Development of a MR Compatible in vivo Angiogenesis Assay

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Introduction:
A reproducible in vivo angiogenesis assay that could be investigated with MR methods would be of significant value in
- Screening and evaluation of anti- and pro-angiogenic agents
- Investigating the influence of physiological factors upon angiogenesis
- Validating MR methods of assessing vasculature

The Matrigel angiogenesis assay has the advantage that quantification by histology is possible and reproducible (1). Matrigel as a component of an invasion assay has been imaged previously using MR (2). This study aimed to investigate whether MR methods could be used in conjunction with a Matrigel chamber assay to investigate angiogenesis in vivo.

Materials and Methods:
Matrigel implants (see figure 1) were prepared as described previously (3). The implants were allowed to remain within the animal from between 12 days and 4 weeks following sub-cutaneous implantation. For ex vivo samples, MR images were acquired using a 2 cm surface coil. For in vivo investigations, a home-built quadrature coil was used. All mice (n=12) were anaesthetised and positioned within the coil inside a SISCO 4.7T imaging and spectroscopy system. Gd-DTPA was administered via a cannulated tail vein. Images were acquired using a variety of spin and gradient echo sequences.

Results:
In all animals, high quality images of the Matrigel implants were obtained using standard 2D spin echo and 2D and 3D gradient echo sequences. Contrast enhanced dynamic MRI studies could also be performed as illustrated in Figure 2 where the enhancement appears heterogeneous and coincides with heterogeneous regions visible in the optical image.

Discussion:
This study showed that high resolution MR images may be obtained from the implants ex vivo and in vivo. The infiltration of the gel due to an angiogenic stimulus may be observed using T2 weighted imaging and may be quantified using the approach described previously (2). Here we show that vascular related information from the infiltrating vascular network could be obtained. The modeling of the contrast agent kinetic data to extract parameters such as vascular permeability and extracellular volume requires further investigation since such a model could be used to validate the MR methodology. In conclusion, the Matrigel implant model could, with refinement, be used to assess and quantify the effects of vascular-targeted agents. Furthermore, the model could also be used to investigate drug mechanism.

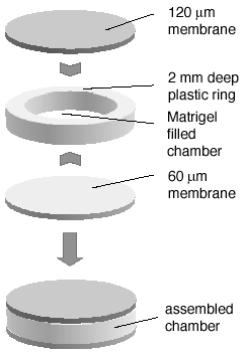

Figure 1: Schematic diagram of the Matrigel chamber

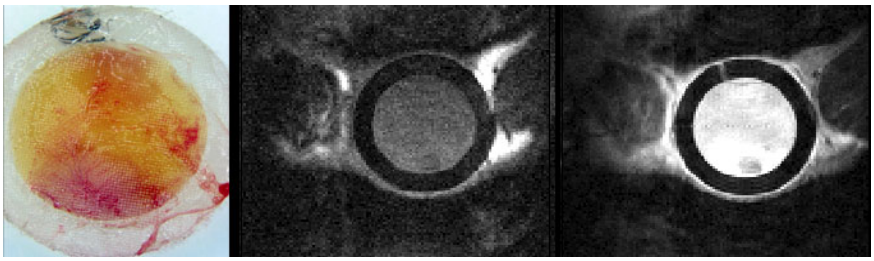

Figure 2: Ex vivo optical image (left) together with in vivo pre- (middle) and post- (right) contrast (Gd-DTPA, 0.5 mmol/kg) spin echo images of the same Matrigel implant. Note the heterogeneous enhancement with greater enhancement apparent in the same region where there is a larger area of red pixels in the optical image.

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