Redx Pharma
(AIM: REDX)
Compelling opportunity to take targeted oncology and fibrosis medicines into clinic

ROCK2 selective inhibitors for the treatment of fibrosis

3rd Annual NASH Summit Europe
23-25 October | London
## Redx Pipeline

Highly selected, targeted small molecules for oncology and fibrosis

<table>
<thead>
<tr>
<th>Target/Product</th>
<th>Indication</th>
<th>Research</th>
<th>Preclinical (CTA/IND enabling)</th>
<th>Clinical (Phase 1)</th>
<th>Milestone Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncology</strong></td>
<td></td>
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<tr>
<td>Porcupine (RXC004)</td>
<td>Monotherapy in solid tumour (colorectal, pancreatic, biliary cancer) followed by combination with anti-PD-1/PD-L1</td>
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<td></td>
<td>Phase 1 mono safety completion &amp; start of Phase 2 mono expansion - <strong>H1 20</strong></td>
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<td></td>
<td>Phase 1 combo with anti-PD-1/PD-L1 safety completion – <strong>H1 21</strong></td>
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<td><strong>Anti-fibrotics</strong></td>
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<tr>
<td>Porcupine (RXC006)</td>
<td>Idiopathic pulmonary fibrosis (IPF)</td>
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<td></td>
<td>Clinic ready - <strong>H2 20</strong></td>
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<tr>
<td>ROCK2 selective</td>
<td>Non-alcoholic steatohepatitis (NASH) / IPF / Kidney disease</td>
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<td></td>
<td>Preclinical development candidate - <strong>H2 19</strong></td>
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<td></td>
<td>Clinic ready - <strong>H2 20</strong></td>
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<tr>
<td>GI-targeted ROCK</td>
<td>Crohn’s-associated fibrosis</td>
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<td></td>
<td>Partnering candidate</td>
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<tr>
<td><strong>Research</strong></td>
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<tr>
<td>Validated targets</td>
<td>Oncology and Fibrosis</td>
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<td></td>
<td>Partnered Pan-RAF inhibitor programme (ongoing milestones)</td>
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</table>

REDX Pipeline as of Oct 2019

NASH Summit Europe | October 2019
ROCK2 is a nodal point in cell signalling pathways associated with fibrotic diseases

- ROCK2 inhibitor PoC in human IPF trial
- Clinical response in lung scores in cGvHD
- ROCK2+/- protected lung fibrosis

- ROCK2 inhibitor = efficacy across multiple organs in cGVHD clinical trial
- ROCK2 inhibitors = ↓ fibrosis in skin (SSc) model
- ROCK2 conditional KO = ↓ hypertension, hypertrophy & atherosclerosis

- ↑ROCK2 in liver fibrosis and diabetic kidney models
- ROCK2 inhibition = ↓ liver fibrosis
- ROCK2 inhibition = ↓ kidney fibrosis
- ROCK2 haplotype KO = ↓ fibrosis in UUO model

- ↑ROCK2 in acute and chronic inflammation
- ROCK2 inhibitors shown to be anti-inflammatory in vivo
- ROCK2 inhibition protects from inflammatory damage in IBD models

ROCK2 inhibition could target many diseases, highlighted by clinical validation across multiple organs in cGvHD
Pan-ROCK inhibitors induce hypotension when dosed systemically in rats

- ROCK1/2 inhibitors deliver an anti-fibrotic effect in preclinical studies
- The pleiotropic effects of ROCK inhibition have previously raised concerns about on-target adverse effects such as hypotension limiting clinical development

Effect of a single oral treatment of azaindole 1 (0, 3, 10 mg/kg) on mean arterial blood pressure in normotensive rats. N=6, data are % change from baseline. *British Journal of Pharmacology* (2007) 152, 1070–1080.
REDX10178, Redx ROCK2 selective tool compound, has no impact on cardiac parameters in telemetered rats

- With REDX10178, Δ 5 mmHg (4%) mean blood pressure and 10-20 bpm (4-8%) in heart rate were observed which are not biologically significant.
- These data are consistent with clinical selective ROCK2 inhibitor KD025, that has shown no CV effects in clinical trials.

