COMBINING RENAL CELLS AND MICRO- AND NANOTECHNOLOGIES: A NEW ROUTE TO THE DEVELOPMENT OF BIOARTIFICIAL PLATFORMS FOR IN VITRO TESTING DRUG NEPHROTOXICITY

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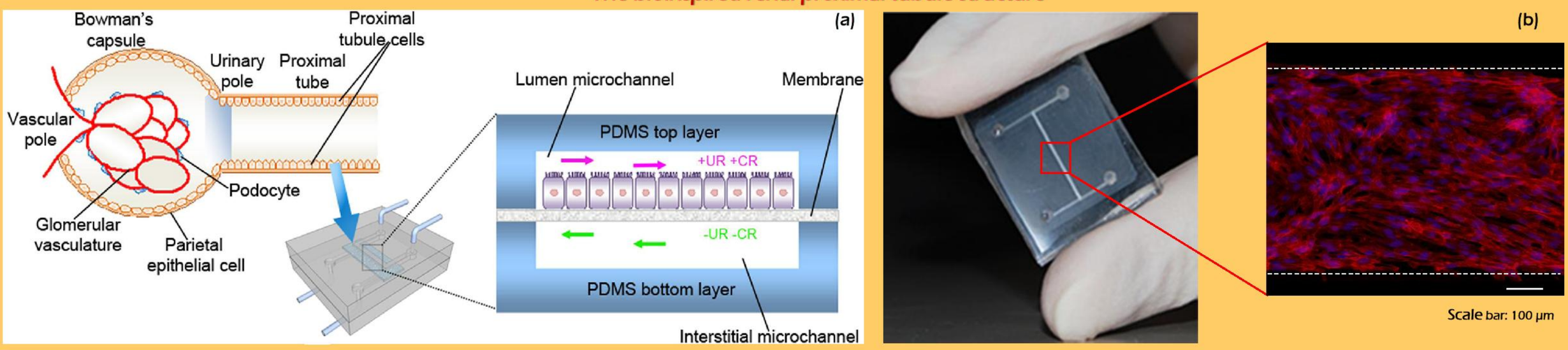
OBJECTIVES

The understanding of both physiological and pathological aspects of the different portions of the kidney may significantly benefit from the realization of miniaturized organ-on-chip devices (a), which, combining biological and engineering approaches, can mimic both the in vivo microenvironment and functions of renal cells. Here we propose the combination of adult renal progenitor/stem cells (ARPCs) with micro- and nanofabrication technologies to develop miniaturized, bioartificial proximal tubule-like platforms (b), which are very promising tools for next-generation bio-analytic assays and for studying the nephrotoxicity of drugs [1].

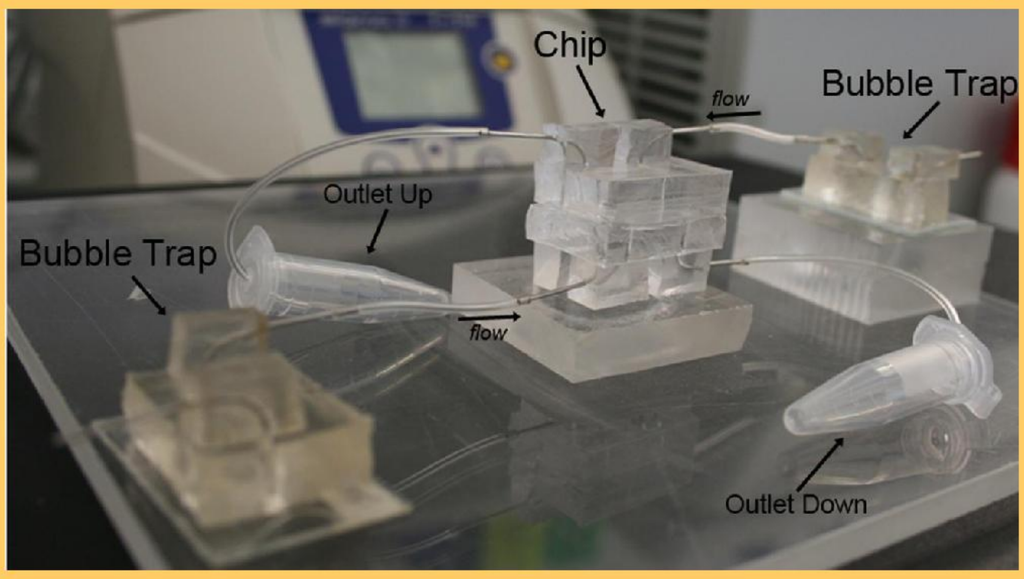
The bioinspired renal proximal tubule structure



