ImmunoTools IT-Box-Cy55M-Award 2013

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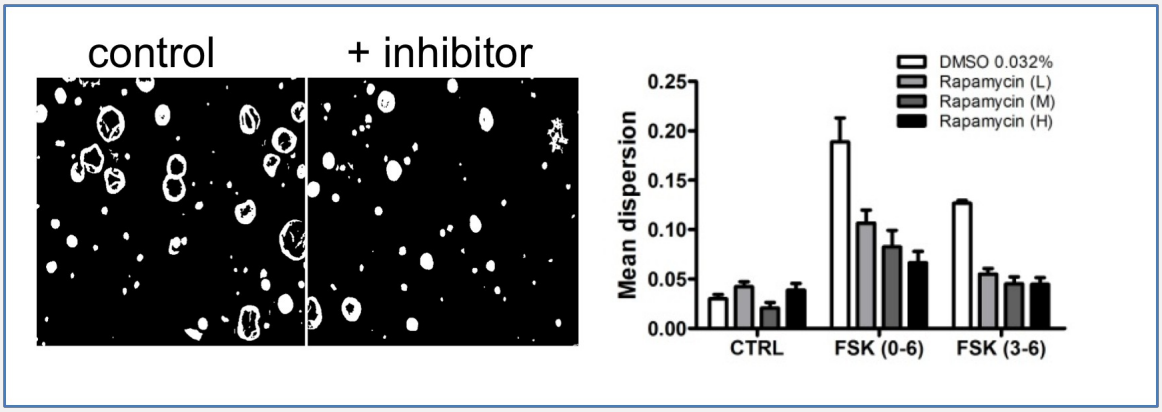
Identifying novel pathways for the treatment of polycystic kidney disease

Background to the project. Polycystic kidney disease (PKD) is a frequent inherited condition (incidence of 1:400-1000) and the major cause of renal failure, for which there is still no effective therapy. The disease is characterised by the formation of thousands of fluid-filled cysts in the kidney. The mechanisms underlying the disease are poorly understood It is thought that autocrine and paracrine signalling drive de-regulated fluid uptake into the cyst, driving cyst growth. Various different signalling pathways have been targeted to stop disease progression, but up to now, no cure has been identified and only the symptoms of the disease can be treated. Progress in the development of drugs to treat PKD has been held back by technological limitations; principally, conventional 2D *in vitro* assays do not adequately simulate the pathophysiology of the disease since cysts cannot form on tissue culture plastic. We have developed a high throughput 3D screening methodology that can recapitulate renal cysts *in vitro* and can be used to identify pathways involved in the proliferation of cyst epithelium and screen for drugs that affect cyst growth. This model uses an immortalised mouse kidney epithelial cell line derived from PKD $^{-/-}$ mice and was validated with test molecules that either stimulate (forskolin) or inhibit (rapamycin) cyst growth (see below).



The figure shows images of cysts cultured in 384 well plates in 3D with and without an inhibitor (rapamycin). Right is a quantification of the activation of cyst growth by an agonist (Forskolin, FSK) and inhibition by different doses of Rapamycin. This model will be used to screen the cytokine panel from ImmunoTools.

Project plan. To identify pathways that may be responsible for driving cyst growth in patients, we will screen the IT-Box-Cy55M cytokines from ImmunoTools to identify those cytokines (and consequently their cognate receptors and signalling pathways) that drive cyst growth. This will be done using our *in vitro* 3D cyst culture assay. When we have identified active cytokines and confirmed these, we will validate their importance with established inhibitors of the cognate receptors. If successful, this research will result in the identification of potential new drug targets and/or pathways for the treatment of this prevalent, incurable disease. These can be readily followed up and further validated using established pre-clinical models for PKD.

ImmunoTools IT-Box-Cy55M for Tijmen Booij
includes 55 recombinant mouse cytokines

rm EGF, rm Eotaxin / CCL11, rm FGF-a / FGF-1, rm FGF-b / FGF-2, rm FGF-8, rm Flt3L / CD135, rm G-CSF, rm GM-CSF, rm GRO-a / CXCL1, rm GRO-b / CXCL2, rm IFNgamma, rm IL-1alpha, rm IL-1beta, rm IL-2, rmIL-3, rm IL-4, rm IL-5, rm IL-6, rm IL-7, rm IL-9, rm IL-10, rm IL-11, rm IL-13, rm IL-15, rm IL-16, rm IL-17A, rm IL-17C, rm IL-17F, rm IL-19, rm IL-20, rm IL-21, rm IL-22, rm IL-25 / IL-17E, rm IL-27, rm IL-31, rm IL-33, rm IP-10 / CXCL10, rm LIF, rm MCP1 / CCL2, rm M-CSF, rm MIP-1α/ CCL3, rm MIP-1β / CCL4, rm MIP3α / CCL20, rm MIP3β / CCL19, rm NGF-beta, rm PDGF-AA, rm PDGF-BB, rm RANTES / CCL5, rm sCD40L / CD154, rm SCF, rm SDF-1α / CXCL12a, rm SDF-1β / CXCL12b, rm TNFα, rm TPO, rm VEGF DETAILS