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In-utero transplantation (IUT) an experimental window into immune self: Basic and applied implications

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The discovery of common placental circulation between twins coupled with the development of erythrocyte profiling in cattle allowed Ray Owen to determine that dizygotic twins were chimeric with their sibling's blood cells after birth as a consequence of intermingling of sibling cells via the placental circulation. Thus, he concluded that self-tolerance is acquired during fetal development. Further, he concluded immune tolerance to self is not genetically determined or innate. Our laboratory has capitalized on these observations to achieve long-term engraftment of allogeneic and xenogeneic stem cells (SC) in sheep and mice following transplantation of SCs during a defined period in fetal development (i.e. IUT). The ease of achieving long-term engraftment and the observed extensive proliferative capacity of transplanted SC confirms Owen's earlier observations. To further understand this tolerance formation process, we performed parallel experiments testing both engraftment receptivity and immune cell ontogeny during fetal development. These studies identified the thymus as the organ responsible for self-tolerance formation. This process is temporally finite and occurs shortly after the thymus demarcates into cortex and medulla. Studies by Porada transplanting genes in utero and experiments by Rodewald using fetal thymic epithelial progenitors suggest that developmental acquisition of self-tolerance is a consequence of transient fetal thymic epithelial progenitor/cell receptivity, incorporation and expression of circulating antigens during a finite period following thymic demarcation. We term this the antigen exposure model. Implications with regard to IUT's ability to improve our understanding of immune reactivity vs. tolerance and potential in applied therapeutics will be discussed.

Biography

John Pixley is trained in Internal Medicine at Westchester County Medical Center and Rheumatology/ Immunology at SUNY-at-Stony Brook in New York. He has been on the faculty of the University of Nevada SOM as Director of the Rheumatology Division and Chief of Rheumatology at the VA Sierra Health Care System since 1987. His publications include experimental observations on in utero transplantation and clinical observations on extra-articular manifestations of rheumatoid arthritis. He serves on the editorial board of *World Journal of Stem Cells* and reviews manuscripts for *World Journal of Stem Cells*, *Clinical Rheumatology*, *Cytotherapy* and *World Journal of Immunology*.

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