Harnessing the Power of RNA Modification to Create 1st in Class Inhibitors of RNA Modifying Enzymes (RME) to Treat Cancer and Other Diseases
Leader in the RNA Modification Enzyme Field

1ST MOVER ADVANTAGE
STC-15 (lead program), a 1st in class METTL3 inhibitor, entered Ph1 in 2022

LEADING PLATFORM
Proven methods and insights to identify & prosecute multiple attractive RME targets, particularly methyltransferases

NOVEL PIPELINE
Multiple novel pipeline assets with potential uses in oncology, immunology, CNS diseases and virology

EXCEPTIONAL TEAM
Experienced R&D team and advisors have a deep understanding of RMEs and are supported by a world-class academic network
RNA Modification: A Novel Mechanism of Gene Regulation

>170 RNA modifications identified
All types of RNA modified (mRNA, miRNA, IncRNA, tRNA)

RNA Modification Enzymes Can...
- Regulate RNA function and immune responses
- Represent novel therapeutic targets including for oncology, virology, CNS and immunology
Founded by Pioneers in RNA Modification

Formed the 1st Company in the RME Space (Cambridge, UK)

World leaders in RNA modification and RNA driven gene regulation and Experts on multiple novel targets within the STORM pipeline

Prof. Tony Kouzarides
Founder & Director

• Professor of Cancer Biology at the University of Cambridge
• Director of the Milner Therapeutics Institute and Deputy Director of the Gurdon Institute
• abcam founder – now £3bn,
• discovery of I-BET and founder of Chroma Therapeutics
• >150 publications, mostly epigenetics (including >30 in Nature, Cell and Science)

Prof. Eric Miska
Founder

• Herchel Smith Professor of Molecular Genetics at the University of Cambridge
• Head of Department of Biochemistry
• Associate Faculty at the Wellcome Trust Sanger and CRUK Cancer Research Institutes
• >80 publications (including >20 in Nature, Cell and Science)

Supported by an extensive academic KOL network (>25 collaborations)
STORM Therapeutics Pioneering Novel Drug Targets for RNA Modification

**nature**
Small-molecule inhibition of METTL3 as a strategy against myeloid leukaemia

**nature**
Loss of ADAR1 in tumours overcomes resistance to immune checkpoint blockade

**nature genetics**
A call for direct sequencing of full-length RNAs to identify all modifications

For most organisms, DNA sequences are available, but the complete RNA sequences are not. Here, we call for technologies to sequence full-length RNAs with all their modifications.

**Molecular Cell**
METTL1-mediated m^7^G modification of Arg-TCT tRNA drives oncogenic transformation

N^7^-Methylguanosine tRNA modification enhances oncogenic mRNA translation and promotes intrahepatic cholangiocarcinoma progression
# Progressing a Novel Pipeline of Proprietary Products

<table>
<thead>
<tr>
<th>Year</th>
<th>Project Details</th>
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| **2022** | METTL3 (STC-15)  
Oncology  
Ph1 Solid Tumors |
|      | Multiple Lead Op Projects in Oncology  
Lead Op and Pre-Clinical Studies |
|      | ADARI (Exelixis)  
Oncology |
|      | COVID - 19 (UKRI)  
Viral Infection  
Hit to Lead and Lead Op |
|      | Pipeline Build  
New RME ID & validation |
| **2023** | Further Ph1/2 Opportunities |

- **Clinical Trial start**
- **Interim Safety PK/PD and early efficacy data**
STORM Corporate History & Achievements

2016 - 2021

- Location at Babraham Research Campus (Cambridge, UK)
- Experienced management, board, and advisors
- Academic network
- Leading technology platform
- CRO partners
- Multi-target pharma license & collab deal (Exelixis - Oct21)
- U.S. subsidiary established
- STC-15 (METTL3) identified

2016

- $55M Series A
- Strong International Investor Syndicate

2022 - 2023

- Global development organization in place
- Initiated STC-15 Phase I (2H 2022)
- Completion of a $30 million Series B financing round (late 2022)
- New investors to the STORM syndicate Fast Track Initiative and the UTokyo Innovation Platform Co., Ltd.
  - Phase 1 safety, PK/PD, biomarker readouts (2023) (Solid cancers)
  - Identify STC-15 Phase 2 dose and regimen
  - Enable Phase 1/2 initiations for STC-15 (2024)
  - Pipeline expansion, BD milestones, new partnerships

- STC-15 METTL3 identified
- U.S. subsidiary established
Technology Platform
RNA Modifying Enzymes

