Harnessing the Power of RNA Modification to

Create 1st in Class Inhibitors of RNA Modifying Enzymes (RME) to Treat Cancer and Other Diseases

STORM THERAPEUTICS

FIERCE Biotech
FIERCE 15
2022 WINNER

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

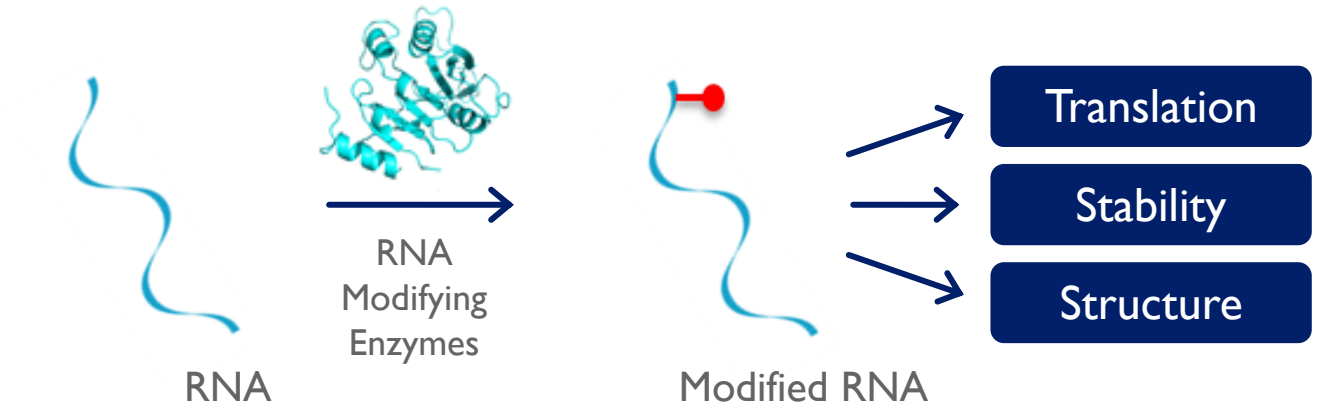
EXCEPTIONAL TEAM

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

RNA Modification

Modulation of RNA function via post-transcriptional modifications



>170 RNA modifications identified

All types of RNA modified (mRNA, miRNA, lncRNA, 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.

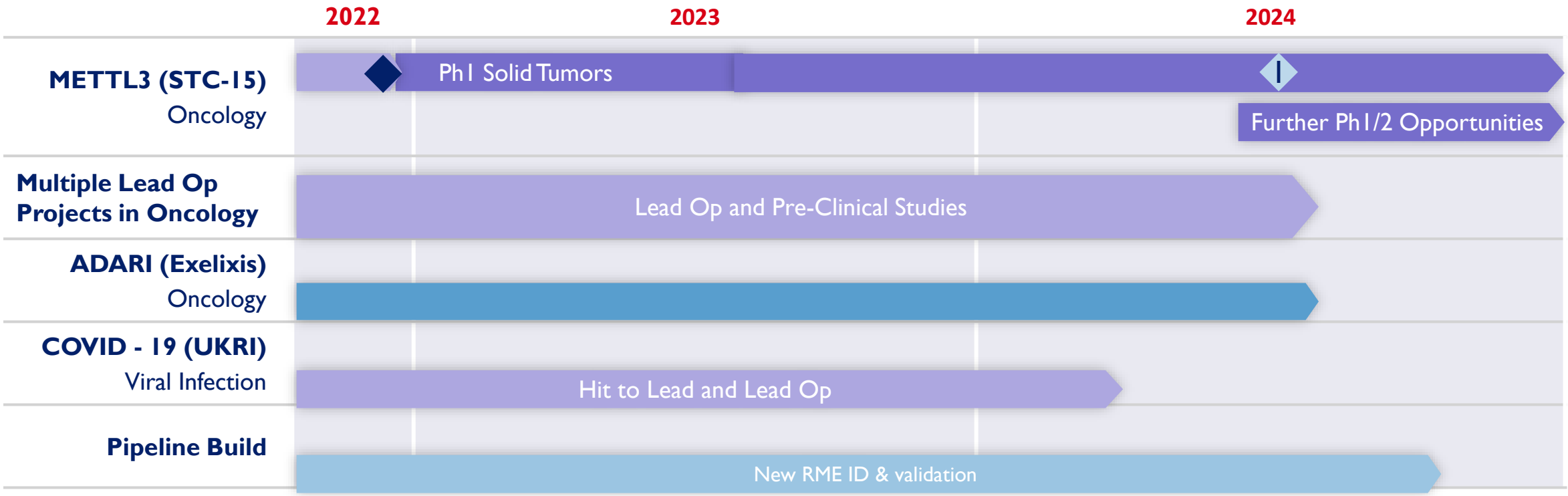
Molecular Cell

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

N^7-Methylguanosine tRNA modification enhances oncogenic mRNA translation and promotes intrahepatic cholangiocarcinoma progression

