Biomaterials science: Prospects for the new millennium?

It is my privilege as the chairman of the 15th European Conference on Biomaterials to introduce a selection of papers related to contributions to this event which took place in Arcachon (near Bordeaux, France) from September 8th to 12th 1999.

As the last meeting of the European Society for Biomaterials before the third millennium, this event provides a unique and symbolic opportunity to summarize what we have learned from the previous quarter of a century and the prospects which can be foreseen at the dawn of the new millennium.

Let us recall firstly that this period began with the birth of biomaterials science and covers its growth towards adult status. Undoubtedly, research on biomaterials was carried out before 1975 but it was not clear that the addition of materials science and biological sciences would be sufficient to fuel significant advances in the field. New concepts and new ways of thinking had to be developed before they became the core of this new science branch which we now call biomaterials science. As a proof of this slow evolution, let us recall that the word ''biomaterial'' was defined only in 1986; the same holds for the unique concept of biocompatibility, which means much more than biotolerance or bioacceptance.

As soon as a biomaterial is unable to release any toxic compound, whether the latter is a constitutive contaminant of the material or generated through biodegradation processes, its biocompatibility relies on a series of events which occur at the interface between its own surface and the host tissues. So it is imperative to keep these events under control, and in this respect, these events must be carefully analyzed as far as their mechanisms, kinetics and outcome are concerned. These events clearly involve molecular and cellular entities belonging to the host tissues on the one hand, and the ultimate surface of the material on the other, and the mediation of water, ions and other small solutes. This interaction is the rationale for the corpus of studies which are classically performed by biomaterials scientists: surface characterization including specific area determination and water wettability studies, protein adsorption, cell behavior including adhesion, growth, migration and differentiation studies. Obviously, the significant advances made during the last decade from methodological and technological points of view, have been beneficial to these investigations. On one side, surface morphology and chemistry can be investigated with more and more accuracy thanks to the development of different microprobes and, more recently, of the atomic force microscopies (AFM). On the other side, cell behavior can be explored at the molecular level, taking advantage of a better knowledge of the signal transduction pathways, and of the availability of molecular biology-based analytical tools. In addition, the confocal microscope allows the observation of ultrastructural features on the living cell, such as its cytoskeleton or focal adhesion sites.

Due to its complexity, biomaterials-tissue relationship is currently investigated with the help of experimental models. Here again considerable evolutions can be noticed; for instance, it is possible to design materials with a well defined surface micromorphology and/or microtopochemistry which makes possible studies of the influence of the local characteristics of a surface on the behavior of biological species involved in the material-biological medium relationship. As far as the latter is concerned, the biological medium is often modeled by cultured differentiated cells, which are obtained from sources and according to selection procedures which increase their relevance towards a desired representativity of a given tissue. In addition the co-culture of other types of cells to interact *in vivo* with a first type of cell increases the relevance of the models. *In vivo* models have been improved as well; in some cases, for instance, where the neovascularization of the implants must be favored, microsurgical techniques may be helpful to ensure a better blood supply to these implants.

In the last part of this introduction I would like to ''evoke'' a specific field of biomaterials science, namely tissue engineering, which has had a dramatic growth for the last ten or fifteen years, and which is expected to open new and fruitful perspectives for the development of efficient bioartificial tissues and/or organ substitutes and of artificial hybrid neoorgans or so-called organoïds which should be helpful to gene therapy. All these products rely upon the same concept which proposes to combine, in the same smartly engineered construct, one or several artificial components which can be either of natural or synthetic origin, and a cellular component. The artificial component may act as an immunoprotective structure which prevents direct contact and controls exchanges between a cellular component of heterologous origin and the host tissues; this approach applies, for instance, to the bioartificial pancreas. The artificial component may act as a host structure on which autologous cells are plated, or in which autologous cells are allowed to migrate and grow; in other words it is intended to play a role similar to that of the extracellular matrix of the tissue which is to be augmented or repaired with the help of the bioartificial substitute. This opportunity explains why numerous research groups focus their interest on the interactions between cells and the extracellular matrix on the one hand, and between cells and artificial matrices specifically designed in terms of structure and architecture to play the same role as its natural model on the other. They also focus their attention on the interactions between different types of

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cells within the same tissue, and in this respect design *in vitro* models which allow the co-culture of such different types of cells. Macroporous artificial matrices can be colonized by different types of cells, this being operated simultaneously but in specifically determined domains of the matrix, or sequentially (skin, vessel). So it appears that cultured cells which have been (and still are) used for a long time as an analytical tool to assess the biocompatibility of biomaterials, are also used to prepare bioartificial tissue substitutes, i.e., as a preparative tool. Such strategies have already found clinical applications; skin equivalents for heavily burned patients, and, more recently, autologous chondrocyte preparations for the repair of joint cartilage defects. But one of the pending issues is the identification of reliable sources of autologous cells, which must be collected without additional morbidity for the patients, and cultivated under conditions which allow them to keep their original phenotype. In addition, these cells can be genetically engineered in order to stimulate the expression of a specific protein or to down-regulate the expression of another one; this opportunity has to be considered positively, but raises ethical and biosafety concerns which are known by gene therapy specialists. Symmetrically, the latter are asking for implantable systems in which genetically modified cells could be hosted and go on expressing the protein (enzyme, hormone) which is missing to the patient, for a long time. Such systems must be biocompatible and open to neovascularization; in other words, they must satisfy requirements which are well-known by biomaterials specialists. No doubt that these two scientific communities will develop exchanges and cooperation in the future.

As one can see, new avenues are open to the development of biomaterials; beside their classical applications for the making of medical devices or the design of drug delivery systems, they will find new applications in cellular and gene therapy.

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