- Untapped Target Class
  - ~300 enzymes

- Writers, Readers and Erasers

- STORM’s disease agnostic platform
  - uniquely placed to generate value

Circles:
- Helicases
- Pseudouridine Synthases
- TUTases
- Methyltransferases
- Others
- Nucleotide Editors
Multiple Unique Advantages

1. Efficiently identify and validate targets
2. Establish a proprietary view of the RME families
3. Measure any RNA modification, in sequence context

Leading RME Platform in Place: Initial Focus on RNA Methyltransferases

- RNA Modification Analysis
- Selectivity Assays and Chemical Probes
- Functional Genomic Screens
Platform enables target validation and drug discovery

- Biochemical assays and CRISPR screen for initial target identification
- Capability & understanding to generate potent/selective inhibitors of RNA modifying enzymes
- Track record of using such compounds to:
  - unlock novel target/disease biology
  - create 1st-in-class drug candidates
STC-15: Lead Program METTL3

1st In Class Clinical Candidate discovered by STORM and a first for the Field

HTS to clinical candidate in <3 years on an unprecedented target class / novel biology area

✓ Novel efficacy mechanisms identified in solid tumors (immune based) and in leukemia models (stem cell)
✓ Preclinical data indicating upregulation of interferon signaling and synergy with T cell checkpoint blockade
✓ STC-15 combination activity with anti-PD1 antibodies observed in multiple syngeneic tumor models
✓ First patient treated in Phase 1 multiple ascending dose trial Q4 2022 (NCT05584111)
✓ Potential for multiple Phase 1/2 clinical trials in solid tumors and leukemia driven by the novel anti-cancer mechanisms of METTL3 inhibition.
Novel Mechanisms of METTL3 Inhibitor Efficacy

#1
DIRECT KILLING
of cancer cells

MOA
- Intrinsic dependency of cancer cells on METTL3 activity.
- Differentiation/apoptosis of cancer stem cells.

#2
STIMULATION
of anti-tumor immunity

MOA
- Induction of innate immune response in cancer cells.
- Enhancement of Checkpoint inhibitor efficacy.

#3
DRUG RESISTANCE

MOA
- Inhibition of METTL3’s role in DNA repair and ability to promote chemoresistance & radiotherapy resistance.
METTL3: a novel cancer target

- RNA methyltransferase – methylates N6-position of A (m6A) in selected mRNAs
- m6A regulates mRNA translation and stability
- Inhibition of METTL3 and loss of m6A can inhibit key oncogenes
- Inhibition of METTL3 activates innate immune responses in cancer cells via induction of dsRNA
STC-15 may ‘set the scene’ for efficacious CPI treatment

Litchfield et al., Cell, 2021: Meta-analysis of tumor and T cell-intrinsic mechanisms of sensitization to checkpoint inhibition

- Report analysis of CPI response in >1000 CPI-treated patients
- Authors identified tumor- and TME- related predictors of patient response to checkpoint inhibitors:
  - CD8a
  - CXCL9 (CXCR3 ligands)
  - CD274 (=PD-L1)
  - CCR5 (binds CCL3, 4, 5, 8)
  - ICOS
  - Antigen presentation
  - IFN signalling
  - TNFα signalling
  - CXCL13

Upregulated by STC-15 treatment in in-vivo models
Combination of STC-15 and Anti-PD1 Induces Tumor Regression and Anti-cancer Immunity in Mouse Syngeneic Models

**STC-15 / anti-PD1 Treated Mice Appear To Be Cured: No Regrowth of Regressed Tumors**

- Mice with regressions are immune to the cancer (rechallenge with tumor cells fails to generate new tumors)
- STC-15 efficacy is CD8 T cell dependent (no activity if deplete CD8 T cells).
- Combination activity seen in multiple syngeneic models

**A20 Average Tumor Volumes**

**Primary Study**

**Efficacy Study**

**Rechallenge Study**
STC-15 Phase 1 Data Emerging in 2H 2023

- Trial sites at MD Anderson, Honor Health and START (NCT05584111)
- Multiple Ascending Dose study in adults with advanced malignancies
- Objectives:
  - Safety and PK of STC-15
  - Recommended Phase 2 dose/regimen (RP2D)
  - Biomarker rich translational study
    - (m6A PD marker, immune MOA markers, tumor genetic/immune profiling)
STORM Team
# STORM Leadership Team

