Pharmaceuticals & Biotechnology

Source: Eikon Thomson Reuters

Market data	
EPIC/TKR	REDX
Price (p)	7.2
12m High (p)	23.7
12m Low (p)	3.5
Shares (m)	126.5
Mkt Cap (£m)	9.1
EV (£m)	3.5
Free Float*	69%
Market	AIM

*As defined by AIM Rule 26

Description

Redx Pharma (REDX) is focused on the discovery and development of proprietary, small molecule therapeutics to address areas of high unmet medical need, in cancer and fibrosis. The aim is to develop putative drugs through early trials and then to partner them for late-stage development and commercialisation.

Company information

CEO	Lisa Anson
CFO	Dominic Jackson
Chairman	Iain Ross

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Key shareholders

Directors	0.5%
Jon Moulton	18.2%
Seneca Partners	12.5%
AXA	9.8%
Aviva	8.4%
Paul & Thelka Blackmore	4.0%

Diary

19 Dec	Full-year results
1H'19	Resume Ph. I with RXC004

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REDX PHARMA

ROCK2 inhibitors in chronic kidney disease

REDX's new management team is continuing to focus its financial resources on progressing lead candidates in oncology and fibrotic disease into the clinic. An extensive internal review, led by the new CEO Lisa Anson has reinforced the vision of a streamlined pipeline in these two disease areas, with the aim of progressing drug candidates to deliver clinical proof-of-concept. 2019 is expected to be a busy year for REDX, with several major milestones due. Meanwhile, REDX has disclosed, for the first time, the profiles of its ROCK2 inhibitors in *in vitro* and an *in vivo* kidney damage model, showing potential best-in-class results.

- **Strategy:** REDX is focused on the discovery and early clinical development of small molecule therapeutics in oncology and fibrotic disease. It is also focused on taking assets through proof-of-concept clinical trials and then partnering them for late-stage development and commercialisation.

- **Poster presentation:** REDX's poster at the American Society of Nephrology in San Diego, presents, for the first time, the profile of its ROCK2 inhibitors. *In vitro* and *in vivo* data show selective modulation of markers of fibrosis pathways through ROCK2 inhibition, with no cardiovascular safety concerns.

- **ROCK2 programme:** REDX is primarily investigating the effect of ROCK2 inhibition in fibrotic diseases (including IPF), with CKD an area of secondary interest. The ROCK2 programme is expected to enter preclinical development in 2H'19 in non-alcoholic steatohepatitis (NASH), and then the clinic in 2H'20.

- **Risks:** After a difficult period, REDX has emerged in much better shape. While all early-stage pharma/biotech companies carry substantial risks and are capital-intensive, the rewards can be substantial, as evidenced by the successful disposal of the company's BTK programme for $40m in cash in 2017.

- **Investment summary:** The strengthened management team is moving forward with a revised business plan that focuses cash resources on progressing its drug leads in oncology and fibrotic disease to proof-of-concept early clinical development. Big pharma has been shown to pay handsome prices for novel and/or de-risked assets with clinical data, reinforcing REDX's strategy. This can generate good returns and shareholder value for companies such as REDX.

Financial summary and valuation

Year-end Sep (£000)	2015	2016	2017	2018E	2019E	2020E
Other income	2,648	2,380	1,291	1,000	1,000	1,000
R&D investment	-9,463	-14,315	-13,000	-6,528	-11,078	-11,410
SG&A (corp. cost)	-2,008	-2,212	-5,698	-3,150	-3,276	-3,407
Underlying EBIT	-8,823	-14,147	-17,407	-8,678	-13,354	-13,817
Underlying PBT	-9,112	-14,606	-17,737	-8,648	-13,327	-13,817
Statutory PBT	-8,825	-15,407	1,646	-9,240	-13,547	-14,057
R&D tax credit	650	637	-118	392	665	685
Underlying EPS (p)	-14.6	-17.8	-15.8	-6.5	-8.8	-8.2
Statutory EPS (p)	-14.1	-19.8	1.4	-7.0	-9.0	-8.4
Disposals	0	0	30,474	0	0	0
Net (debt)/cash	7,436	3,758	23,806	5,595	2,718	-10,382
Capital increase	13,447	9,296	11,066	0	10,000	0

