greater than the concentrations that would potentially be reached *in vivo* by progressive release. Figure 1c shows the results of cell viability assays obtained with endothelial cells incubated for 48h in the presence of different concentrations of the taggant. Statistical analysis of three independent experiments demonstrated lack of acute cytotoxicity at the studied doses of the sequence-coded oligourethane.

The oligourethane taggant was then incorporated in small amount (1 wt%) in model crosslinked PVA films with a thickness of about 250 µm. Taggant-inclusion was performed *in situ* during PVA film formation. The oligourethane was first dissolved in DMF and the obtained solution was mixed with an aqueous solution of PVA and sodium trimetaphosphate.[17b] After obtaining crosslinking in basic conditions, the membranes were washed several times with water and analyzed by ^{1}H NMR (Figure S4) and electrospray (ESI) mass spectrometry. These measurements indicated that the taggant was homogeneously dispersed inside the PVA films. Furthermore, the taggant can be selectively extracted from the films using a methanol/ammonium acetate incubation procedure and its sequence was identified by ESI-MS/MS (Figure S5).

The PVA films were then cut into 1 cm^2 implants (about 50 mg each, thus containing about 0.5 mg of taggant), sterilized by a UV treatment and placed inside live rats. Figure 1d shows a picture of an anesthetized rat during surgery. Four abdominal incisions were performed - two intramuscular (cuts 1-2) and two subcutaneous (cuts 3-4) - and a PVA sample was placed in each of them. Both oligourethane-tagged and control non-tagged films were implanted. The location of the tagged and control implants was intentionally varied in some animals (Table S1). After one week, one month and three months of *in vivo* storage, rats were sacrificed (Table S1) and the corresponding PVA films were explanted. After one week of implantation, the inserted samples were easily separated from the rat tissues, whereas for longer periods of implantation the PVA films appeared integrated in a newly-formed tissue. There was no noticeable differences between oligourethane-tagged films and non-tagged control samples, thus suggesting that the taggants are not harmful and probably not leaching out of the implants. The latter claim was supported by an *in vitro* experiment, in which an oligourethane-tagged PVA film was stirred at 37°C in a phosphate-buffered saline (PBS) solution. The mass spectrometry analysis of aliquots of the aqueous phase over a period of 14 days indicated that there is almost no release of the poorly-hydrophilic oligourethane from the PVA film (Figure S6). Furthermore, histological examination of organs (Figure S7) and hematological tests (Figure S8) were performed after 3 months and gave no noticeable signs of toxicity.

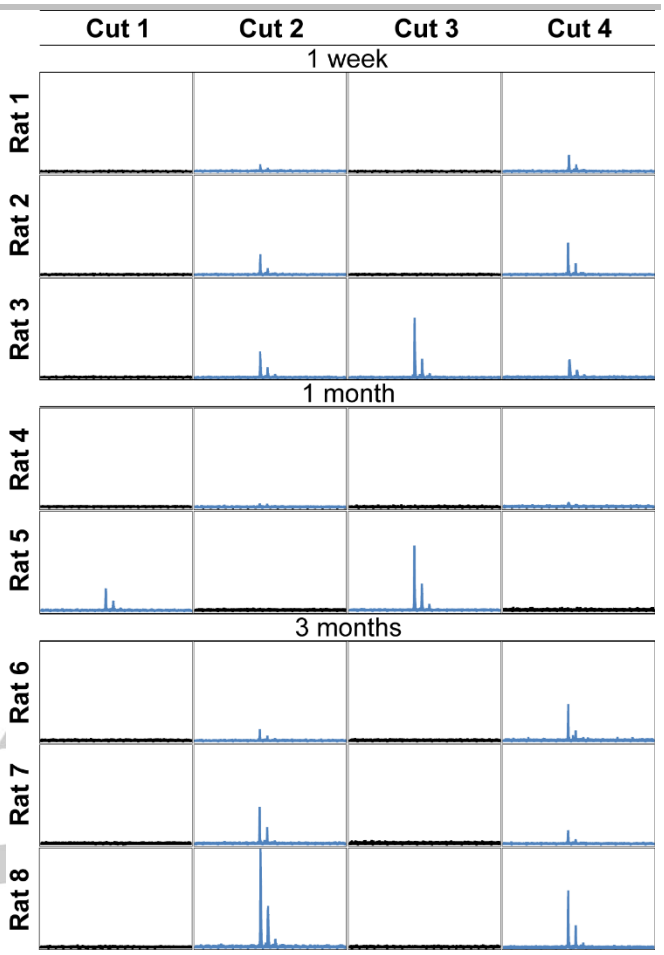

Figure 2. Normalized ESI mass spectra (expanded on the 1071-1091 *m/z* range) recorded for methanolic extracts of explanted PVA, showing that the oligourethane label was systematically recovered from tagged implants (as revealed by the whole isotopic pattern of the *m/z* 1079.7 anion, in blue) while it remained undetected from control non-tagged films (in black).