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<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Experience and Achievements</th>
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| Dr Jerry McMahon         | CEO                                        | • >30 years drug discovery and development experience  
• Former CEO at Harpoon Therapeutics leading the company from discovery into clinical stage alongside a successful IPO and fundraising rounds.  
• Successful track record of executive industry roles including the discovery and development of Sunitinib |
| Dr Oliver Rausch         | CSO                                         | • >20 years drug discovery and development experience  
• Ex NIHR, Cellzome, UCB and GSK                                                                                                                                                                                                                                                                                                   |
| Dr Josefin-Beate Holz     | MD CMO                                      | • >25 years drug development experience in oncology, immunology and other disease areas.  
• Held Exec level roles in pharma and biotech (BMS, Gilead, Ablynx, GPC-Biotech and LEO Pharma)                                                                                                                                                                                                                                    |
| Dr Matthew Fyfe          | Senior Vice President Therapeutics         | • >20 years’ experience in drug discovery and development  
• Successfully led research endeavors in multiple therapeutic areas that have reached Phase 2, with several purchased by major pharma companies                                                                                                                                                                |
| Dr Beth Thomas           | Vice President Medicinal Chemistry         | • >20 years’ experience in medicinal and computational chemistry  
• Worked at Celltech, UCB, BioFocus, University of Cambridge and was Head of Discovery Chemistry at the Cambridge Crystallographic Data Centre                                                                                                                                                                            |
| Dr Angus Lauder          | Senior Director of Business Development and Alliance Management | • >15 years of Business & Development experience working with biotech, pharma and academia  
• Extensive deal sheet across licensing, discovery partnerships and spin-out company formation                                                                                                                                                                                                                     |
| Margaret Daniel          | CFO                                         | • Experienced biotech CFO providing CFO services to prominent biotechs  
• Co-founder of Daniel-Bradshaw, a bespoke CFO and Accounting Services company to biotech sector                                                                                                                                                                                                                     |
# Board Members & Investors

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<tr>
<th>Name</th>
<th>Position</th>
<th>Company/Institution</th>
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<tbody>
<tr>
<td>Dr Jerry McMahon</td>
<td>CEO &amp; President</td>
<td></td>
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<tr>
<td>Hakan Goker, PhD</td>
<td>M Ventures</td>
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<tr>
<td>Christopher O’Donnell, PhD</td>
<td>Pfizer Ventures</td>
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<tr>
<td>Sakae Asanuma</td>
<td>Taiho Ventures</td>
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<tr>
<td>John Haurum, PhD</td>
<td>Independent</td>
<td></td>
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<tr>
<td>Prof. Tony Kouzarides, PhD, FMedSci, FRS</td>
<td>Founder</td>
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<tr>
<td>Prof. Paul Workman</td>
<td>Independent</td>
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<tr>
<td>Tim Edwards</td>
<td>Chairman</td>
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Leader in the RNA Modification Enzyme Field

**1ST MOVER ADVANTAGE**

**LEADING PLATFORM**

**NOVEL PIPELINE**

**EXCEPTIONAL TEAM**

- Partnerships:
  - Pipeline Asset Collaborations (METTL3 and beyond)
  - Discovery partnerships in novel RME target space:
    - Oncology
    - Virology
    - CNS
    - Immunology

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Appendix
Recent Presentations Highlight STC-15 Novel Mechanisms

STC-15, an oral small molecule inhibitor of the RNA methyltransferase METTL3, inhibits tumour growth through activation of anti-cancer immune responses and synergizes with immune checkpoint blockade.

Joanna Olczak1, Yuca Ofir-Rosenfeld1, Lina Vuillod-Baltsch1, Claire Saunders1,2, Alexandra Sapetchnich1, Georgia Tsigougeorga1,3, Mark Arlert1,3, Marco Curci1, Jerome SoffFordham1, Josefina-Beato Hols1, Oliver Rausch1 and Jerry McPherson1

1 Storm Therapeutics Ltd, Cambridge, UK, 2 Miller Therapeutics Institute, University of Cambridge, Cambridge, UK, 3 Charls River Periklis, UK

1 Current address: UCL Cancer Institute, London, UK, 2 Current address: Oncology R&D, Amgen, Cambridge, UK

**Introduction**

METTL3 is an RNA methyltransferase responsible for the deposition of 5-4- methylinosine (m4A) modification on mRNA and long non-coding RNA (lncRNA) targets, to regulate their stability, splicing, transport and translation.

Small molecule inhibitors of METTL3 catalytic activity have previously demonstrated direct anti-tumour efficacy in models of acute myeloid leukaemia (AML) (Yeknik et al., Nature, 2011) and solid tumours. Here we present pre-clinical data showing that the orally bioavailable small molecule METTL3 inhibitor STC-15 inhibits cancer growth and induces anti-cancer immunity, by mechanisms involving the activation of CDB8+ suppressor T-cells.