*Data are plotted LS mean ±SEM n=6 animals. Statistical effect of treatment analysed by one way ANOVA with Fisher’s LSD post test, compared to vehicle treated animals, *p<0.05.*
Redx ROCK2 inhibitors are potent and selective in biochemical assays

ROCK2 compounds have greater than 100-fold selectivity over ROCK1 in biochemical assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>REDX10178 IC₅₀ (µM)</th>
<th>REDX10616 IC₅₀ (µM)</th>
<th>REDX10843 IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical Activity ROCK2 [ATP 20 µM]</td>
<td>0.002</td>
<td>0.004</td>
<td>0.017</td>
</tr>
<tr>
<td>Biochemical Activity ROCK1 [ATP 20 µM]</td>
<td>0.2</td>
<td>3.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Fold selectivity ROCK2/ROCK1</td>
<td>90-fold</td>
<td>730-fold</td>
<td>150-fold</td>
</tr>
</tbody>
</table>

Note: data are all from n≥2; KD025: Kadmon’s ROCK2 selective compound.
Redx ROCK2 inhibitors are potent and selective in cellular mechanistic assays

- MCF7 cell line expresses both ROCK1 and ROCK2 isoforms (parental line)
- ROCK1 or ROCK2 was stably knocked down using shRNA to develop cell lines selective for each ROCK isoform
- ROCK inhibition in cells is analysed by the inhibition of pMYPT1, downstream of ROCK signalling
Redx ROCK2 inhibitors are potent and selective in cellular mechanistic assays

<table>
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<tr>
<th>Assay</th>
<th>REDX10178 IC$_{50}$ (µM)</th>
<th>REDX10616 IC$_{50}$ (µM)</th>
<th>REDX10843 IC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular activity ROCK2</td>
<td>0.9</td>
<td>1.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Cellular activity ROCK1*</td>
<td>20</td>
<td>&gt; 30</td>
<td>26</td>
</tr>
<tr>
<td>NanoBRET ROCK2 HEK-293</td>
<td>0.4</td>
<td>0.2</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Note: data are all from n≥2; ELISA MCF7 ROCK1 KD pMYPT1 T853 (ROCK2 selective); ROCK2 KD pMYPT1 T853 (ROCK1 selective); *Expect low activity for ROCK2 selective compounds. KD025: Kadmon’s ROCK2 selective compound.
Redx ROCK2 inhibitors reduce pro-fibrotic and pro-inflammatory activity of kidney mesangial cells cultured in high glucose

- Protein expression of secreted detected in the culture media
- High glucose stimulates a profibrotic phenotype in kidney mesangial cells
- Cells secrete growth factors and cytokines into the supernatant e.g. CTGF, PDGF-BB, TIMP-1 and MCP-1
- Redx ROCK2 inhibitors reduce pro-fibrotic and pro-inflammatory activity of kidney mesangial cells
Redx ROCK2 inhibitors reduce pro-fibrotic and pro-inflammatory activity of kidney mesangial cells cultured in high glucose

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<th>REDX10616 IC$_{50}$ (µM)</th>
<th>REDX10843 IC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotypic activity TIMP-1 Mouse mesangial cells</td>
<td>0.2</td>
<td>0.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Phenotypic activity PDGF-BB Mouse mesangial cells</td>
<td>0.2</td>
<td>0.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Phenotypic activity MCP-1 Mouse mesangial cells</td>
<td>0.3</td>
<td>1.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Phenotypic activity CTGF Mouse mesangial cells</td>
<td>0.4</td>
<td>0.4</td>
<td>1.5</td>
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</table>
Hepatic stellate cells are activated by stiff matrix and drive liver fibrosis