Source: Hardman & Co Life Sciences Research

ROCK2 in chronic kidney disease

In the recent *poster* entitled "ROCK2 inhibitors for the treatment of chronic kidney disease", presented at the American Society of Nephrology (ASN) Kidney Week 2018 in San Diego, CA, on 25 October, REDX gave an update on its ROCK2 programme. While the prime focus of the ROCK2 research programme is on non-alcoholic steatohepatitis (NASH), the poster provides the first disclosure of REDX's ROCK2 selective compounds, with *in vitro* and *in vivo* data demonstrating the inhibition of pro-fibrotic factors in a model of acute kidney injury, engaging pathways also associated with chronic disease. Chronic kidney disease (CKD) is a potential second opportunity for the ROCK2 programme. REDX presented a direct comparison between its two lead molecules – REDX10178 and REDX10325 – with KD025 in *in vitro* assays. We note that Kadmon's ROCK2 inhibitor KD025 is currently in Phase II trials in multiple indications, including idiopathic pulmonary fibrosis (IPF).

The key messages from REDX's ROCK2 inhibitors are:

- potent inhibition of ROCK2 with an excellent selectivity against ROCK1 and other kinases;
- bioavailable, with a suitable pharmacokinetic and cardiovascular safety profile;
- inhibition of the expression of pro-inflammatory and pro-fibrotic factors in an *in vitro* kidney model;
- suppression *in vivo* of the inflammatory, fibrosis and kidney injury pathways and
- potential for a best-in-class product.

REDX's ROCK2 selective compounds

Activity and selectivity

Both REDX compounds show a higher potency and selectivity profile compared with KD025

The two lead compounds, REDX10178 and REDX10325, show excellent *in vitro* IC_{50}[1] inhibitions of ROCK2 at 1.4 nM and 0.65 nM, respectively – more potent than Kadmon's compound KD025. The selectivity against the close analogue ROCK1 is crucial with respect to off-target effects (e.g. cardiovascular), and both compounds show a selectivity between 71 and 402 times, respectively (KD025: 73 times selective). In terms of cellular activity, REDX molecules show a higher inhibition compared with Kadmon's product in ROCK2 selective cell lines, and weak to no inhibition in cell lines not expressing the ROCK1 protein.

Activity and selectivity vs. KD025

ASSAY	KD025 IC_{50}	REDX10178 IC_{50}	REDX10325 IC_{50}
ROCK2 activity	70 nM	1.4 nM	0.65 nM
ROCK1 activity	5.1 µM	0.1 µM	0.3 µM
Cellular ROCK2 selective pMYPT1	1 µM	0.8 µM	0.2 µM
Cellular parental MCF7 pMYPT1*	0.9 µM	3.9 µM	> 30 µM
Cellular ROCK1 selective pMYPT1*	0.8 µM	8.8 µM	> 30 µM

**Cell lines that do not express ROCK2*
Source: REDX, ASN poster, San Diego, 25 October 2018

[1] Concentration of a drug that is required for 50% inhibition

In addition, both REDX molecules showed an excellent selectivity score across the DiscoverX panel of 468 kinases, and an excellent profile in the CEREP safety panel of 44 targets providing further evidence of the clean profiles of the lead molecules.

Anti-pro-inflammatory and anti-pro-fibrotic efficacy

In cellular assays, both REDX's lead compounds show a good efficacy in preventing the release of pro-inflammatory and pro-fibrotic factors in kidney mesangial cells grown in high glucose, in a dose-dependent manner (REDX10178 as an example). These results are superior to the response of Kadmon's compound KD025.

REDX inhibitors prevent the release of pro-inflammatory and pro-fibrotic factor in a kidney model

A: Schematic of the experimental conditions

ASSAY	KD025 IC_{50}	REDX10178 IC_{50}	REDX10325 IC_{50}
CTGF assay – WB	Inactive	0.1 µM	0.4 µM
Fibronectin ELISA	Induction	0.4 µM	0.4 µM
Secreted TIMP-1 – ELISA	0.9 µM	0.2 µM	0.2 µM
Secreted MCP-1 – ELISA	2.9 µM	0.3 µM	0.2 µM
Secreted PDGF-BB – ELISA	10 µM	0.2 µM	0.2 µM

***Table 2**. Summary of analysis of culture supernatant from cells cultured with Redx's ROCK2 inhibitors. Data are from n≥3.*

B: CTGF expression in culture supernatant

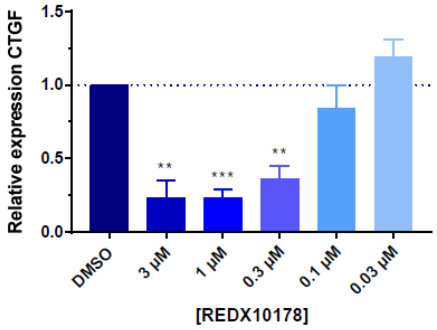


***Figure 5**. Mouse mesangial cells cultured for 8 days in high glucose with compound addition on day 3 and media refresh on day 6 (A). Culture supernatant harvested for protein analysis, representative data in (B).*

