

Correspondence

To Matrigel or Not to Matrigel

To the Editor-in-Chief:

Being in the business of axial vascularization and its application on tissue engineering and basic science for almost a decade, we still simmer with excitement every time a new publication from the Bernard O'Brien Institute of Microsurgery surfaces in the literature. In the article entitled "Angiogenic Growth Factor Synergism in a Murine Tissue Engineering Model of Angiogenesis and Adipogenesis,"¹ the authors present a well planned, well conducted study on the effects of vascular-related growth factors on adipogenesis and angiogenesis. They confirm that modulation of the assembly process is the result of a complex spatial and temporal interplay of signals and that to augment angiogenesis one has to avail oneself of several vasoactive molecules rather than one single substance. The use of Matrigel, however, prompts controversy, even when used as a factor-poor version. The authors themselves have shown it to be both adipogenic and angiogenic. Because it retains its adipogenic properties in this study, it is conceivable to believe that it retains its angiogenic properties as well. That would render it a black box for studies on angiogenesis. Using fibrin clots to perform similar studies, we have found a double benefit: use of fibrin gives rise to experiments with a clinical perspective^{2,3} because it is FDA approved (Matrigel, on the other hand, with the maximum thinkable likelihood, will never be granted approval), and the effects of vasoactive substances immobilized in fibrin are more readily attributable to the substances themselves rather than the matrix.⁴ We would also like to note that the effects of vascular endothelial growth factor/basic fibroblast growth factor are not species-specific in this setting, and the use of human recombinant variants of the growth factors produces equally vivid angiogenesis in our rodent model.⁴

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Author's Reply

Polykandriotis and colleagues have criticized our use of the murine extracellular matrix Matrigel (derived from the Engelbreth-Holm-Swarm sarcoma), in our recent study¹ and imply that we should have used the FDA-approved fibrin glue as the matrix in this mouse model. Their group has used commercially available fibrin glue in *in vivo* studies involving the rat arterio-venous chamber model.^{2,3} Their use of fibrin glue is not necessary to support angiogenesis in this rat model because an endogenous fibrin matrix forms between 0 to 3 days, nearly filling the chamber, and providing a proangiogenic scaffold that supports an intense angiogenic response in which 23% of the new tissue volume at 10 days is new blood vessels.^{4,5}

However, the murine model used by us (Rophael et al¹) differs somewhat from the rat model—it is based on the epigastric vascular pedicle and produces little endogenous fibrin. Therefore to create a mouse tissue engineering construct that will support adipogenesis and angiogenesis, we chose growth factor-reduced (GFR) Matrigel. Matrigel is widely used in *in vitro* studies, has been the subject of a number of *in vivo* studies on adipogenesis,^{6,7} and has been known to support angiogenesis since the work of Passaniti and colleagues.⁸ Two recent studies have described in detail the angiogenic process within Matrigel.^{9,10}

It is unclear what Polykandriotis and colleagues mean by stating that Matrigel "is a black box for studies on angiogenesis." Preliminary investigations by us in our mouse model with implanted myoblasts indicate that at 2 weeks the percent vascular volume of constructs with added natural fibrin scaffold (plasma clot harvested from

mice of the same strain) is $6.79 \pm 1.59\%$ and that of GFR Matrigel is $7.60 \pm 0.73\%$ (mean \pm SEM; Tilkorn D et al, unpublished observations). Thus, at least in the first 2 weeks, angiogenesis in GFR Matrigel is supported to approximately the same degree as in a biological fibrin scaffold.

It must be acknowledged, as Polykandriotis and colleagues suggest, that Matrigel is unlikely to receive FDA approval and that it is not a suitable option in human tissue engineering. Fibrin glue may be suitable in human tissue engineering as a carrier of cells or growth factors if its ability to support early vascularization is improved.^{5,11}

Matrigel is considered by many, including our group, as a legitimate research tool in studies of murine adipogenesis and angiogenesis. In using any extracellular matrix, its appropriateness to support the specific tissue being grown and its compatibility with the animal model must be considered. To this end our group is working on species-specific biological alternatives to Matrigel that will support adipogenesis.¹²

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