Glomerulus-on-a-Chip. Life Up

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Organ-on-chip is an emerging technology for drug testing, disease modelling, and organ function modeling. Despite development of nephron-on-chip[1] and its components, such as proximal-tubule-on-chip,[2] glomerulus-on-chip has not been realized mostly due to lack of functional podocytes. To achieve this, Musah et al[3] obtained terminally differentiated podocytes from human induced pluripotent stem cells, through stem cell differentiation. Previously, podocytes were also generated in organoids obtained from amniotic fluid stem cells,[4] obtained from renal progenitors from urine,[5] from renal progenitors located in the Bowman's capsule,[6] and from human iPSCs using efficient protocol.[7] Myeloid cells with immunosuppressive features were recently developed from iPSCs to accompany iPSC-derived allografts to prolong their survival.[8] This may be integrated into the system in the future. Podocyte-like cells developed extensions and tight contacts resembling normal podocytes. In a microfluidic system, podocytes were cultured on one side of a laminin-coated membrane and endothelial cells on the other side (Figure 1). The system had also channels mimicking urine and blood flow. Production of basement-membrane collagen, tissue-tissue interface, and differential clearance of albumin and inulin were observed (99% of albumin was retained in the capillary side, whereas 5% of inulin was filtered to urinary side). In a renal injury model, podocyte disruption, loss of function, and death were seen. Neither podocyte cell-line conventional culture can mimic glomerular structure and function nor can animal studies always mimic human physiology. Alternatively, organ-on-a-chip can be precisely controlled and have high throughput. Although, authors argue that the system is not designed to engineer whole organ, it can be a part of *multiorgan-on-chip* or *human-on-chip* system to study multiorgan effect, secondary drug, and systemic toxicity. Ultimately, it may help replace animal testing, dialysis, or even organ function. By adding sensors and remote control, vast possibilities are open in the future for using data from *point-of-care diagnostic* microfluidic devices.[9] Personalized medicine can be advanced using a person's own stem cells with patient involvement in planned care. Regenerative medicine may benefit by using 3D bioprinting of developed podocytes. Global organs-on-chips market projection is US $6.13 billion by 2025.[10] Hence, the importance of this work is highlighted and greatly appreciated.

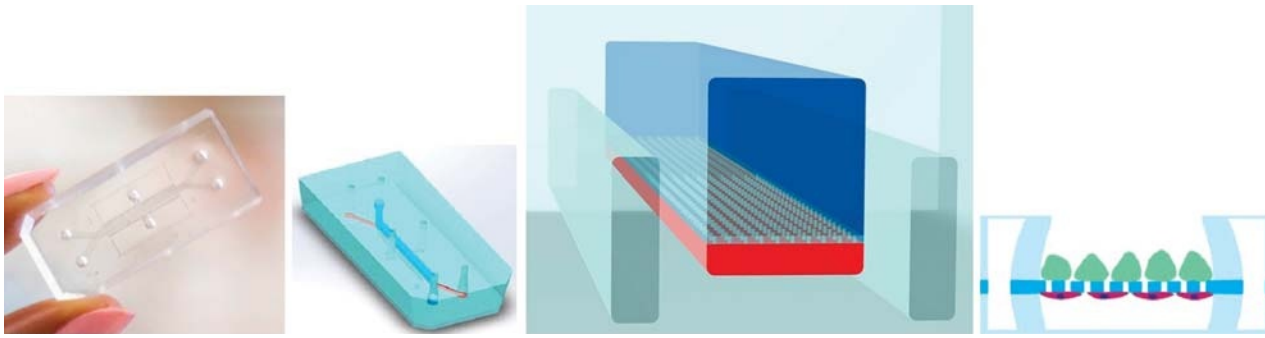

FIGURE 1. Arrangement of glomerular organ-on-a-chip microfluidic device. Photograph (left two) and schematic illustration (right two) of the device having microchannels replicating glomerular urinary and capillary compartments separated by laminin-coated porous and flexible membrane on which cells were cultured. Cyclic mechanical strain was applied by stretching the membrane using vacuum. Reproduced with permission from Xinaris C, Benedetti V, Novelli R, et al. Functional human podocytes generated in organoids from amniotic fluid stem cells. *J Am Soc Nephrol*. 2016;27:1400–1411.[4]

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Letter

Refractory Vascular Rejection in a Hand Allograft in the Presence of Antibodies Against Angiotensin II (Type 1) Receptor

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Although acute cell-mediated rejection is experienced by most hand transplant recipients, antibody-mediated rejection is rare. Antibodies against angiotensin II (type 1) receptor (anti-AT_1RAb) cause refractory vascular renal allograft rejection[1] and severe disease in systemic sclerosis.[2] We report a case of refractory vascular rejection in a hand transplant recipient in the presence of anti-AT_1RAb.

The recipient, presented 4.5 years posttransplantation during winter with a palmer rash and edema of the transplanted hand. A donor specific antigen (DSA) (A24 MFI 974) recorded pretransplantation, however, was undetectable 2 years later. Immunosuppression comprised tacrolimus (level, 4.9 ng/mL), mycophenolic acid 540 mg twice daily and prednisolone 5 mg daily. Biopsy revealed a dense perivascular $CD4^+$ T cell dermal infiltrate, intimal arteritis, and evidence of fibrin thrombus (Figure 1), C4d staining was negative. Rejection persisted despite systemic corticosteroids and antithymocyte globulin. A DSA (A24 MFI 1750) was recorded. Anti-AT_1RAb were detected before (14.7 U), 5 months (8.2 U), 2.5 years (6.7 U), after, and at the time of rejection (4.1 U). Clinically and histologically, the rejection resolved with plasma exchange (PLEX), intravenous immunoglobulin and angiotensin receptor blocker (ARB) therapy. Eighteen months later, anti-AT_1RAb titre remains low (2.1 U), and there are no DSA detected.

The recipient harbored a moderately high titre of anti-AT_1RAb pretransplantation. The classic features of

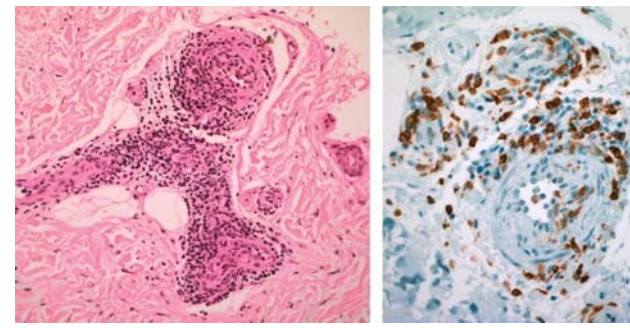

FIGURE 1. Punch biopsy of skin from hypothenar eminence 4.5 years posttransplant demonstrating a dense transmural lymphocytic infiltrate with endothelialitis and luminal fibrin thrombi (A). Haematoxylin and eosin stain. Original magnification, ×250. There is a predominance of CD4-positive lymphocytes (B). Immunoperoxidase stain for CD4. Original magnification, ×400.

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All authors were involved in the clinical management of this patient. K.M.D. oversaw the clinical management of this patient and wrote the article. R.C. provided clinical advice and wrote the article. P.H. interpreted histopathology and provided the images. S.B. provided clinical management and edited the article. C.B. provided clinical advice and edited the article. R.G.L. provided clinical advice and edited the article. W.M., lead surgeon, provided clinical input and edited the article.

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