Source: REDX, ASN poster, San Diego, 25 October 2018

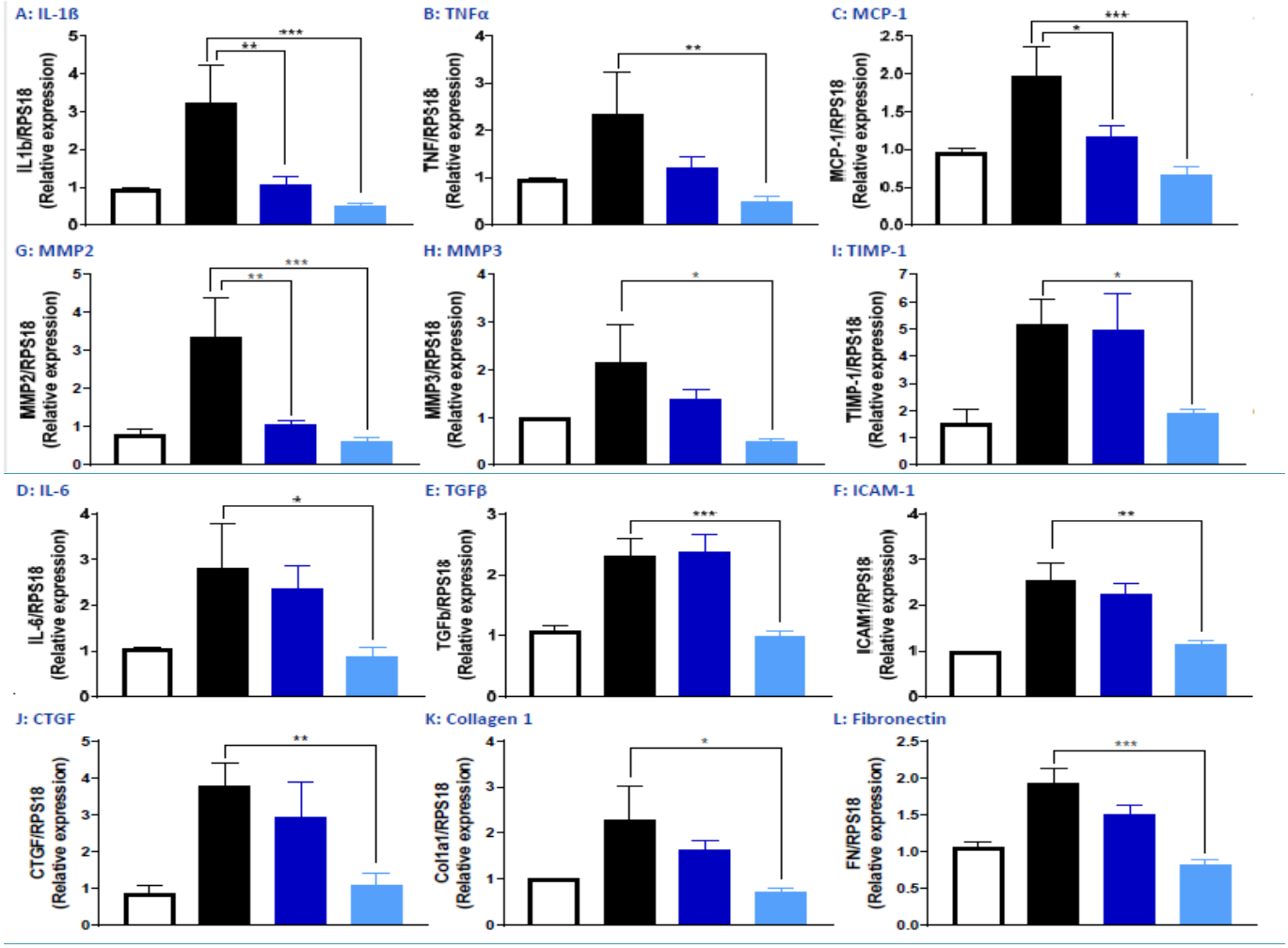
- **CTGF:** a connective tissue growth factor associated with wound healing and fibrotic pathology.
- **Fibronectin:** a protein involved in wound healing, cell adhesion, growth, migration and differentiation. It forms an insoluble network that separates and supports the organs and tissues of an organism.
- **TIMP-1:** plays a crucial role in wound healing.
- **MCP-1:** a cytokine involved in inflammation and recruitment of inflammatory cells, and produced in response to tissue injury or infection.
- **PDGF-BB:** a growth factor that regulates cell growth and division.

