

Human kidney patient-derived organoids are a promising tool for modeling drug-induced nephrotoxicity and for assessing preclinical toxicity of immunotherapy

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Introduction

Toxicology studies are essential to assess drug safety and represent a pivotal step of the preclinical drug development. However, advances in drug discovery are often hampered by the lack of suitable preclinical models that recapitulate the *in vivo* physiology of the tissue. For instance, findings in animal models are not always translatable to humans due to species specificity, and *in vitro* cell lines might display abnormal expression of the relevant targets, enzymes, and transporters. Lastly, primary human cells from tissue explants have limited availability and are unstable in culture. Thus, there is a compelling need for advanced *in vitro* preclinical models to address drug-induced toxicity, especially for organs most frequently affected by toxicity, such as the kidneys.

HUB Organoids[®] are innovative “mini-organs in a dish” derived from adult epithelial stem cells, which form 3D structures resembling the architecture of the epithelial tissue of origin and recapitulating the parental tissue physiology. They are genetically and phenotypically stable in culture and can be scaled up for screening purposes, providing a unique platform for toxicity studies.

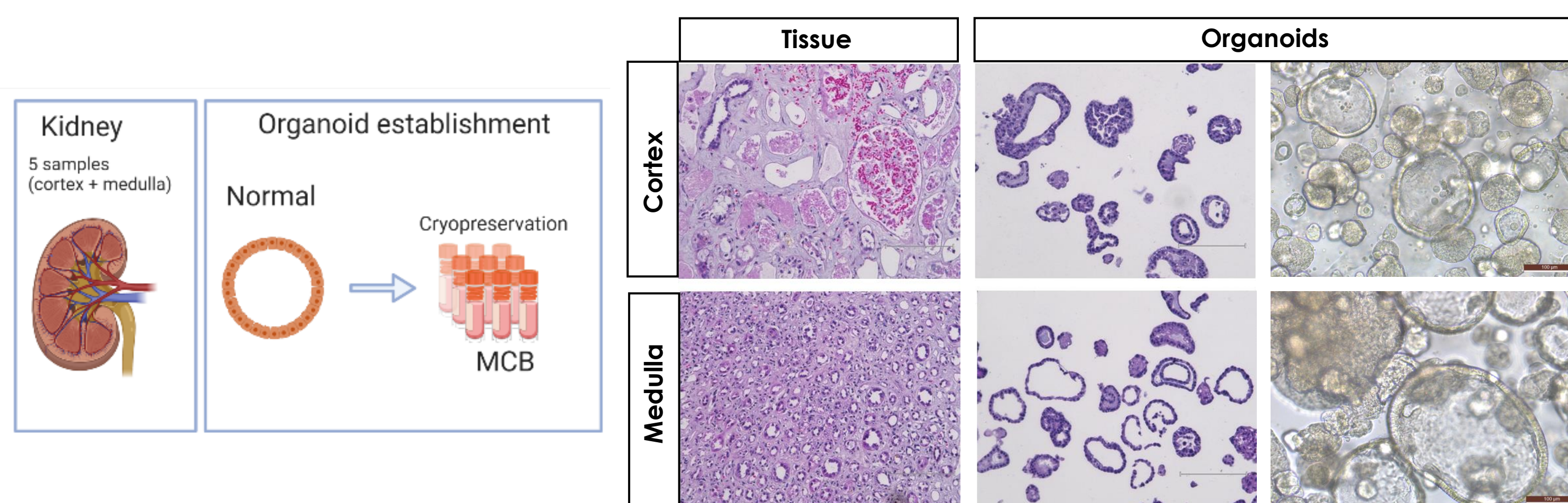
Here, we established kidney patient-derived organoids (PDOs) from the renal cortex, the portion of the kidney containing proximal tubules; these structures play a major role in eliminating waste products and can be particularly susceptible to drug-induced toxicity. For this reason, we employed our newly established models to assess the effect of known nephrotoxic compounds and to determine the safety profile of a T Cell Bispecific (TCB) antibody in a coculture assay with allogeneic T cells.

