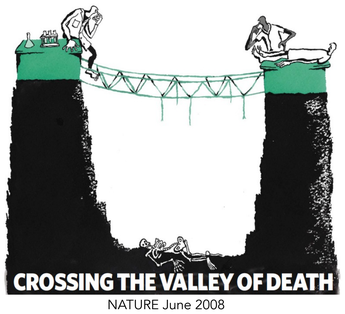
Back to the Future: Using Clinical Trial Design to Enhance the Utility of Preclinical Testing in Fibrotic Diseases

Yanling Zhang, Hai Wang, Linda Nghiem, Richard E. Gilbert, MatrileX Laboratories, Unity Health Toronto, Canada

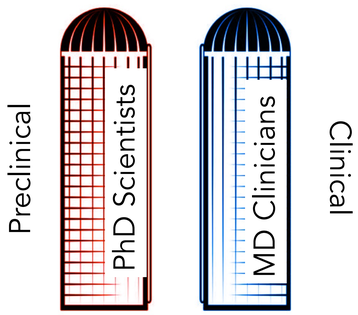
The Translational Gap in Antifibrotic Research

- High failure rates in fibrosis trials
- Preclinical models often lack clinical relevance
- Disconnect between model outcomes and patient endpoints



false +ve:
- huge $ loss at clinical phase

false -ve:
- lost opportunity for new therapies



Silos: Preclinical proof of concept and clinical studies are run separately by different groups with vastly different training and expertise

Models: often minimal relevance to humans

Outcomes: not directly relevant, 'cherry picked'

Lessons from Misused Model Systems and Outcomes

- UUO mouse ≠ human CKD

Limitations of UUO model

- Minimal/no clinical relevance
- No functional readout
- Local not systemic
- Exuberant, synchronous
- Misleading: +ve UUO, -ve clinical eg
  pirfenidone
  pamrevlumab (anti-CTGF)
  PPARδ agonists

- The Ashcroft Score: not clinically relevant to IPF

Limitations of Ashcroft score in lung

- Patchy Injury: uneven fibrosis and limited sampling skews Ashcroft scores.
- Scoring Limits: The semi-subjective scale misses total fibrotic area and distribution.
- Structure vs. Function: Histology shows damage; function tests show performance—often not correlated.

Applying Clinical Trial Principles to Preclinical Design

(1) Model. Choose an animal model that recapitulates, as closely as possible, its human counterpart.

(2) Outcomes. Select functional outcomes that reflect those evaluated in the clinical phase, e.g. in kidney fibrosis these should be attenuation in GFR decline (1° outcome), and reduction in albuminuria (2° outcome), while leaving the assessment of glomerulosclerosis and/or tubulointerstitial fibrosis as a 3° outcome.

(3) Prespecify. Outcomes should be prespecified a priori and not cherry-picked post hoc.

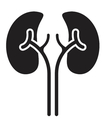
(4) Standard of care (SoC). Whenever possible, the efficacy of a new potential therapy should not only be tested alone but added to SoC as well.

(5) Controls. In many cases it is necessary to include a negative control rather than just vehicle. For instance, IgGs have generalized anti-inflammatory and thus anti-fibrotic actions that can lead to misinterpreting what are, in reality, merely non-specific effects of a mAb.

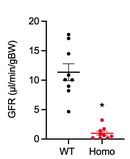
(6) Dosing. Much higher drug concentrations (usually many fold >IC_{90}) are often used in the ex-vivo setting than would be anticipated for their in vivo use. This can lead to false positive findings due to a lack of selectivity for the target.

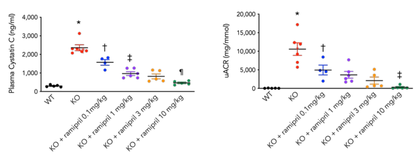
MatrileX Preclinical Models Predict Clinical Outcomes

Col4A3 mouse: model of CKD

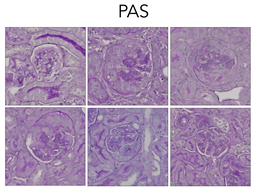


Sinistrin GFR

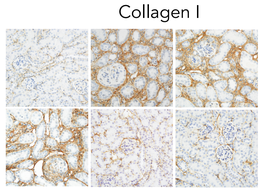




PAS



Collagen I



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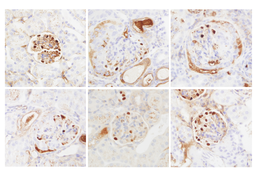
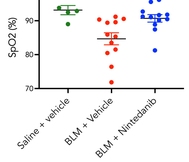
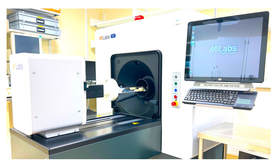


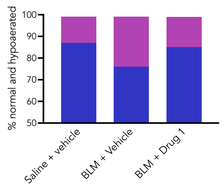
BLM mouse model of lung fibrosis

MouseOx® Plus

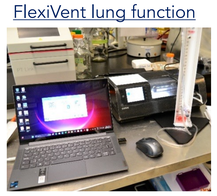


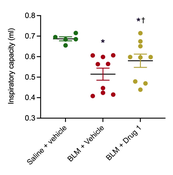
MILabs Micro-CT



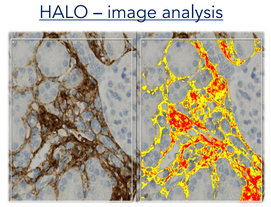


FlexiVent lung function



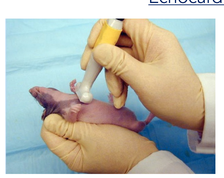


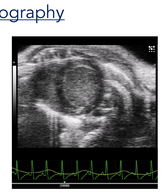
HALO – image analysis



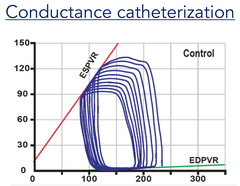
Cardiac fibrosis post – MI, TAC, PAB

Echocardiography





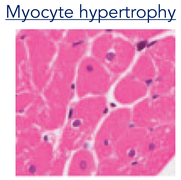
Conductance catheterization



CODA non-invasive blood pressure

Cardiac fibrosis

Myocyte hypertrophy



By aligning preclinical design with clinical trial rigor, we can reduce false leads, rescue missed opportunities, and accelerate antifibrotic drug discovery.

We are here to help!
yanling.zhang@unityhealth.to
Yanling@matrilex.com

MatrileX

UNITY HEALTH TORONTO