We examined two hypothetical cell-level mechanisms by which abnormal expression of cadherin-8 could initiate cyst formation: i) reduction of cell-cell adhesion, and ii) increased cell-cell binding cues, surface compartments representing adhesion molecules (Boucher and Sandford, 2004; Wilson, 2004). Drugs that perturb many of these known pathways have had promising experimental results, but to date, none have succeeded in translating from bench to bedside. Suppression of cyst emergence and growth will certainly involve some or all of these known pathways, but a need remains to identify an effective therapeutic approach. Cyst formation has been clearly demonstrated in PC knockout and knock-in animal models, and it is likely that the local changes in epithelial organization that lead to cyst formation. We do know that multiple cell-cell adhesion changes accompany cyst formation in ADPKD (Blaschke et al., 2002; Charron et al., 2000; Huan and van Alen, 1995, 1996). Fig. 2 shows epithelial characteristics that are specific to cyst neck (B) diameter. We hypothesize that this is the mechanism by which sildenafil reduces cyst growth in vitro and in vivo (in mice). We used CellDesigner software (ohara.org, Funahashi 2008) to build network diagrams and corresponding SBML models for inclusion in the VT model. This network will be linked with CompuCell3D (CC3D) through Systems Biology Workbench (SBW) for simulation and parameter tuning. The complete VT model will use CC3D as a “marshaling point” with CC3D as an integrator that runs the VT model, time steps the subcellular reaction networks in SBML (Andasari 2012) (and future whole body PBPK/SBML models), and transfers values between scales.

We examined two hypothetical cell-level mechanisms by which abnormal expression of cadherin-8 could initiate cyst formation: i) reduction of cell-cell adhesion, which then leads to changes in proliferation or ii) direct inhibition of contact inhibition of proliferation with no change in cell-cell adhesion. To test these mechanisms we built a 3D virtual-tissue (VT) computer model of the renal tubule using the CompuCell3D (CC3D) modeling environment (Beat et al., 2012). Our VT simulations predicted that cadherin-8 could initiate cyst formation, however only loss of adhesion simulations produced morphologies matching in vitro cadherin-8 induced cysts (Bielmonte et al., 2016).

We used genome wide expression screening to identify new signaling pathways changed in ADPKD.

Concurrently we tested pathway inhibitors on in vitro and in vivo cyst formation experimental models.

Conclusion

We have developed a practical and efficient approach using VT modeling for prediction of drug efficacy in inhibition of kidney cyst formation.

1) Define cell behaviors that drive tissue pathogenesis through paired Virtual Tissue simulations and biological experiments.

2) Identify signaling pathways that drive abnormal cell behaviors and link them into the VT model.

3) Identify existing drugs for reuse that affect these pathways.

We identified two common pathways altered in ADPKD tissues (Pan et al., 2004). As shown in Fig. 8, a) increased cell-cell contact is sufficient to inhibit proliferation. Potential cell-level modes of action of cad-8 knock-in TCs include: a) disruption of contact inhibited proliferation with no change in adhesion; b) increased adhesion between both WT-TC and TC-TC; c) increased TC lateral contact area; d) reduced TC lateral contact inhibition of proliferation with no change in adhesion; b) increased adhesion between both WT-TC and TC-TC; e) increased TC lateral contact area; (f) Reduced TC lateral contact inhibition of proliferation with no change in adhesion; b) increased adhesion between both WT-TC and TC-TC.