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MacuSIM: An *in-vitro* model of the outer retina as an experimental platform for macular disease and therapeutic trials

J. Arjuna Ratnayaka; David A Johnston; Ben Mills; Andrew J Lotery; Tracey A Newman; Savannah Amy Lynn

+ Author Affiliations & Notes

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Abstract

Purpose : The lack of an anatomical macula in widely utilised animal models led us to design an *in-vitro* system of the macula in a dish (MacuSIM). When fully developed, this will include salient elements of the outer retina including the RPE monolayer, Bruch's membrane and a vascular network with features of the choriocapillaris. Similarly, it incorporates a central avascular region to mimic physiological tension in macula RPE cells to model elements of cellular stress. Here, we test the hypothesis that MacuSIM recapitulates some key characteristics of the human macula and presents an improved platform for studying disease pathways linked with age-related macular degeneration (AMD).

Methods : Computer aided design was used to optimise models for manufacture using FDM 3D printing (PLA) and CNC machining (polycarbonate). CES EduPack evaluated fabrication substrate durability and biocompatibility in combination with LDH assays. Microvascular elements were produced by high-precision laser machining 2D 5-140µm channel networks into glass coverslips or CNC milling of PC, with surface finish and cell growth visualised by SEM. The co-culture/morphology of ARPE-19 transwells and HUVECs within channels was assessed by microCT and CD31, VWF, CD62E, VEGFR2, ZO-1, RPE-65 and Na^+/K^+ATPase immunofluorescence compared to control monocultures.

Results : MacuSIM was manufactured to the design in Figure 1, with PC and PLA identified as optimal substrates. These displayed normal cell growth, low LDH activity and cytotoxicity with HUVEC (p=0.89, 3.7%) and ARPE-19 (p=0.01, 7.4%). Similarly, ZO1 and CD31/VWF expression remained unaffected (p=0.17, p=0.8, p=0.22). SEM of

precision-etched microvascular channels confirmed cell growth and morphology along with staining for endothelial markers. Assessment of co-cultures by microCT demonstrated the seamless juxtaposition of all elements within the *in-vitro* model.

Conclusions : Using precision engineering techniques we developed an accessible *in-vitro* model that mimics features of macular physiology. Our approach enables reproducibility, standardised scalability and the set-up of identical systems elsewhere, which are amenable to studies and exploitation by the pharmaceuticals sector. This may be an attractive alternative to rodent models and could accelerate trials through rapid screening of anti-AMD compounds.

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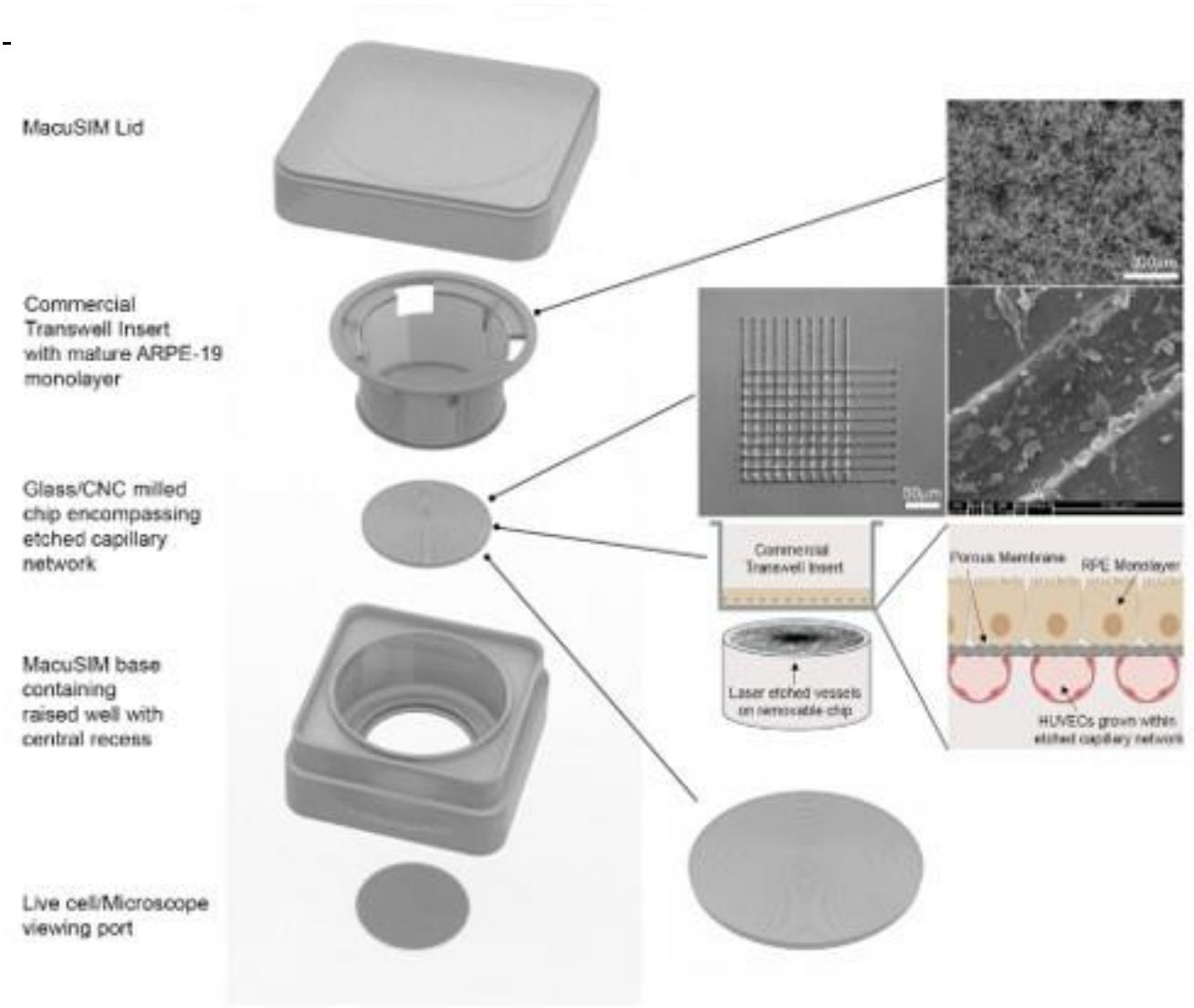

Figure 1: Component parts and assembly of MacuSIM.

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