**STC-15 enhances PBMC-mediated killing of cancer cells in a co-culture system**

A. STC-15 enhancement of NK cell killing by PBMC assays in pre-inflammation conditions in the presence of STC-15.

**Increased CDB8+ tumour infiltration following STC-15 treatment, alone or in combination with anti-PD1**

A. Donor-dependent efficacy of STC-15 in TCR-transgenic syngeneic cancer model. Multiple reagents in high dose group combined with PD-1+ TCR-transgenic gene expression analysis using the C57 Bl6 panel was performed on complete bone set immune isolated by mouse. DBB was obtained with the anti-PD1-mediated synergy activation of CDB8+ nonsense pathways in all treatment groups (circles).

**The in vivo activity of STC-15 in A20 syngeneic lymphoma model is dependent on CDB8**

A. STC-15 efficacy in A20 syngeneic lymphoma model (left) in the combination group was highly synergistic. B. Tumours that developed under A20 mice with tumours were scored as Tumour free (TFF) or non-tumour (NT) development. C. Dose-dependent in vivo synergy activation was observed in tumour xenograft models in the absence of CDB8+ cells.

**Summary**

In pre-clinical cancer models, STC-15 treatment inhibits tumour growth, activates innate immune pathways, and enhances the anti-tumour properties of anti-PD1 therapy, to generate a durable anti-tumour immune response.

The anti-tumour effect of STC-15 is mediated via CDB8+ T-cell recruitment and activation. These data provide a rationale for the development of STC-15 as a novel treatment for solid tumour malignancies, as well as in combination with checkpoint inhibitors.

A Phase I First-In-Human clinical trial started in Q4 2022 (NCT05584111).
**Recent Presentations Highlight STC-15 Novel Mechanisms**

**STC-15**, a novel METTL3 inhibitor, and its combination with Venetoclax confer anti-tumour activity in AML models

*Lisa Yavuzkutlu*, *Yura Ohk-Rosenfeld*, *Mark Alterrelli*, *Anabelle Congrais*, *Caroline Hourant-Awali*, *Jerry McNaboo*, *Oliver Raschle*

*Storm Therapeutics Ltd., Cambridge, UK*

**Evotec S.A./Laba, Paris, FR**

**Introduction**

METTL3 is an RNA methyltransferase responsible for the deposition of N4-methylcytidine (m^4^A) modification on mRNA and tRNA to regulate their stability, splicing pattern and translation. Its role, however, has remained elusive. In recent years, METTL3 has been implicated in the initiation and progression of multiple cancer types, with the highest expression observed in acute lymphoblastic leukemia (ALL). Currently, few lines of standard care therapy for ALL patients are Venetoclax, which targets the anti-apoptotic protein BCL2. It was shown that mRNA deposited by METTL3 on BCL2 transcript affects BCL2 mRNA stability and translation. Storm Therapeutics has developed potent and selective METTL3 inhibitors, including STC-15, which is in clinical development (clinical trial NCT01558461). Here, we explore pharmacological inhibition of METTL3 as monotherapy or in combination with Venetoclax in AML models in vitro and in vivo.

**Multiple human AML cell lines and PDXs are sensitive to METTL3 inhibition**

METTL3 inhibition leads to downregulation of BCL2 protein in AML cell lines

**Summary**

Here, we have demonstrated that multiple AML cell lines and AML PDX models were sensitive to pharmacological inhibition of METTL3 by STC-15 or other METTL3 inhibitors. In addition, METTL3 inhibition led to a dose-dependent downregulation of BCL2 protein. Protein-lysine experiments have shown a high degree of synergy between STC-15 and Venetoclax in MOLM-13 cells, the most synergetic dose was a point of 31, which indicates a 51% higher degree of inhibition than expected by an additive effect. An in vivo AML PDX model also revealed that combination therapy extended median group survival to 85 days in comparison to 51.5 days in the vehicle group, while STC-15 monotherapy outperformed Venetoclax (median survival 48 days in 58 days, respectively). The survival results were supported by reduced overall cell viability of human CD34+ cells and lower spleen weight when compared therapy and control groups.

**In conclusion,** we demonstrated that METTL3 inhibition results in anti-tumour effects across different AML models. Moreover, we demonstrated a synergistic effect between the novel METTL3 inhibitor STC-15 and Venetoclax, both in vitro and in vivo. These studies provide evidence for the utility of METTL3 inhibitors as a new therapeutic agent to treat AML. Currently, STC-15 is in phase I/II clinical trials for human multiple ascending dose study (NCT01558461).