Healthcare Research

Roquefort Therapeutics (ROQ.L*)

New *in vitro* data on STAT-6 programme shows activity in modulating inflammation

Non-Independent Research
MiFID II Exempt

6th November 2024

**SP Angel acts as Broker to Roquefort Therapeutics*

Stock Data

Ticker	ROQ.L
Share Price:	5.8p
Market Cap:	£7.5m

Source: London Stock Exchange (prior trading day's close)

Company Description

Preclinical stage developer of novel therapeutics for difficult to treat cancers

Share price (p)

Contacts

Healthcare Research

Liam Gascoigne-Cohen
liam.gascoigne-cohen@spangel.co.uk
+44 20 3470 0530

Vadim Alexandre
vadim.alexandre@spangel.co.uk
+44 20 3470 0532

Sales

Rob Rees
+44 20 3470 0535

Abigail Wayne
+44 20 3470 0534

Richard Parlons
+44 20 3470 0472

Grant Barker
+44 20 3470 0471

Key points

- **STAT-6 gene silencing constructs showed a 10x reduction in STAT-6 expression** compared to the control in a cell-based model for inflammation.
- **Additional key inflammatory biomarkers were also modified** including cytokines TRAC/CCL17 and CD23.
- **Study similar to *in vitro* work presented by Recludix (Private)** regarding REX-4671 a preclinical STAT-6 inhibitor which was licensed to Sanofi (SAN.EPA) in 2023 in return for a US$125m upfront payment and up to $1.2bn in conditional milestones.

New data from STAT-6 gene silencing programme in inflammation

Roquefort Therapeutics ("Roquefort", "the Group", "the Company") announced new data from its STAT-6 gene silencing programme. The Group has designed small interfering RNA (siRNA) constructs which inhibit translation of the STAT-6 protein, a protein overexpressed in several immunology and cancer indications.

In vitro reduction in STAT-6 and modification of other inflammatory biomarkers

STAT-6 siRNA constructs were evaluated in a cell-based model for inflammation (THP-1). STAT-6 siRNA constructs generated a 10-fold reduction in STAT-6 expression at 24 and 48 hours post treatment compared to negative controls. STAT-6 siRNA treated cells also saw a modification in inflammatory biomarkers, including TRAC/CCL17 and CD23, two forms of cytokines which play important roles in the regulation of inflammatory responses.

Industry interest in developing STAT-6 inhibitors

There is considerable industry interest in STAT-6 targeting treatments in the immunology space. In 2023, Sanofi (SNA.EP) struck a deal with Recludix (Private) to licence a preclinical program targeting STAT-6. The deal came with a US$125m upfront payment and potential milestone payments totalling $1.2bn. The recent *in vitro* study generated by the Group is similar to studies conducted by Recludix.

Results builds on oncology data generated on STAT-6 siRNA programme

STAT-6 targeting siRNA constructs have previously been shown to generate significant *in vivo* anti-cancer activity in validated models of colon cancer. STAT6 siRNAs demonstrated a significant reduction in the proliferation of colorectal cancer with an c.50% reduction in cell growth at seven days. This anti-cancer effect was replicated in a validated *in vivo* model of colorectal cancer with a significant reduction in cancer weight and volume at 28 days.

Data supporting partnership discussions

The Company is actively pursuing an out-licensing deal for the STAT-6 siRNA programme. The positive data expands the potential utility of this asset into an immunology setting. This should make the asset more attractive to potential partners.

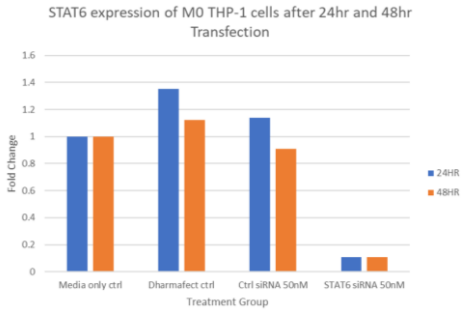
Efficacy in a validated *in vitro* model of inflammation

Roquefort has developed siRNAs which target the SH2 (Src-homology-2) domain of STAT6. The Company has evaluated STAT-6 targeting siRNA constructs in a cell-based model for inflammation. STAT-6 siRNA constructs were evaluated in a THP-1 macrophage cell line which is used to evaluate treatment effects on inflammatory response. Key findings were:

- STAT-6 targeting siRNA generated a 10-fold reduction in STAT-6 expression compared to controls.
- The phosphorylated (activated) form of STAT-6 was also reduced.
- Levels of CCL17 and CD23, two key mediators in inflammatory processes were also modified.

The data shows how STAT-6 siRNA constructs can reduce STAT-6 gene expression and modulate inflammatory biomarkers. CCL17 is involved in allergic and Th2-type immune responses whilst CD23 acts as a receptor that can trigger the production of inflammatory cytokines, while CCL17 is a chemokine involved in cell recruitment during inflammation.