STORM THERAPEUTICS

Progressing a Novel Pipeline of Proprietary Products



◆ Clinical Trial start I Interim Safety PK/PD and early efficacy data

STORM THERAPEUTICS

STORM Corporate History & Achievements

2016

$55M Series A

Strong International Investor Syndicate

M. VENTURES · Pfizer Ventures · FTI Fast Track Initiative · UTokyoIPC · Cambridge Innovation Capital · ipgroup · Seroba · TAIHO VENTURES, LLC

2016 - 2021

Platform, Pipeline, and People

- ✓ 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

2022 - 2023

Clinical Stage Company

- ✓ Global development organization in place
- ✓ Initiated STC-15 Phase 1 (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

STORM THERAPEUTICS

Technology Platform

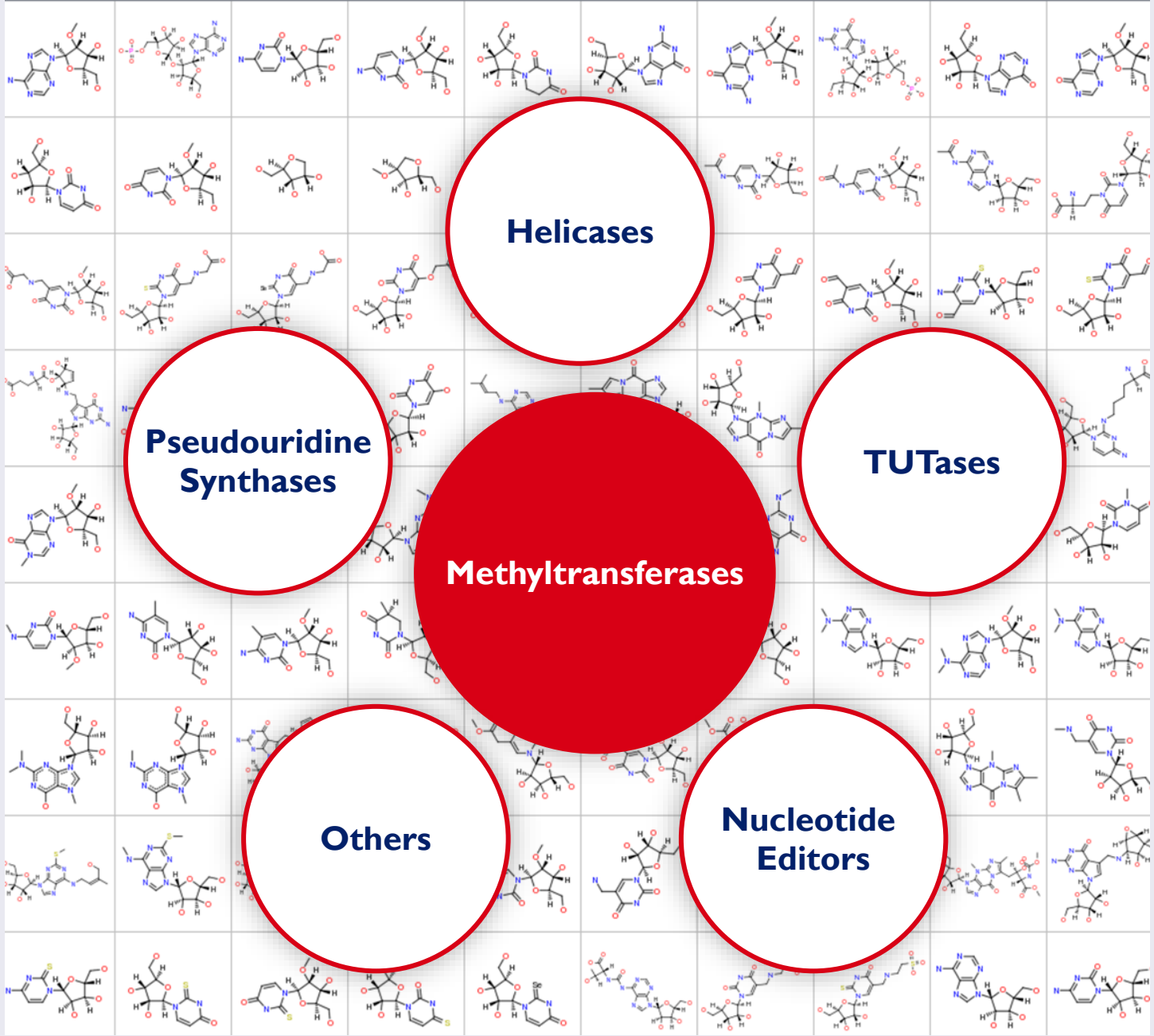
STORM THERAPEUTICS

RNA Modifying Enzymes

Untapped Target Class
~300 enzymes

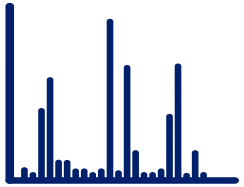
Writers, Readers and Erasers

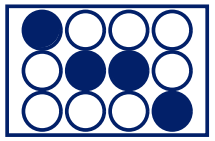
STORM's disease agnostic platform uniquely placed to generate value



STORM THERAPEUTICS

Leading RME Platform in Place: Initial Focus on RNA Methyltransferases





RNA Modification Analysis + **Selectivity Assays and Chemical Probes** + **Functional Genomic Screens**

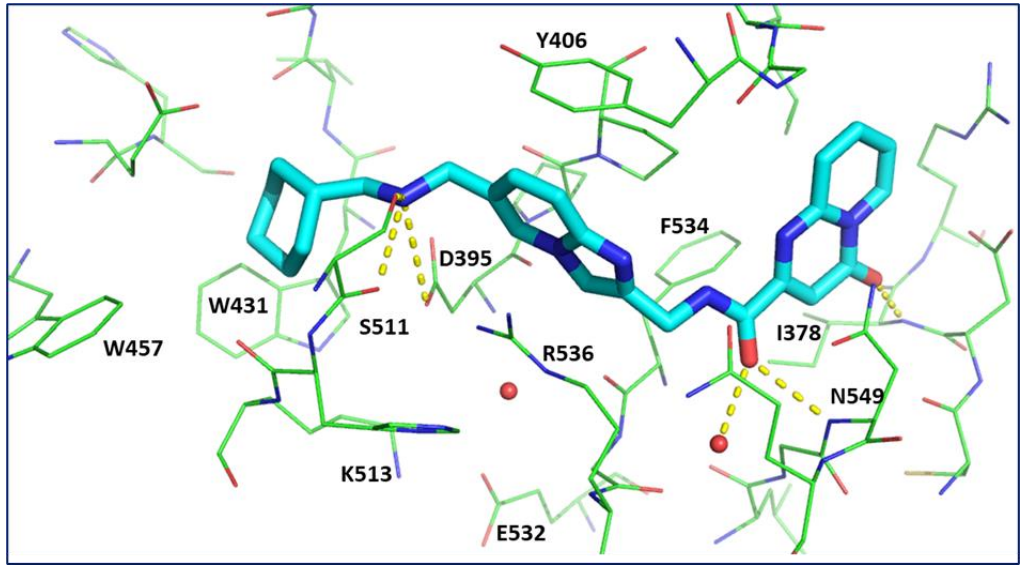
Multiple Unique Advantages

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

STORM THERAPEUTICS

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.