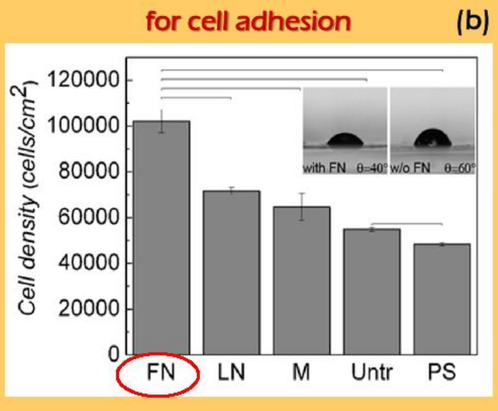
METHODS

Our class of devices is composed of overlapped elastomeric layers, embedding microfluidic connections, porous and functionalized membranes, and polymeric valves, as well as suitable pumps to control all the involved flows, besides living cells (a). All the tested experimental geometries are designed and realized to mimic the in vivo kidney structures, and specifically renal tubules. Employed microtechnologies include optical and soft lithography, and particular care is paid to ensure the biocompatibility of all the involved device surfaces. In the devices, functionalized membranes (b) are covered to confluence by living renal tubule cells (c).

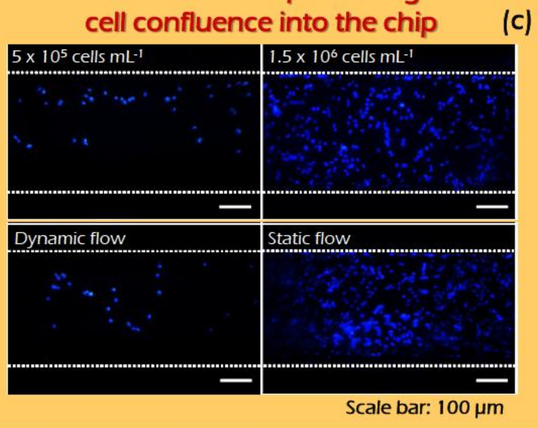
Setup of microfluidic biochip (a)



Membrane functionalization for cell adhesion (b)



Conditions for promoting cell confluence into the chip (c)