Figure 1: STAT-6 targeting siRNA generated a 10-fold reduction in STAT-6 expression

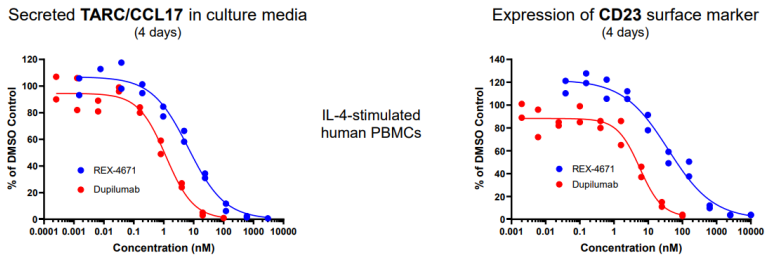


Source: Company presentation

Study similar to *in vitro* work presented by Recludix

The study is similar to preclinical work completed by Recludix which compared REX-4671, a STAT-6 inhibitor, to Dupixent (dupilumab), an anti-IL-4 antibody approved for asthma and atopic eczema in terms of levels of CCL17 and CD23, albeit over a shorter time period (2 vs 4 days). In 2023, Sanofi (SNA.EP) licenced the preclinical programme a US$125m upfront payment and potential milestone payments totalling $1.2bn.

Figure 2: Recludix STAT-6 inhibitor reduced TARC/CC17 and CD23 expression



TARC is a clinical biomarker for atopic dermatitis

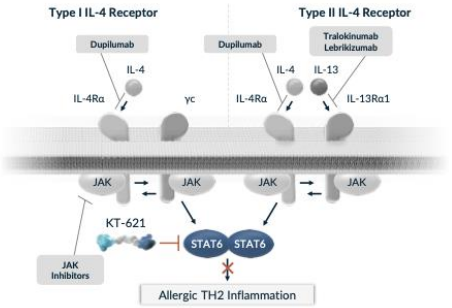
	TARC IC_{50} (Avg.)	CD23 IC_{50} (Avg.)
REX-4671	8.7 nM	33 nM
Dupilumab	0.79 nM	9.3 nM

Source: Recludix presentation (September 2023)

Results should support licensing discussions

Results from these experiments alongside the oncology data generated to date should support out-licencing discussions for the STAT-6 siRNA programme. STAT-6 is a key protein within the JAK/STAT pathway that mediates cellular inflammation responses. STAT-6 promotes the activation of T helper 2 (Th2) immune cells, a form of T-cell that produce cytokines that can trigger inflammatory responses and is implicated in autoimmune disorders including asthma, atopic dermatitis and eczema.

Figure 3: STAT6 method of action



Source: Kymera Therapeutics

Significant industry interest in new immunology treatments

There are several approved treatments which target various components of the JAK/STAT pathway for a range of autoimmune disorders (Table 1). This includes Dupixent (dupilimab), an antibody treatment developed by Sanofi. For Q3-24, Dupixent registered sales of €3.5bn with FY24E guidance of €13bn. A STAT-6 inhibitor could provide an alternative approach to these treatments within a large addressable market.

Table 1: Autoimmune drugs command significant revenues

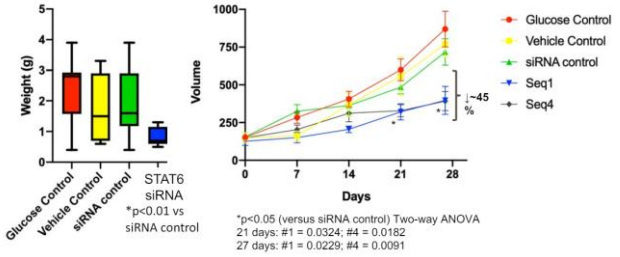
Drug Name / Developer	Latest quarter sales	Approval indication and dates	Drug type
Dupixent (Dupilimab) / Sanofi	EUR3.5bn	Eczema 2017 ; atopic dermatitis (2019 COPD (2024).	IL-4 and IL-13 inhibitor
Adbry (tralokinumab / LEO Pharma	Undisclosed	Moderate-to-severe atopic dermatitis: 2021	IL-13 inhibitor
Rinvoq (upadacitinib) / AbbVie	$1.4bn	Crohn's 2023 ; UC: 2022, Atopic Dermatitis 2022	Oral Janus kinase (JAK) inhibitor
Xeljanz (Tofacitinib) / Pfizer	$818m	Rheumatoid arthritis 2012, UC 2018	Oral Janus kinase (JAK) inhibitor
Rinvoq (Upadacitinib)/ Abbvie	$1.2bn	Crohn's 2023; Atopic Dermatitis 2022; rheumatoid arthritis 2019	Oral Janus kinase (JAK) inhibitor

Source: Company websites

Build on existing cancer data

STAT-6 targeting siRNA constructs have shown significant *in vivo* anti-cancer activity in validated models of colon cancer. STAT6 siRNAs demonstrated a significant reduction in the proliferation of colorectal cancer with an c.50% reduction in cell growth at seven days. This anti-cancer effect was replicated in a validated in vivo model of colorectal cancer with a significant reduction in cancer weight and volume to 28 days.

Figure 4: Anti-STAT-6 siRNA showed significant anti-cancer activity in vivo



Source: Company Reports

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Recommendations are based on a 12-month time horizon as follows:

Buy - Expected return >15%
Hold - Expected return range -15% to +15%
Sell - Expected return < 15%