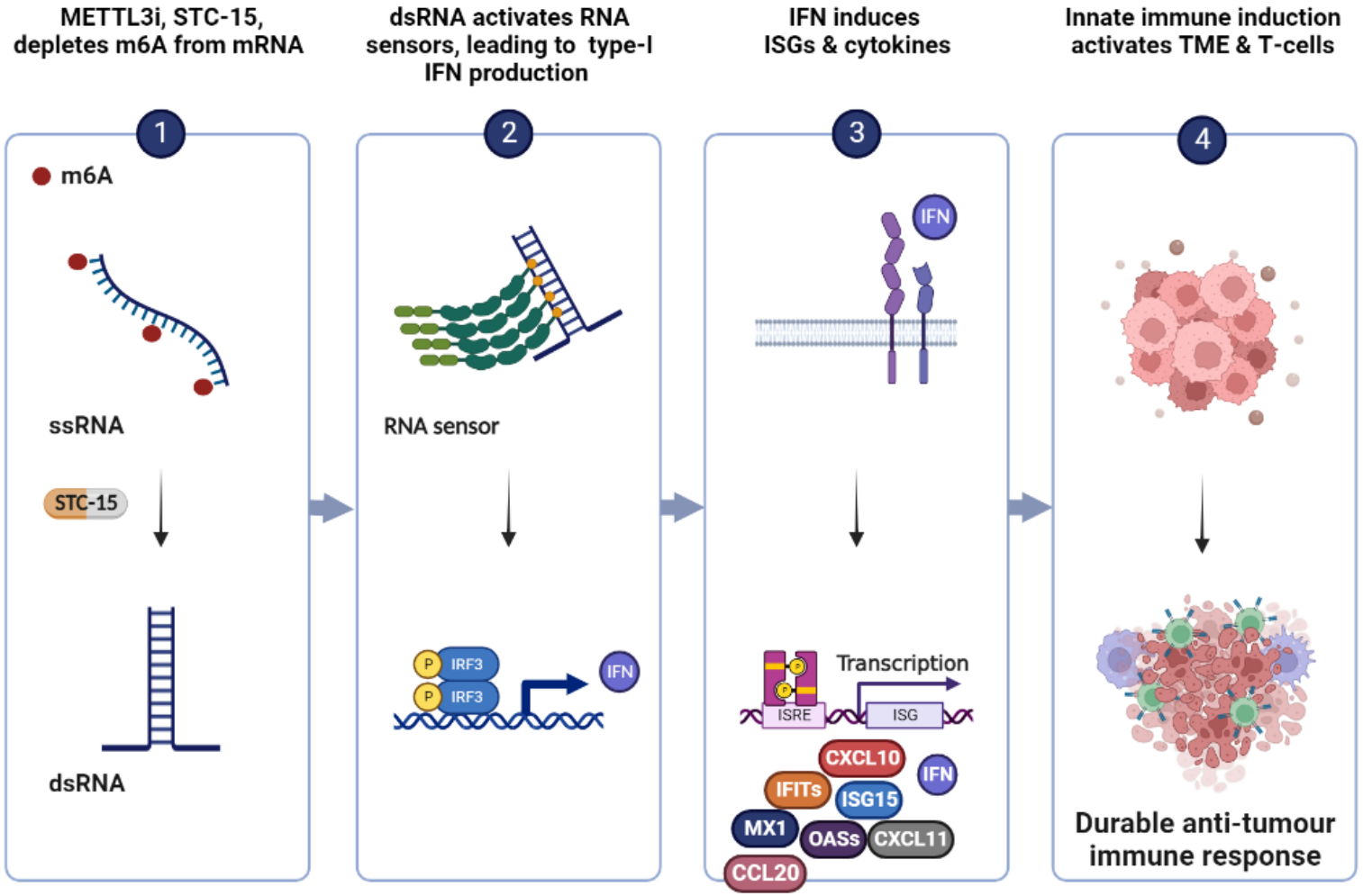
#3
DRUG RESISTANCE

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

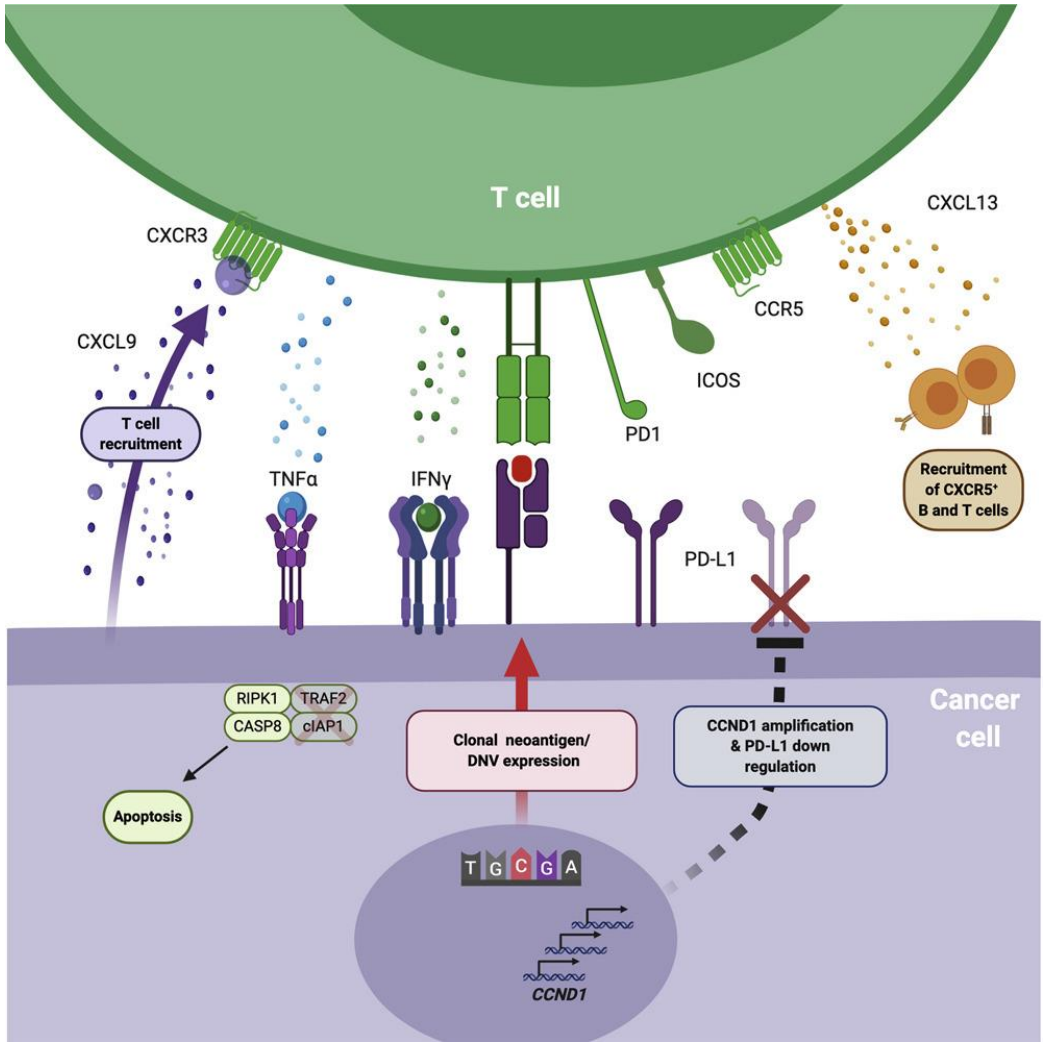


STC-15 may ‘set the scene’ for efficacious CPI treatment

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
  - TNFa signalling
  - CXCL13