Methods

- Human kidney Organoids establishment according to proprietary technology
- Nephrotoxin viability screens using ATP-based and live-imaging readouts
- T cell coculture assay using live-imaging and cytokine release quantification

Establishment of human kidney organoids

Human kidney organoids were successfully established from both the renal cortex and medulla from 6 different patients.



Nephrotoxin viability screens in cortical PDOs

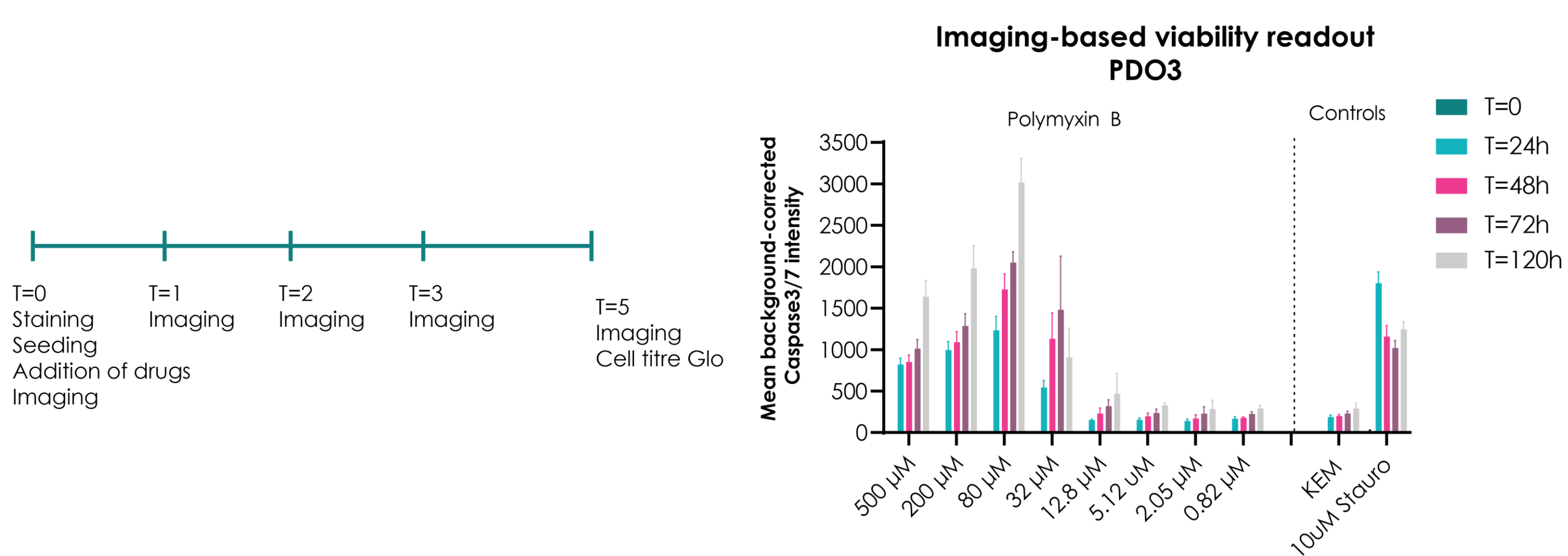
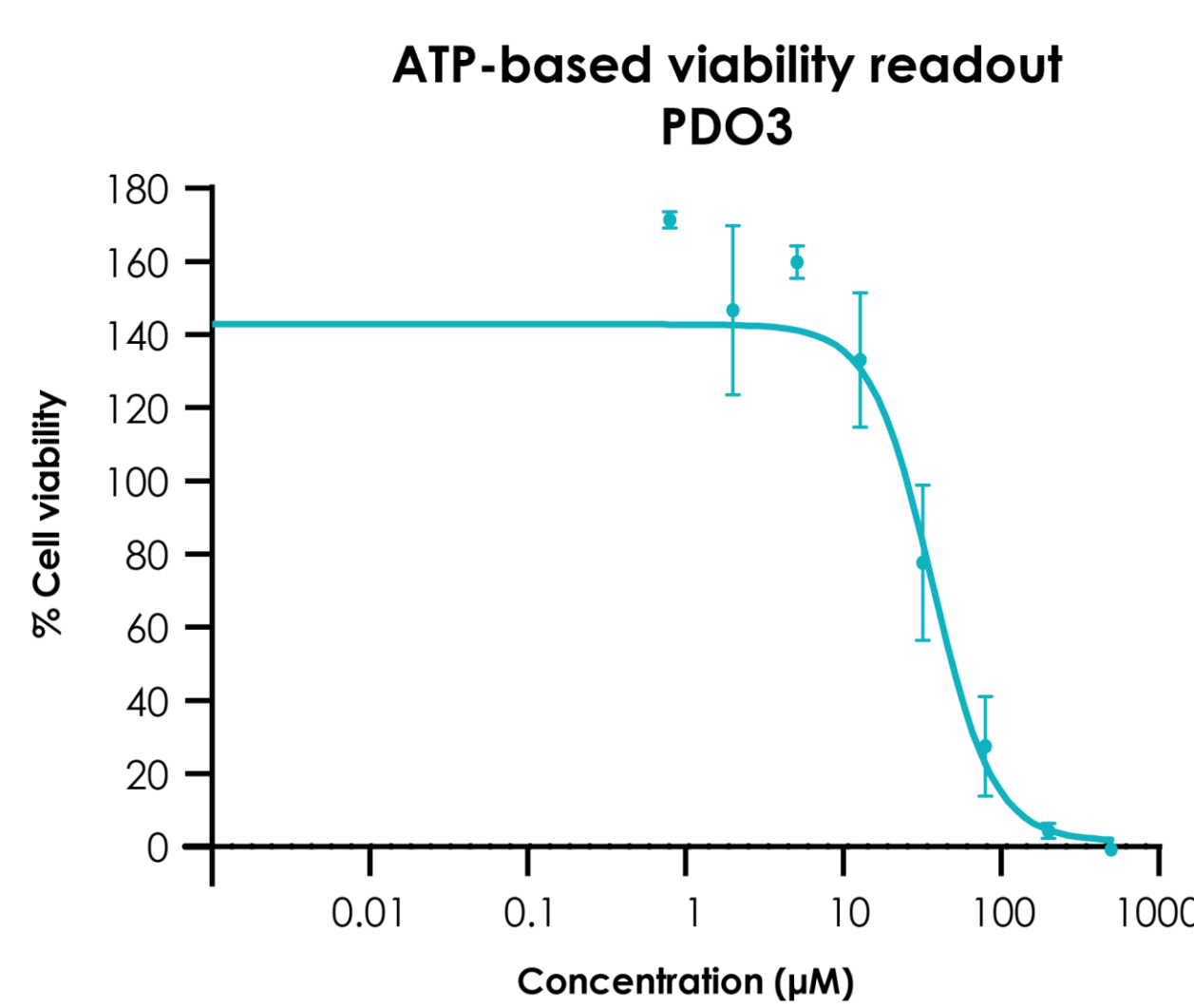