REDX10178 modulates genes associated with inflammation and fibrosis in an animal model, when taken orally

In vivo studies

REDX10178 is an orally bioavailable ROCK2 inhibitor with a good ADME (absorption, distribution, metabolism and excretion) profile. Using an animal model of acute kidney injury induced by cisplatin – that lead to renal toxicity and a concurrent increase in the expression of ROCK2 protein – REDX10178 reduces or supresses the expression of a number of genes associated with kidney damage, inflammation and tissue remodelling. The pathways modulated are also associated with chronic fibrosis, indicating target engagement of the fibrosis pathway. Again, this is shown in a dose-dependent manner.

REDX10178 modulation of inflammatory and fibrosis pathway in a acute kidney injury model



Source: REDX

REDX10178 has a clinically acceptable cardiovascular safety profile

REDX10178 does not induce cardiovascular side effects

While pan-ROCK inhibitors are known to have effects on the cardiovascular system, ROCK2 selective REDX10178 does not induce hypotension or increase the heart rate in a telemetered rat model. The study has been performed on a high dose of compound, at 100 mg/kg.

Only marginal changes have been monitored, despite sustained consistent plasma exposure of compound for around 10 hours, and this provides a clinically acceptable cardiovascular safety profile. As a published comparison, a pan-ROCK inhibitor with similar plasma exposure results in a 40% drop in blood pressure and 30% increase in heart rate, when used in similar conditions.[2]

REDX's ROCK2 selective programme

REDX is developing a ROCK2 selective inhibitor for NASH

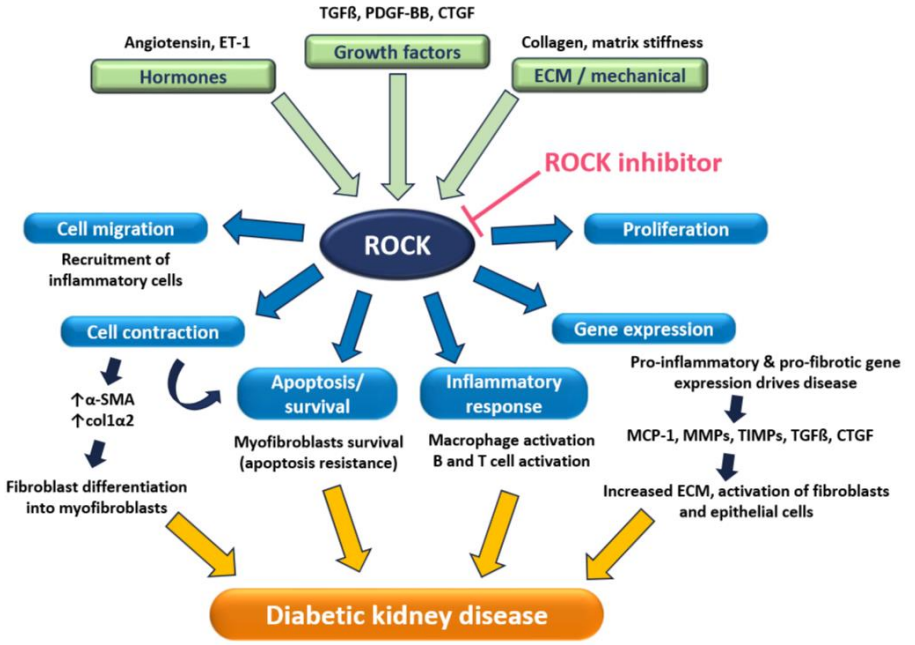
Background in renal fibrosis

CKD is caused by recurrent inflammation and damage in the kidney, induced by various factors, most commonly high glucose in diabetes. This damage and remodelling ultimately leads to renal fibrosis and loss of kidney function. ROCK signalling has been shown to be involved in renal fibrotic processes.[3] Indeed, ROCK

[2] Kast R. et al, *Br J Pharmacol* **2007**, 152(7), 1070-80.
[3] Baba I. et al, *Mol Med Rep*. **2016**, 13(1), 231-6.

proteins (ROCK1 and ROCK2) are central to many cellular processes implicated in wound healing, chronic injury and organ fibrosis. In *in vivo* models of kidney fibrosis, pan-ROCK inhibitors have been shown to have an anti-fibrotic effect. In addition, upregulation of ROCK2 protein expression has been seen in diabetic models and in the vascular network of diabetic patients at risk of CKD.