- Hepatic stellate cells (HSCs) differentiate to a myofibroblast like phenotype in liver fibrosis
- Increasing matrix tension is believed to be a major driver of HSC differentiation – perpetuating increased fibrosis
- ROCK signaling is central to the mechanosensing of the ECM tension that drives the pro-fibrotic response
- Increased expression of α-SMA and stress fibers are observed
- Activated and myofibroblast-like-HSCs secrete profibrotic cytokines and generate extracellular matrix (ECM)
In vitro liver fibrosis assay – HSC activated to myofibroblast phenotype

Experiment time course

- HSC cell line (LX2) cultured for 2-3 weeks on plastic to induce differentiation into myofibroblasts (LX2-MF)
  - Phenotype and activation status confirmed by expression of α-SMA
- No exogenous stimuli: cells are activated by matrix stiffness and autocrine factors
- LX2-MF are plated for assay and allowed 48-72 h to recover and re-organise stress fibres
- Redx ROCK2 inhibitors are dosed for 48 h and expression of α-SMA (with DRAQ5 as nuclear stain) is detected by immunocytochemistry
ROCK2 inhibitors reduce markers of fibrosis in human liver *in vitro* models

Selective ROCK2 inhibitors reverse the myofibroblast phenotype of activated human hepatic stellate cell myofibroblast

- Selective ROCK2 inhibitors suppress α-SMA in the LX-2 cells – suggesting a reversal of the myofibroblast like phenotype
- No toxicity was observed with compounds (up to 10 µM)

Expression of α-SMA detected by immunocytochemistry

Green: αSMA; purple: nuclei (DRAQ5)
REDX10843 is highly selective when tested against 468 kinases and in a CEREP SafetyScreen44 panel.

- 16 targets inhibited with more than 65% at 10 µM.
- Follow up IC_{50} determination shows that no target is likely to have significant potency in cells.

- No target inhibited more than 50% at 10 µM.
REDX10843 has a favourable ADMET profile and is orally bioavailable across preclinical species

<table>
<thead>
<tr>
<th>Feature</th>
<th>Values</th>
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<tbody>
<tr>
<td><strong>Solubility</strong></td>
<td>FaSSIF</td>
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<tr>
<td><strong>Microsomal stability</strong></td>
<td>$\text{CL}_{\text{int}}$ (µL/min/mg) – Mouse</td>
</tr>
<tr>
<td><strong>Hepatocyte stability</strong></td>
<td>$\text{CL}_{\text{int}}$ (µL/min/10⁶ cells) – Mouse</td>
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<tr>
<td><strong>Mouse PK IV (2 mpk)</strong></td>
<td>$\text{CL}$ (mL/min/kg)</td>
</tr>
<tr>
<td><strong>Rat PK IV (2 mpk)</strong></td>
<td>$\text{CL}$ (mL/min/kg)</td>
</tr>
<tr>
<td><strong>Dog PK IV (2 mpk)</strong></td>
<td>$\text{CL}$ (mL/min/kg)</td>
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<tr>
<td><strong>Cardiotoxicity</strong></td>
<td>hERG</td>
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<tr>
<td><strong>Mutagenicity</strong></td>
<td>Mini-Ames 5 strains ± S9 (plate based)</td>
</tr>
<tr>
<td><strong>Genotoxicity</strong></td>
<td>Micronucleus test using TK6 cells (± S9 metabolic activation)</td>
</tr>
<tr>
<td><strong>Cytotoxicity</strong></td>
<td>Hepatotoxicity assessment using HepG2 C3A spheroids $IC_{50}$</td>
</tr>
<tr>
<td><strong>CYP inhibition</strong></td>
<td>$IC_{50}$ (µM) – 8 isoforms</td>
</tr>
<tr>
<td><strong>CYP time dependent inhibition</strong></td>
<td>$IC_{50}$ Shift – 8 isoforms</td>
</tr>
<tr>
<td><strong>CYP Reaction Phenotyping</strong></td>
<td>7 isoforms</td>
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</table>
REDX10843 demonstrates therapeutic anti-fibrotic efficacy in multiple tissue types