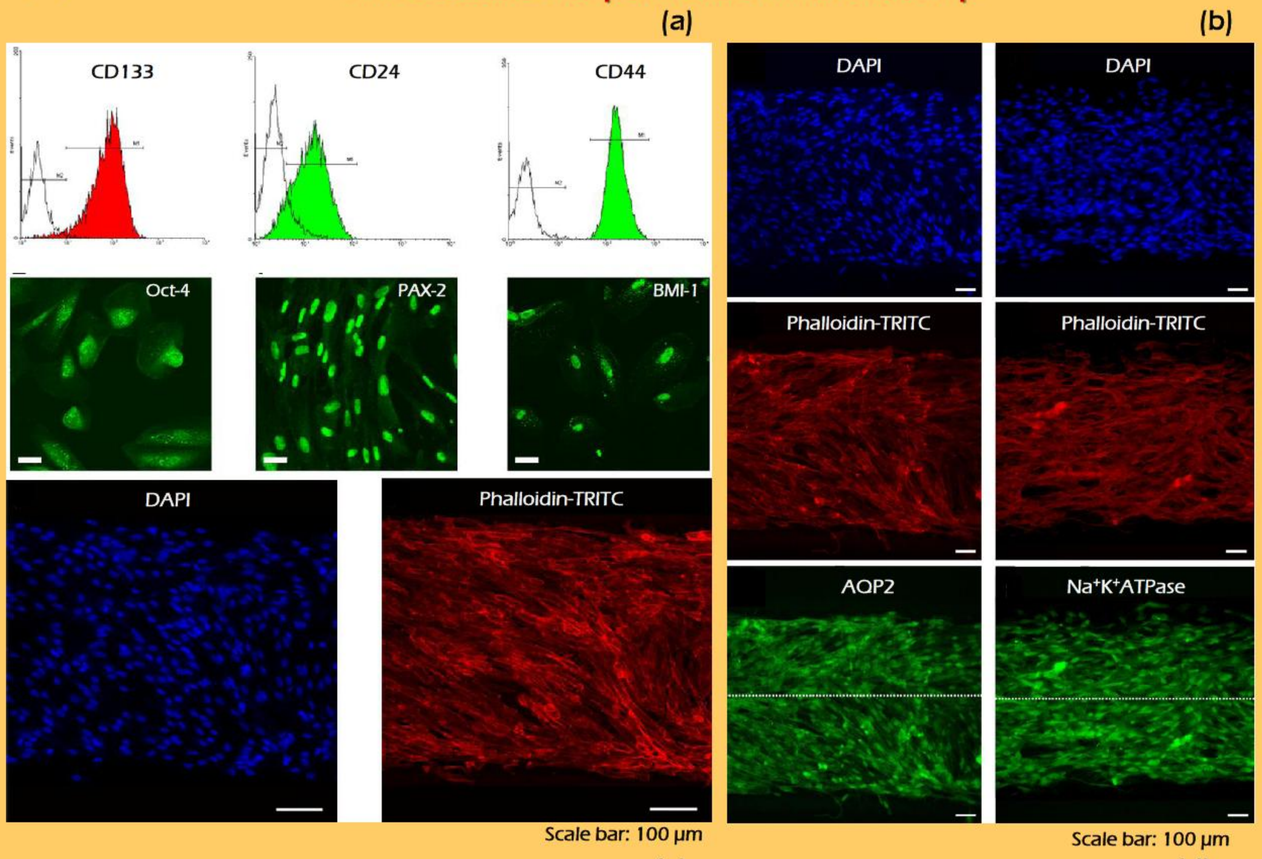


RESULTS

ARPCs extracted from the tubular portion of the renal cortex and characterized for renal stem cell markers are cultured into the device (a,b), where are exposed to a fluid shear stress (FSS) of about 0.2 dyn cm^{-2}. Urea and creatinine transport across membranes is studied in detail, and found to be modulated by the embedded cells up to permeability values of the order of 0.5 μm/s. (c). The on-chip induction of cell polarity in ARPCs exposed to FSS is characterized with apical and basolateral marker proteins (d).

ARPC culture and polarization in the biochip

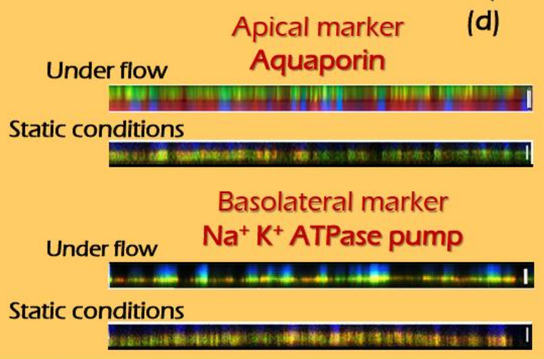
(a) (b)



(c)

Devices	Urea recovery (%)	Creatinine recovery (%)
With ARPCs cells	(20±5)%	(13±5)%
Without ARPCs cells	(64±7)%	(45±7)%

(d)



CONCLUSIONS

Bioartificial proximal-tubule like device platforms represent an interesting model for studying the nephrotoxicity of drugs by microfluidic approaches. The combination of cross-cutting technologies derived from complementary disciplines will certainly constitute a strategic pathway to implement novel bio-assays of remarkable nephrologic interest in the near future.

REFERENCES:

[1] Sciancalepore AG, Sallustio F, Girardo S, Gioia Passione L, Camposeo A, Mele E, Di Lorenzo M, Costantino V, Schena FP, Pisignano D. (2014) PLoS ONE,9: e87496.

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