Abstract: Polymyxin B (PMB) is an antibiotic used to treat various gram negative bacterial infections. It is extremely nephrotoxic and frequently causes acute kidney injury and chronic kidney disease. To obtain an in depth understanding of polymyxin B’s toxicity in kidney proximal tubule epithelial cells, the Kidney on a Chip device was used to simulate proximal tubules in a 3D in vivo environment. The inside of the tubes in the Kidney on a Chip were coated with a collagen scaffold, then renal proximal tubule cells were injected into the device. A traditional 2D cell culture using immortalized MDCK (chicken) and LLC-PK1 (pig) cells was also made to compare results, and the safer alternative to those from the 2D culture. Deceased kidney tubule cells fell off the inside of the tube, and the viability of the cells increased as the antibiotic concentration decreased.

Background: Antibiotic resistant bacterial infections have been treated using polymyxin B (PMB). It is not commonly used because 30% of patients treated with polymyxin B experience acute kidney injury. The Kelly lab is working with a company that has developed a less nephrotoxic alternative to polymyxin B called NAB741. Its nephrotoxicity was compared to PMB in the 2D cell culture and the 3D Kidney on a Chip.

Introduction: The Kidney on a Chip
The kidney proximal tubule is the part of the kidney nephron that is responsible for the excretion of waste products and is the primary site for drug induced nephrotoxicity. The Kidney on a Chip is a 3D microphysiological system (MPS) that replicates the kidney proximal tubule. Cells in the Kidney on a Chip remain viable after long periods of time, the proteins responsible for absorptive and secretory transport still function, they respond to physiological stimuli, and perform biochemical synthetic activities.

Methods: 3D Device
- Collected and minced human kidney tissue from a nephrectomy.
- Isolated proximal tubule cells using the collagenase type IV enzyme.
- Dosed cells in devices with 50μM NAB741 and PMB with a cell media control at 5 μg/min, while they were being incubated at 37°C.
- Effluent was collected every 24 hours and frozen. Then it was tested for biomarker observed in treated cells and quantified.

Results: 2D Cell Culture:
- As the concentration of the antibiotics increases, the viability of the cells decreases.
- LLCPK-1: NAB741 is not as nephrotoxic.
- MDCK: Anomaly-PMB

3D Cell Culture: Red= Dead Cells (HO-1 kidney injury Biomarker observed in treated cells and quantified).

PMB:
- PMB (n=5), NAB741 (n=6), Control (n=4)
- As the drug concentration increases, more cells die until the viability becomes zero.
- NAB741 can be a lot more concentrated than PMB before it begins to kill cells

NAB741:
- NAB741 is less nephrotoxic than polymyxin B.

Control:
- The Kidney on a Chip is fully capable of producing accurate and more detailed data on nephrotoxicity.

Conclusion:
- NAB741 is a brand new alternative to PMB; we tested how its nephrotoxicity compares to PMB.

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Methods: 2D Cell Culture
- Plated MDCK and LLCPK cells at 100,000 cells per well.
- Dosed cells with 1000μg of PMB and NAB741 over 8 dilutions, for 24 hours.