Upregulated by STC-15 treatment in in-vivo models

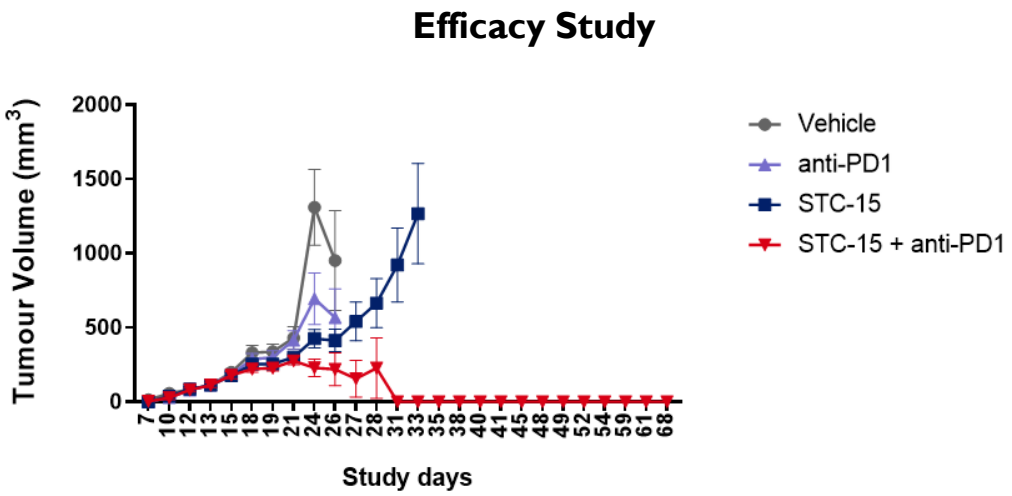


Combination of STC-15 and Anti-PD1 Induces Tumor Regression and Anti-cancer Immunity in Mouse Syngeneic Models

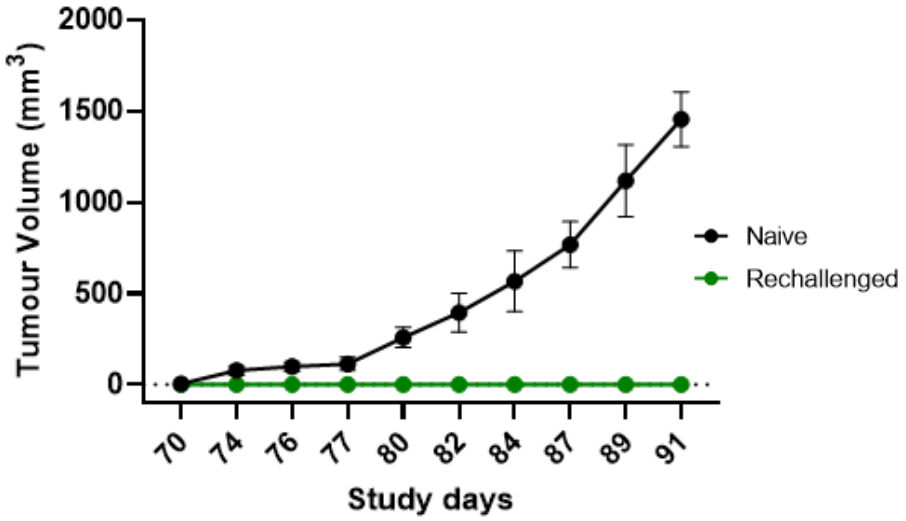
STC-15 / anti-PD1 Treated Mice Appear To Be Cured: No Regrowth of Regressed Tumors