**Lung**
REDX10843 was dosed therapeutically in the murine bleomycin induced lung fibrosis model at 50 mg/kg BID
Pirfenidone was used as positive control and dosed at 100 mg/kg BID
Oropharyngeal administration of 1.5 U/kg bleomycin on day 1, compound dosing initiated from day 7-21

**Kidney**
REDX10843 was dosed therapeutically in the unilateral ureteral obstruction (UO) murine model at 50 mg/kg BID
Surgery performed on day 0, compound dosing from day 6-11

**Liver**
REDX10843 was dosed therapeutically in the murine STAM NASH model at 50 mg/kg BID or 50 mg/kg QD
Telmisartan was used as positive control and dosed at 10 mg/kg QD
STZ administration at day 2, HFD induced from week 4, compounds dosed weeks 6-9
REDX10843 suppresses fibrosis in murine bleomycin-induced IPF model

**Reduced fibrosis and collagen deposition in the lung**

- Significantly reduced fibrosis (Ashcroft score) and collagen deposition (Masson’s trichrome) with REDX10843
- Pirfenidone used as positive control

**PD lung gene expression**

- Highly significant reduction in pro-fibrotic and pro-inflammatory gene expression in the lung
- Reduced plasma and BAL expression of PD biomarkers

**Plasma PD biomarkers**
REDX10843 reduces kidney tubular damage and fibrosis in UUO model

Protection from tubular damage and atrophy and reduced collagen deposition with REDX10843

• Enhanced tubular cell survival and reduced damage as measured by auto-fluorescence
• Reduced collagen deposition as measured by Masson’s trichrome & Sirius red
• Reduction in gene expression markers of tissue injury, inflammation and fibrosis

PD gene expression in kidney

Gene

- MMP2
- Nephrin
- IL-1β
- TNFα
- IL-6
- MCP-1

Reduction from vehicle (%)

REDX10843 50 mg/kg BID
REDX10843 suppresses fibrosis in murine STAM NASH liver model

**REDX10843 reduced collagen deposition in the liver**

![Graph showing Sirius Red (collagen I/III) positive area (%) for different treatments.]

- **Sirius Red positive area (%)**
  - Control
  - Vehicle QD
  - Vehicle BID
  - REDX10843 50 mg/kg QD
  - REDX10843 50 mg/kg BID
  - Telmisartan 10 mg/kg QD

**REDX10843 reduced profibrotic fibroblasts in the liver**

![Graph showing Reticular fibroblasts (ER-TR7) positive area (%) for different treatments.]

- **Reticular fibroblasts** produce and deposit collagen III in the liver, positive cells determined by automated quantification
- **Significant reduction of pro-fibrotic fibroblasts** in the liver when REDX10843 dosed QD or BID
- **Significant reductions in both liver collagen quantity and bridging fibrosis with QD and BID dosing**
Redx ROCK2 inhibitor programme summary

• Selective inhibition of ROCK2 is an exciting approach to target fibrosis
• Redx series has good preclinical profile
  - Potent and highly selective ROCK2 inhibitors against ROCK1 and against a panel of kinases and other receptor targets.
  - Redx ROCK2 inhibitors suppress pathways associated with fibrosis in \textit{in vitro} kidney and liver models.
  - Demonstrated CV safety in telemetered rats with REDX10178.
  - No safety issues observed in preliminary \textit{in vitro} studies (cardiotoxicity, genotoxicity, mutagenicity, CYP profile).
• Early PK/PD evidence of target engagement of physiologically relevant pathways for fibrosis.
• Robust preclinical efficacy demonstrated with REDX10843, a lead from the series, in murine liver, kidney and lung fibrosis models
• Currently profiling our lead compound for candidate selection by end of 2H2019 (undisclosed data)
Acknowledgments

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- Katie Anderson
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- Rebecca Taylor

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- Gayle Douglas
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- Neil Hawkins
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- Sam Smith

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- Peter Bunyard
- Clifford Jones

Thank You