From Biocompatibility to Immune Engineering

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***Experimental Biology and Medicine* 2016; 241: 889–890. DOI: 10.1177/1535370216651367**

Studies of biocompatibility (understanding host response to a material) and immune engineering (modifying the host response, as in a DNA vaccine) would seem to be a natural progression of the field of biomaterials. These areas began in the 1970's and 1980's respectively, and have shown strong growth in published literature (Figure 1). However the most exciting advances have only come in the last few years as immune engineering research has taken the field out of the area of DNA vaccines and throughout all of immunology (Figure 1 inset). In fact, DNA vaccine publications have remained constant, and even declined, during the last few years, while the rest of the field of immune engineering has grown. We have assembled two special issues in *Experimental Biology and Medicine*, which we hope can serve as a state-of-the-art review of recent advances, suitable for experts in the field, as well as a primer for the novice to understand what areas are involved and gain a rapid understanding of how these different topics have come together.

Biocompatibility was a term first introduced in the literature in 1970, in an article by Homsy et al.¹ However the working definition of biocompatibility has been much harder to tie down. They range from the broad and simple definition by David F. Williams, 'The ability of a material to perform with an appropriate host response in a specific application';² to the ISO 10993 standard battery of *in vitro* tests which lead to extensive animal studies and eventual clinical trials.³ From both definitions it is easy to see that the term is highly complex and highly variable depending on both material and situation. This further shows why publications which point to one test (e.g. cytotoxicity assay, endotoxin assay, demonstration of cell attachment) and make claim to 'biocompatibility' are erroneous and can even be dangerous, without knowing the bigger picture.

Early studies in biocompatibility (termed here as Era I) were strictly observational, and passive in their approach. Essentially certain materials were being used clinically with only limited understanding why some failed in some applications and not in others. From these early studies quick and dirty rules were created about both the materials (e.g. some materials such as titanium and silicone seemed to have broadly favorable host responses), and about the applications (e.g. implants in oral tissues suffered fewer

complications than transdermal implants elsewhere). Once such observations were made, investigators entered Era II, and began to take more active approaches in biocompatibility studies, generating new materials with perhaps better biocompatibility profiles. During this Era, the literature showed a shift from basic science investigators who were investigating what it meant to be a compatible material, to applied investigators trying to determine whether their materials were compatible.

In a separate, but parallel, track the field of immune engineering grew from similar, albeit not such discrete, roots. While terms such as 'immune-engineering', 'immunoengineering', and 'immunobioengineering' are relatively new, the concepts of applying engineering strategies toward immunological challenges are much older. One early example is in the creation of DNA vaccines, where animal cells are introduced with genetically modified DNA to cause it to produce an antigen, resulting in an immunological response. While this research strategy was being investigated in multiple labs in parallel, it was first reported by Panicali et al. in 1983.⁴ Recent advances in 'Big Science', such as from the Human Genome Project, and high-throughput discovery-based research has led to an explosive advance in the field of immunology, facilitating advances in immune engineering.

The first published use of the term 'immunoengineering' was perhaps in an opinion piece in 2003 by Wendel et al.,⁵ where he broadly applied that term to both the area of vaccines (possibly all vaccines) as well as to stem cell transplantation and more specifically in the application of CAMPATH-1 antibodies to reduce Graft-versus-Host Disease in bone marrow recipients.⁶ In an era where translational research and intellectual property are gaining an equal footing with basic research, a quick search of US patents shows the earliest evidence of immunoengineering to occur in 2006, again in reference to the Wendel publication.

Even with all of this progress in DNA vaccine research, there are very few approved products. In the US a veterinary DNA vaccine to protect horses from West Nile virus has been approved;⁷ and abroad the only human DNA vaccine approved is IMOJEV, a Yellow fever virus-based vaccine to combat Japanese encephalitis virus.⁸ In fact, recent trends in

Figure 1 Histogram of Pubmed articles on various related topics. 'Biocompatibility' (blue) has shown as steady gain since its advent in 1970. 'DNA Vaccines' (red), one of the earliest topics in immune engineering showed steady early growth leading to a current plateau. 'Immune Engineering' (inset, orange), taking advantage of new discoveries in immunology, such as the heterogenous role different macrophages play, has shown a new resurgence in the field (A color version of this figure is available in the online journal)

publications on DNA vaccines have at best remained constant, although when compared to the total number of publications reported in that same time, their ratio has actually decreased. During that same time, however, the rest of the field of immune engineering has continued to grow as the field has moved from only using only T- and B-cells to discoveries in other areas (e.g. macrophages). The macrophage once thought to be a simple, homogenous cell, has grown in complexity from two types (pro- and anti-inflammatory), to four types or more.

It is understandable that this transition has sparked new interest in the field of biocompatibility, and changed what we believe we can do with implanted materials. This required moving from the study of T- and B-cells (the cells involved in cellular immunity, which are only modestly activated in the presence of a synthetic material, if at all) to the study of the macrophage, one of the major players in inflammation (particularly chronic remodeling that takes place in response to a biomaterial). With this emergence we have again seen a rise in the field of immunoengineering, paralleling the rise in the field of biocompatibility (Figure 1 inset). It is in this rise that the field of biocompatibility has entered its newest active phase, Era III, moving from actively changing material choice to elicit a better response to actively manipulating the host to modulate toward a preferred response.

We hope you enjoy the next two issues which we believe represent an excellent collection of reviews and basic research papers from senior investigators in the field to

young rising stars in the fields progressing from biocompatibility to immune engineering.

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