- 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)



A20 Average Tumor Volumes (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 THERAPEUTICS

STORM Leadership Team

	**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

Dr Jerry McMahon	CEO & President
Hakan Goker, PhD	M Ventures
Christopher O'Donnell, PhD	Pfizer Ventures
Sakae Asanuma	Taiho Ventures

John Haurum, PhD	Independent
Prof. Tony Kouzarides, PhD, FMedSci, FRS	Founder
Prof. Paul Workman	Independent
Tim Edwards	Chairman

M. VENTURES · Pfizer · TAIHO VENTURES, LLC · Seroba. · ipgroup · CAMBRIDGE INNOVATION CAPITAL · UTokyoIPC · FTI Fast Track Initiative

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

STORM THERAPEUTICS

Recent Presentations Highlight STC-15 Novel Mechanisms

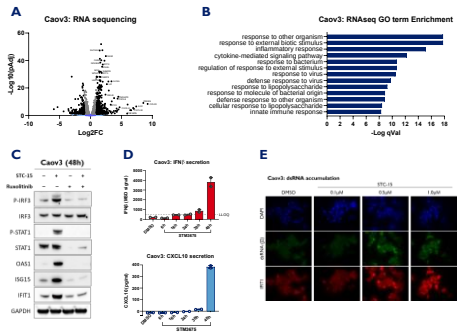
STC-15, an oral small molecule inhibitor of the RNA methyltransferase METTL3, inhibits tumour growth through activation of anti-cancer immune responses and synergizes with immune checkpoint blockade

Joanna Obacz[1], Yaara Ofir-Rosenfeld[1], Lina Vasiliauskaitė[1], Claire Saunders[1*], Alexandra Sapetschnig[1], Georgia Tsagkogeorga[1,2], Mark Albertella[1+], Marie Carkill[3], Jezrom Self-Fordham[3], Josefin-Beate Holz[1] Oliver Rausch[1] and Jerry McMahon[1]
[1]Storm Therapeutics Ltd, Cambridge, UK | [2]Milner Therapeutics Institute, University of Cambridge, Cambridge, UK | [3]Charles River, Portishead, UK
*Current address: UCL Cancer Institute, London, UK | +Current address: Oncology R&D, AstraZeneca, Cambridge UK

1 Introduction

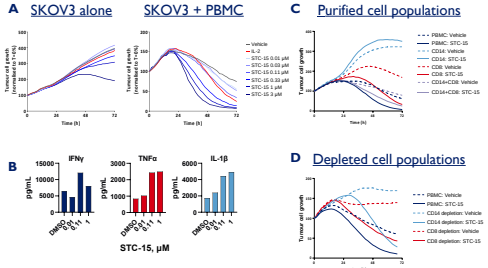
METTL3 is an RNA methyltransferase responsible for the deposition of N-6-methyladenosine (m6A) modification on mRNA and long non-coding RNA (lncRNA) targets, to regulate their stability, splicing, transport and translation.
Small molecule inhibitors of METTL3 catalytic activity have previously demonstrated direct anti-tumour efficacy in models of acute myeloid leukemia (AML) (Yankova et al., *Nature*, 2021) 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 involve the activation of CD8⁺ cytotoxic T-cells.

2 STC-15 induces innate immune signalling



A. RNAseq: Differential Expression (DE) analysis of Caov3 ovarian cell line treated with STC-15 for 48 hours, compared with DMSO control. **B.** Gene Ontology (GO) Biological Process (BP) analysis of DE genes (Log2FC>1, pAdj<0.05), showing activation of innate immunity, including the interferon and NF-kB signalling pathways. **C.** Validation of the activation of the interferon signalling pathway by Western blot. The activation can be blocked by co-treatment with Ruxolitinib, a JAK1/2 inhibitor. **D.** Secretion of IFNβ (top) and the chemokine CXCL10 (bottom) from cells following treatment with STM3675, a METTL3 tool compound inhibitor. **E.** Double-strand RNA (dsRNA) accumulation is likely the cause of innate immunity activation.

