

Biocompatible, biofunctional bioresorbable polymers for temporary therapeutic applications: The Concept of Artificial Biopolymers

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Historically, the search for polymeric systems that can better respect living systems in applications requiring a biomaterial for a limited period of time, started in the late sixties with the development of the so-called "bioabsorbable sutures" based on glycolic and lactic acids. As early as 1974, J. Leray and myself became interested in the use of synthetic polymers derived from hydroxyl-2 ethyl methacrylate after the pioneering work of G. Winter who showed that sponges of the Hydron®-type promoted calcification *in vivo* (1). One of the shortcomings of this type of sponges was their poor mechanical properties and resistance to compression.

For the sake of circumventing this shortcoming, we came to the idea that degradable polymers could behave like a sponge, degradation forming pores schematically. Starting from earlier work dealing with sutures and mandibula osteosynthesis, we selected lactic and glycolic acid-derived aliphatic polyesters (PLAxGAY where x and y stand for the percentage of L-lactyl and glycolyl units, respectively) as candidates. However, after a short period of preliminary animal investigations with L. Sedel and P. Christel, it appeared necessary to revisit the polymerisation processes in order to improve very much both intrinsic mechanical strength and lifetime to match the requirements of osteosynthesis.

This period led us to select PLA98 for practical reasons that will be emphasised (2). The first application in human was performed in 1981, thanks to a traumatologist, Dr M. Audion. A company, Phusis, was created in 1984, thanks to A. Tornier, to develop bioresorbable materials for effective bone surgery. The commercial success came only on 1990 under the form of an interference screw (3).

It is later on that we justified this choice after the identification of the number of factors that affect the hydrolytic degradation of PLAGAY polymers, such as chemical, physical and configurational structures, polymerisation initiator and also size (4). From there, other devices were developed (5).

It is from the success of lactic and glycolic-derived polymers that we introduced the concept of artificial biopolymers, i.e. of non-natural bioresorbable polymers made of building blocks that are normally present in biochemical pathways and that generate metabolites upon degradation or biodegradation. Accordingly, degradation by-products are biocompatible and can be eliminated and/or bioassimilated via natural pathways.

As a consequence, we introduced polymers like poly(β -malic acid)s, poly(L-lysine citramide), poly(amino serinate and various copolymers (6), thus extending the fields of applications to functional bioresorbable polymers and polymer therapeutics, including drug delivery and drug targeting, domains that are still at the pioneering stage.

However, because of the high therapeutic potential of PLAGAY polymers, a demand appeared recently for methods aimed at modifying their intrinsic properties.

The anionic activation of aliphatic polyesters using lithium di-isopropyl amide (LDA) was introduced to make PLAGAY surfaces functional and to create novel artificial biopolymers from poly(ϵ -caprolactone). Functionalisation of lactic and glycolic-derived polymers was also achieved by introducing gluconyl residues by copolymerisation. This route provides a original means to perform chemistry on PLAGAY-type macromolecules (6).

Recently, we approached the field of tissue engineering starting from the point that matching the degradation rate of the scaffold with the rate of tissue growth or tissue reconstruction is a key factor. The strategy was applied to skin culture and reconstruction. Our first approach was based again on PLAGAY polymers. However, it was found that glycolic acid is unfavourable to keratinocyte growth whereas it does not affect the growth of other cell types. Once again PLAGAY appeared performing better in this type of application (7).

According to the same strategy, we recently challenged the problem of bioresorbable stenting of coronary arteries. It was shown that PLAGAY-based stent prototype can be implanted in rabbit according to angioplasty and stenting in human (8).

At the present time, the future of artificial biopolymers appears promising in surgery, in pharmacology and in tissue reconstruction. However, the most open domain is probably that of the medication of bioresorbable surgical devices made of artificial biopolymers and antibiotics, antitumoral agents, growth factors, etc., as already done with non-degradable polymers. A few more years are necessary to reach that ambitious stage.

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