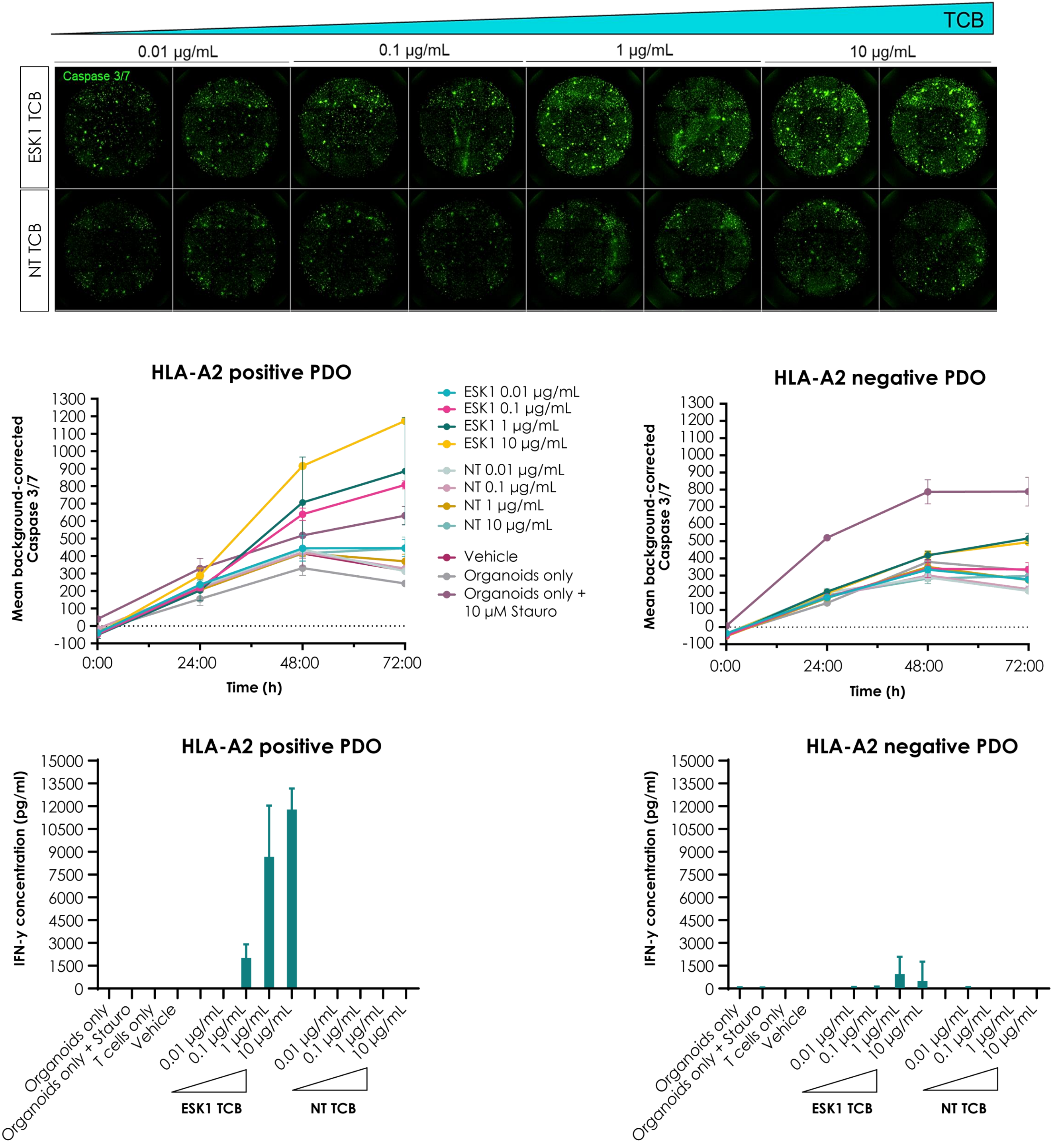
Table 01. IC₅₀ value for Polymyxin B in cortical PDOs