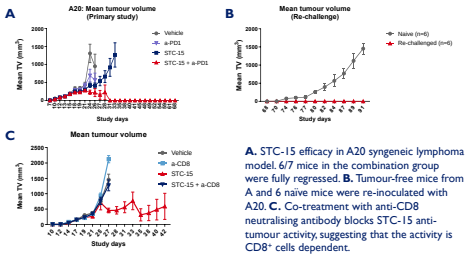
3 STC-15 enhances PBMC-mediated killing of cancer cells in a co-culture system



A. STC-15 enhancement of SKOV3 killing by PBMC occurs in low concentrations, which do not affect SKOV3 viability directly. **B.** Dose-dependent secretion of pro-inflammatory cytokines in the co-culture. **C.** Co-culture assay comparing PBMC to purified cell populations of CD14⁺ (myeloid cells), CD8⁺ (cytotoxic T cells) or CD14⁺ + CD8⁺, treated with either 0.3 μM STC-15 or DMSO control. **D.** As above, but using either CD14⁺ or CD8⁺ depleted PBMC.

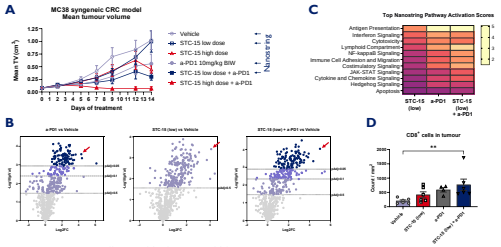
The data suggest that both CD14⁺ and CD8⁺ populations are affected by STC-15 treatment, and both populations contribute to effective cancer cell killing in the co-culture.

4 The in-vivo activity of STC-15 in A20 syngeneic lymphoma model is dependent on CD8⁺ cells



A. STC-15 efficacy in A20 syngeneic lymphoma model. 6/7 mice in the combination group were fully regressed. **B.** Tumour-free mice from A and 6 naïve mice were re-inoculated with A20. **C.** Co-treatment with anti-CD8 neutralising antibody blocks STC-15 anti-tumour activity, suggesting that the activity is CD8⁺ cells dependent.

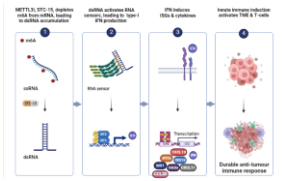
5 Increased CD8⁺ tumour infiltration following STC-15 treatment, alone or in combination with anti-PD1



A. Dose dependent efficacy of STC-15 in MC38 syngeneic colon cancer model. Multiple regressions in high dose group combined with a-PD1. **B.** Nanostring gene expression analysis using the IO-360 panel was performed on samples from the 4 groups indicated by arrows in A. DE was calculated for each treatment group compared to vehicle control. Note that the Cd8a gene was among the top upregulated genes in all treatment groups (red arrows) . **C.** Nanostring pathway activation score for the most upregulated pathways. **D.** CD8⁺ tumour infiltration was assessed by IHC.

6 Summary

STC-15 Mechanism of Action



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 CD8⁺ 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 inhibition.
A Phase I, First-in-Human clinical trial started in Q4 2022 (NCT05584111).

Harnessing the Power of RNA Modification

SITC, Nov 2022

Recent Presentations Highlight STC-15 Novel Mechanisms

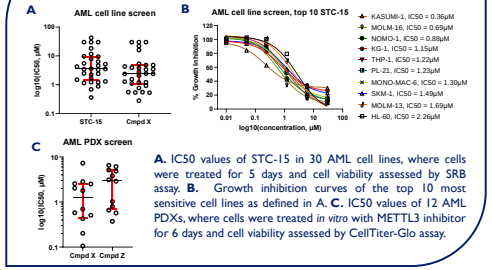
STC-15, a novel METTL3 inhibitor, and its combination with Venetoclax confer anti-tumour activity in AML models

Lina Vasiliauskaitė[1], Yaara Ofir-Rosenfeld[1], Mark Albertella[1], Annabelle Congras[2], Coralie Hoareau-Aveilla[2], Jerry McMahon[1], Oliver Rausch[1]
[1]Storm Therapeutics Ltd., Cambridge, UK
[2]Evotec SAS, Toulouse, FR