Activity and selectivity vs. KD025



Source: REDX, ASN poster, San Diego, 25 October 2018

While two pan-ROCK inhibitors (fasudil and ripasudil) are already on the market, their use is very limited due to cardiovascular incidences through the combined ROCK1 and ROCK2 proteins leading to hypotension and hyperaemia.

- **Fasudil** has been approved in China and Japan (not in the US and Europe) for improvement and prevention of cerebral vasospasm and the cerebral ischemic symptom after subarachnoid haemorrhage surgery.
- **Ripasudil** is a derivative of fasudil approved in Japan for the treatment of glaucoma and ocular hypertension.

ROCK2 programme

REDX focus on progressing ROCK2 inhibitors in NASH…

The prime focus for the ROCK2 programme is liver fibrosis, targeting NASH, where there are currently no approved therapies to limit the progression of, and potentially reverse, liver fibrosis. Existing treatments are limited, targeting diet intervention and medications to reduce cholesterol, triglycerides and blood pressure, and to control diabetes. There are only a few therapies currently in clinical development that aim to target the fibrosis process; ROCK2 inhibition is one of them. The main complication of liver fibrosis is the progression of NASH into liver cirrhosis. Patients with liver cirrhosis have permanent scarring and hardening of the liver, complete loss of function, and require transplantation. In addition, cirrhosis can ultimately lead to liver cancer.

… with the view to enter the clinic in 2020

The ROCK2 programme is at a late lead optimisation stage, and as ROCK2 has a central role in fibrotic and inflammatory pathways that are conserved across organs, REDX's ROCK2 inhibitors could potentially treat a large spectrum of diseases. The benefit of having a potent selective ROCK2 inhibitor is that systemic anti-fibrotic

effects can be achieved without the cardiovascular side effects seen with pan-ROCK1/2 inhibition. REDX anticipates to enter the clinic in 2020.

The ROCK2 inhibitor demonstrated a good pre-clinical profile

REDX has indicated that its orally available ROCK2 inhibitor demonstrated a good pre-clinical profile showing improvements compared with Kadmon's ROCK2 inhibitor KD025 *in vitro*, currently in Phase II trials in multiple indications: chronic graft-versus-host disease, IPF and scleroderma.

Kadmon indicated, in its Phase II study, that KD025 slowed the decline in lung function over 24 weeks of treatment and that it was well tolerated with no drug-related serious adverse events. This represents a great endorsement for REDX in treating fibrotic conditions with ROCK2 inhibitors.

Conclusion

REDX compounds have the potential to become best-in-class in various fibrosis conditions

The poster presentation at the ASN conference provides the first outlook of REDX's ROCK2 programme and follows its strategy of developing therapy in clinically validated targets in disease areas with high unmet clinical need. REDX has leveraged its excellent medicinal chemistry expertise to develop a very selective series of ROCK2 inhibitor compounds, available orally. REDX believes that it has the potential for a best-in-class agent for the treatment of fibrotic diseases of the kidney and liver associated with poor metabolic health, where ROCK2 is thought to play an important role. No safety concerns have been raised, with encouraging data of the tool compound REDX10178 showing no effect in the cardiovascular system in early *in vivo* experiments. Further *in vivo* studies in various animal models of fibrosis are ongoing. REDX has also indicated that new compounds with improved profiles are currently under evaluation in these fibrotic animal models.

REDX aims to enter the clinic with its ROCK2 selective compound in 2020

Current treatment modalities are not effective in halting the progression of most CKD. While REDX aims to enter into the pre-clinical development stage in NASH in 2H'19, with the view to being in the clinic in 2020, this represents a new opportunity in fibrosis with its ROCK2 inhibitor, which could be used in CKD.

In addition to the ROCK2 selective programme, REDX is progressing two other projects in anti-fibrotic diseases:

- The porcupine inhibitor REDX06109 targeting IPF, REDX's most advanced programme in fibrosis.
- The locally-acting ROCK inhibitor (GI-targeted ROCK); this targets the gastro-intestinal region for Crohn's-related fibrosis.

Redx's fibrosis pipeline

Years		2018	2019	2020
Anti-Fibrotics	GI-targeted ROCK	✓ *Patents filed, series assessment ongoing*	1H Development candidate selected in Crohn's disease	2H First time in man ready
	PORCN/ 06109	✓ *Progressing to development compound*	1H Development candidate selected for IPF	2H First time in man ready
	ROCK2 selective	✓ *Patents filed, series assessment ongoing*	2H Development candidate selected for NASH	2H First time in man ready

Source: REDX

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