	IC ₅₀ (μM)	
	Rep. 1	Rep. 2
PDO1	45.8	44.9
PDO2	43.2	63.1
PDO3	36.7	-



- Consistent IC₅₀ values among different PDOs and experiments
- Analogous results from the ATP-based and Caspase3/7-based readouts

TCB titration in cocultures of cortical PDOs and T cells



- ESK1 TCB targeting the WT1 peptide presented by the HLA-A2 complex and CD3 led to increased organoid killing specifically in cocultures of HLA-A2 positive PDOs
- Increased IFN-γ (and Granzyme B) release specifically in cocultures of HLA-A2 positive PDOs
- No increased organoid killing, or cytokine release observed with a non-targeting (NT) TCB and in the cocultures of HLA-A2 negative PDOs.

Summary

Kidney organoids:

- Can be successfully derived from different kidney regions
- Can be employed in high-throughput screening assays for assessing drug nephrotoxicity
- Can be cocultured with allogeneic T cells for determining immunotherapy safety

Conclusions

HUB Organoids developed from patient-derived kidney tissue represent a promising model system for drug toxicity. HUB has developed a living biobank of kidney cortical PDOs that can be employed for large scale screening of nephrotoxic compounds as well as immunotherapeutics, providing a valuable *in vitro* tool to predict drug-induced nephrotoxicity and to assess preclinical immunotoxicity.

References

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