1 Introduction

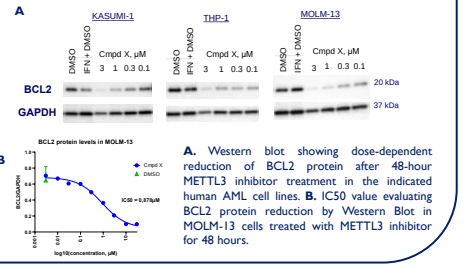
METTL3 is an RNA methyltransferase responsible for the deposition of N-6-methyladenosine (m^6A) modification on mRNA and lncRNA targets to regulate their stability, splicing, transport and translation. To date, METTL3 has been implicated in the initiation and progression of multiple cancer types, with the highest expression of METTL3 mRNA observed in acute myeloid leukemia (AML). Currently, one line of standard of care therapy for AML patients is Venetoclax, which targets the anti-apoptotic protein BCL2. It was shown that m^6A, 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 NCT05584111). Here, we explore pharmacological inhibition of METTL3 as monotherapy or in combination with Venetoclax in AML models *in vitro* and *in vivo*.

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



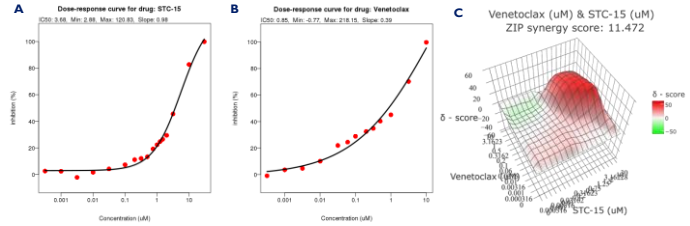
A. IC50 values of STC-15 in 30 AML cell lines, where cells were treated for 5 days and cell viability assessed by SRB assay. **B.** Growth inhibition curves of the top 10 most sensitive cell lines as defined in A. **C.** IC50 values of 12 AML PDXs, where cells were treated *in vitro* with METTL3 inhibitor for 6 days and cell viability assessed by CellTiter-Glo assay.

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



A. Western blot showing dose-dependent reduction of BCL2 protein after 48-hour METTL3 inhibitor treatment in the indicated human AML cell lines. **B.** IC50 value evaluating BCL2 protein reduction by Western Blot in MOLM-13 cells treated with METTL3 inhibitor for 48 hours.

4 STC-15 shows synergy with Venetoclax *in vitro*



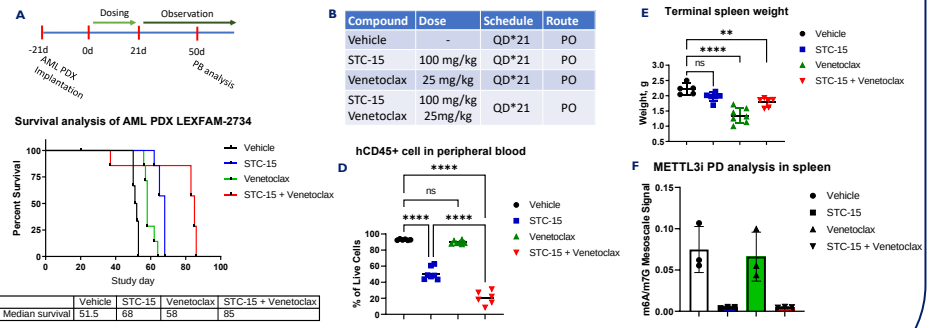
A. A dose-response curve of STC-15 in MOLM-13 cells treated for 72 hours. **B.** A dose-response curve of Venetoclax in MOLM-13 cells treated for 72 hours. **C.** A synergy plot generated in MOLM-13 cells treated with combination of STC-15 and Venetoclax for 72 hours.

Synergy score at the **highest synergistic area is 51**.

Data presented in figures A-C is a representative example of 3 independent experiments.

Plots and synergy analysis performed with www.synergyfinder.fimm.fi

5 STC-15 and Venetoclax combination treatment enhances survival in an AML PDX model *in vivo*



A. Scheme representing the outline of the study (PB – peripheral blood). **B.** Table showing group assignment and therapy schedule. **C.** Survival analysis of all treatment groups in the study. **D.** Flow cytometry analysis of human CD45+ cells in mouse peripheral blood on study day 50. **E.** Spleen weight recorded in mice post termination. **F.** Measurement of m^6A levels in spleen samples (study day 21) as a direct readout of METTL3 enzymatic inhibition.

6 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 tool inhibitors. In addition, METTL3 inhibition led to a dose-dependent downregulation of BCL2 protein. Matrix-combination experiments have shown a high degree of synergy between STC-15 and Venetoclax: in MOLM-13 cells the most synergistic area had a score of 51, 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 68 days *vs* 58 days, respectively). The survival results were supported by reduced numbers of circulating human CD45+ 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 a phase I, First-in-Human multiple ascending dose study (NCT05584111).

AACR AML, Jan 2023