RenaSci – Business Status

- Established in 2001 in BioCity, Nottingham
- CRO offering consultancy and specialised preclinical experimental services to the global pharmaceutical industry
- Key strength – *in vivo* pharmacology (90% of revenue)
- Part of the Sygnature Group since July 2018
- Complements the services of Sygnature Discovery which was founded in 2004 and is also based in BioCity, Nottingham
Sygnature Group Overview

- **Sygnature Discovery** provides high quality integrated or single discipline drug discovery support to pharma, biotech and not-for-profit organisations (from target validation to translational biology)
- Strong track record in drug discovery
  - 14 compounds delivered into the clinic (Phases I and II) since 2011
  - 13 compounds into pre-clinical development (excluding clinical compounds)
- 240 staff
  - 80% of scientists have PhDs
  - Considerable pharmaceutical industry R&D experience
- Private equity-backed company since September 2017
  - Senior management team are co-investors
  - Financially stable
  - Investment to fund expansion of capabilities & capacity

**Peak Proteins** - affiliated company provides protein production and crystallography

**RenaSci** - *In vivo* pharmacology expertise supports drug discovery & development
RenaSci – Overview

• We design, evaluate and validate biochemical and pharmacological techniques for use in drug discovery and development
• Experimental services focus on :
  – Abuse and Dependence
  – CNS
  – Obesity
  – Diabetes
  – NASH and Kidney Disease
• Key strength – *in vivo* studies including highly specialised animal models
• Consultancy offered on all aspects of drug discovery, preclinical and clinical development, regulatory approval, intellectual property protection and market positioning
• We have a successful track record in pharmaceutical R&D having assisted in taking >30 candidates into clinical development and 10 drugs to the market
• Our clients are from pharma, biotech, virtual companies and healthcare investors in UK, mainland Europe, Japan and USA
• We offer fee for service and FTE arrangements
RenaSci – Leadership

Executive Directors

- Sharon Cheetham, PhD
  Assistant Professor (Uni. Nottingham)

- Rob Jones, PhD, MBA

- David Heal, PhD, DSc
  Visiting Professor (Uni. Bath)
  Honorary Senior Lecturer (UCL)

Senior Vice President, Pharmacology

- Steve Vickers, PhD
RenaSci – Experimental Services

We work closely with our clients from study design through to study completion

• Experimental services tailored to meet specific requirements of each client including novel assay development if required
• State-of-the-art facilities
• Highly skilled and experienced team of over 30 scientists
• Data analysis by our fully-qualified statisticians
• Regular client updates from designated study director
• Flexible and responsive if studies change when in progress
• Agreed timelines
• Collection of samples for analysis by client or other CROs
  − For example, plasma and tissues for DMPK
• Necropsy and preparation of tissues for histology and immunohistochemistry
• Analysis of externally generated samples
• Data reporting from tabulated screening results to regulatory quality reports

Excellent reputation for reliability and high standard of work
Abuse and Dependence

Intravenous self-administration (IVSA)
- Wide range of reinforcers including stimulants, opioid agonists, nicotine and cannabinoid agonists
- Fixed and progressive ratio schedules
- ‘Break-point’ analysis to quantify the relative reinforcing effects of drugs

Drug discrimination
- Wide range of cues including stimulants, opioid agonists, dissociative anaesthetics, entactogens, hallucinogens and benzodiazepines

Tolerance and dependence
- 28 day on-dose/7 day withdrawal studies

Treatment of substance use disorders
- Use of procedures (eg IVSA) to assess novel treatments for substance use disorders including a rodent model of relapse to drug-seeking behaviour

Consultancy
- Study design and management
- Dossier preparation
- 8-factor analysis for drug scheduling
- Face-to-face meetings with FDA, DEA, EMA and other global agencies

ALTeC Abuse Liability Testing Collaboration
- Group of experts (RenaSci and Pinney Associates, USA) providing an integrated strategy for abuse liability testing in animals and man
CNS