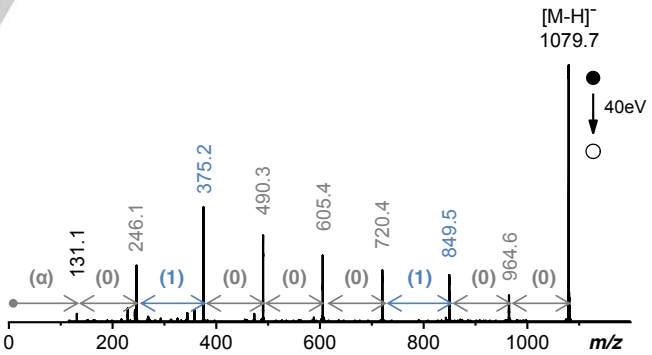

Figure 3. ESI-HR-MS/MS spectrum recorded for the oligourethane taggant α-01000100 after 3 months of *in vivo* implantation and selective extraction from the host PVA film. This particular spectrum corresponds to the film that was implanted in the subcutaneous cut 4 of rat 6 (Table S1 and Figure 2).

Importantly, the explanted PVA films were analyzed by ESI mass spectrometry. Prior to these measurements, the films were rinsed with water and dried. Afterwards, the methanol/ammonium acetate extraction procedure described above was applied. Extracts from both tagged and non-tagged films were analyzed. It should be specified that these measurements were conducted as a blind study. In other words, the mass spectrometry experimenters did not have hints about which film contained a

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taggant or not. Nevertheless, as shown in Figure 2, the oligourethane taggant was detected in all labelled films and undetected in all control films (Table S1). The *m/z* 1079.7 deprotonated oligourethane was measured with different abundances in mass spectra shown in Figure 2, as a result of different amount of membrane being extracted in each case. However, when relating this peak intensity (in arbitrary units a.u.) to the mass of the extracted membrane, the oligourethane MS response were similar (40-50 a.u./mg, on average). Furthermore, the coded sequence of the taggants could be recovered by MS/MS in all cases. For instance, Figure 3 shows a MS/MS spectrum obtained after three months of *in vivo* implantation. Very interestingly, after such a period of time *in vivo*, MS/MS analysis yields the same dissociation pattern as the one shown in Figure 1b, thus evidencing the robustness and usefulness of oligourethane taggants. Additionally, the sequence of the oligomer can also be decoded after *in vivo* implantation with the help of the MS-DECODER software. For instance, the analysis of the spectrum shown in Figure 3 required about 20 milliseconds. Comparable results were obtained for all tagged films after one week, one month or three months. Even at the lowest detection level (see for example Rat 4 in Figure 2), the coded sequence of the oligomer was efficiently decoded (Figure S9).

In summary, it was shown in this study that information-containing oligourethanes can be used as molecular taggants for the identification of implants. Such sequence-coded oligomers can be easily dispersed in plastic implants and applied *in vivo*. Quite remarkably, after several months of *in vivo* implantation, the taggant can be recovered and unequivocally decoded by mass spectrometry. Furthermore, the taggant did not induce toxicity or inflammatory tissue reactions in the host organisms. These new findings open up interesting perspectives for the development of traceable biomedical products, which could be useful for forensics and medical lawsuits. It shall be stated that the scope of utilization of the oligourethane taggants is definitely not limited to the model PVA materials tested in this work. Beyond this first proof-of-principle, personalized oligourethane taggants could be useful for the authentication of a wide variety of plastic implants, including intravascular stents, artificial heart valves, surgery screws and breast implants. Yet, for each new type of host material, taggant dispersion, storage, extraction and detection shall be carefully studied and optimized. Nevertheless, when used in small amounts, sequence-coded oligourethanes can potentially be included in a wide variety of host plastics. Therefore, the present results broaden the scope of applicability of so-called precision polymers.[21]

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Keywords: Sequence-controlled polymers • information-containing macromolecules • sequencing • anti-counterfeiting technologies • biomedical implants

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COMMUNICATION

Uniform oligourethanes, containing a defined information sequence, were included in crosslinked poly(vinyl alcohol) model films that were implanted in live rats. After three months of *in vivo* implantation, the tagged films were explanted and the coded sequence of the oligourethane taggant could be unambiguously identified by tandem mass spectrometry.

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