**Ex vivo receptor binding**
- Novel assay development
- Biospace Beta-IMAGER™ technology for high-speed quantitative autoradiography

**Microdialysis**
- Multiple neurotransmitters in one study
- Analysis of drug concentrations in microdialysates (by pharm-analyt)
- Simultaneous microdialysis, blood-sampling and behaviour (Culex Bambino/Raturn)

**Evaluation of antipsychotics**
- Conditioned Avoidance Responding
- Prepulse Inhibition
- Reversal of amphetamine, PCP or MK-801 locomotor activity and stereotypy
- Reversal of DOI-induced head twitch
- Catalepsy testing
- Antipsychotic-induced weight gain
- Plasma prolactin levels

**Rat model of binge-eating disorder**

**Models of compulsivity & impulsivity**

**Other assessments**
- Irwin profile and rotarod (safety assessment)
- Neurotransmitter-specific functional assays
- Seizure testing
- Brain neurochemistry
Obesity

**Animal models**
- DIO mice
- High fat fed 'overweight' rats
- DIO rats (cafeteria diet)
- Genetically obese animals
  - *ob/ob* and *db/db* mice, Zucker rats
- Drug-induced weight gain

**Experimental measures**
- Acute and chronic feeding studies
- Behavioural specificity
- Energy expenditure (metabolic profiling using the TSE PhenoMaster)
- Plasma analysis (OGTT/lipids)
- Collection and analysis of urine
- Faecal fat analysis
- Body composition analysis (chemical analysis, DEXA, FoodScan)
- Energy content by bomb calorimetry (faeces/carcasses)
- Cardiovascular measurements
- Inhibition of gastric emptying

**In vitro/ex vivo assays**
- Lipolysis in adipose tissue explants
Diabetes

In vitro techniques
- Perifused pancreatic islets

Animal models
- Insulin resistance
  - Glucocorticoid-induced
  - DIO mice and rats
- Type 2 diabetes/diabetic complications
  - Genetically predisposed animals, for example, \( db/db \) mice, ZDF rats and ZSF1 rats
  - STZ-treated mice and rats on high fat diet

Experimental measures
- Glucose tolerance tests
- Plasma glucose, insulin, fructosamine
- HbA1c
- Plasma triglycerides, cholesterol, LDL-C, HDL-C, NEFA and leptin
- Urinary glucose excretion
- Pancreatic insulin content
- \( \beta \)-cell mass (performed out-of-house)
- Immunostaining for insulin and glucagon

Diabetic complications
- Diabetic neuropathy
  - Thermal pain sensitivity (Hargreaves test)
  - Mechanical allodynia (von Frey test)
- Diabetic nephropathy (see Kidney Disease)
NASH and Kidney Disease

Gene expression analysis
- Collection of tissues to examine changes in gene expression of key markers associated with inflammation, fibrosis and steatosis

Animal models of NASH
- Mice fed methionine and choline deficient (MCD) or choline deficient (CD) diets (6 weeks)
- Normal and genetically obese mice fed high-fat, high-fructose, high-cholesterol diet (12 weeks)

Experimental measures – liver function
- Plasma parameters (ALT, AST, ALP, bilirubin, adiponectin HMW/total)
- Liver parameters (weight, triglyceride, cholesterol, NEFA, collagen)
- Liver histopathology (steatosis, lipid deposition, hepatic ballooning, lobular inflammation, NAFLD activity scores, fibrosis)

Animal models of kidney disease
- Adriamycin-induced nephropathy (mice)
- Diabetic nephropathy (genetic models of type 2 diabetes; STZ-treated mice and rats on high-fat diet)

Experimental measures – kidney function
- Plasma parameters (urea, creatinine)
- Urinary parameters (volume, albumin, creatinine, protein, albumin/creatinine and protein/creatinine ratios, the clinical biomarkers TIM-1 and cystatin-C)
- Glomerular filtration rate (FITC inulin clearance test)
- Kidney weight and histopathology (tubular protein, tubular degeneration/regeneration, tubulo-interstitial inflammation, glomerulosclerosis)