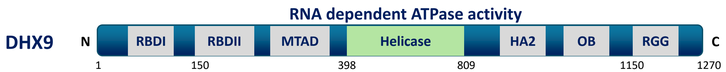
Discovery of an allosteric, potent and selective DHX9 helicase inhibitor with best-in-class potential for the treatment of genomically unstable cancers

Taran Khanam, Helen Harrison, Peter Astles, Harry Wing, Rita Chaouni, Roxine Staats, Tamsin Samuels, Richard Fosbeary, Natalie Webster, Angela Shibu, Giles Pergl-Wilson, Elizabeth Anderson, Beth Thomas, Oliver Rausch

STORM Therapeutics Limited, Babraham Research Campus, Cambridge, United Kingdom

DHX9: an RNA helicase important for maintaining genome stability

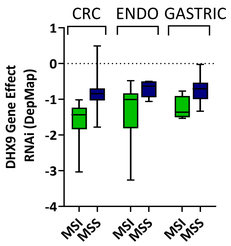


- **DHX9** unwinds dsDNA/RNA, and complex structures including R-loops, circular RNAs and G-quadruplexes
- Functions in replication, transcription, translation, RNA splicing and processing
- Over-expressed in multiple cancers, including colorectal, endometrial and lung tumors
- Cancers with genomic instability, high mutation burden and replication stress e.g. MMR-deficient tumors, depend on DHX9, making it a promising, tumor-selective target for precision oncology in molecularly defined cancer subsets

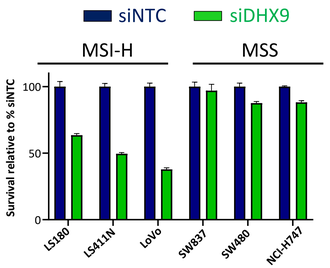
Lee et al., 2016; Aktas et al., 2017; Gulliver et al., 2020; Castro et al., 2025

DHX9 helicase is a vulnerability in genomically unstable DNA mismatch repair deficient (MMRd/MSI-H) cancers

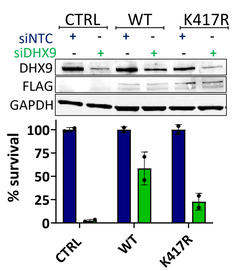
MSI-H cancer cell lines are selectively dependent on DHX9



DHX9 knockdown selectively reduces cell viability in MSI-H cells

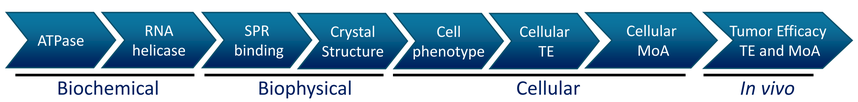


DHX9 helicase activity drives dependency in MSI-H cells



Multiple screening approaches and comprehensive assay cascade identified advanced lead DHX9 inhibitor STM11315*

Extensive pharmacological audit trail underscores STM11315 best-in-class potential

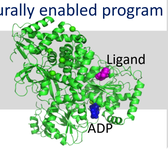


Structurally enabled program

Computational Virtual Screen

High Throughput Screen

Knowledge Based Chemistry



	Optimised molecule	2nd generation
	STM11315	STM11528
RNA Helicase IC_{50}	< 5 nM	< 1 nM
MSI cellular EC_{50}	< 20 nM	< 1 nM
MSS selectivity	>1000x	>200x

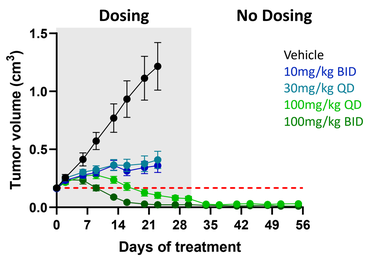
STM11315 has an excellent drug profile with best-in-class potential*

STM11315 is a stable, highly potent DHX9i with good cross-species PK, no safety liabilities, low projected human dose and no safety or CYP DDI liabilities

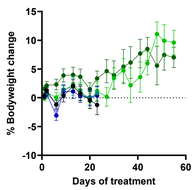
Table 1: STM11315 drug profile	Test System	Result
Biochemical	DHX9 ATPase IC_{50}	<10 nM
	DHX9 Helicase RNA Unwinding IC_{50}	<5 nM
	Selectivity: 10 Other Helicases (incl WRN, DHX36) IC_{50}	>30 μM
	DHX9 SPR Binding KD	<2 nM
Cellular viability, 7 Days CTG	MSI-H: LS411N EC_{50}	<20 nM
	Selectivity-MSS: SW480 EC_{50}	>10 μM
Cellular Target Engagement	LS411N EC_{50}	<20 nM
PK	**Mu** Cl (ml/min/kg) / Vss (L/Kg) / %F	26 / 3.5 / 63
	Rat Cl (ml/min/kg) / Vss (L/Kg) / %F	11 / 1.9 / 94
	Dog Cl (ml/min/kg) / Vss (L/Kg) / %F	16 / 6 / >100
Safety	hERG / Nav1.5 / Cav1.2 IC_{50}	>10 / >30 / >30 μM
	Kinase safety panel	> 1 μM
	In vitro safety panels	No liability

STM11315 drives robust and durable MSI-H tumor regression*

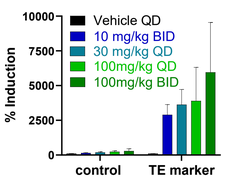
Complete and durable tumor regression



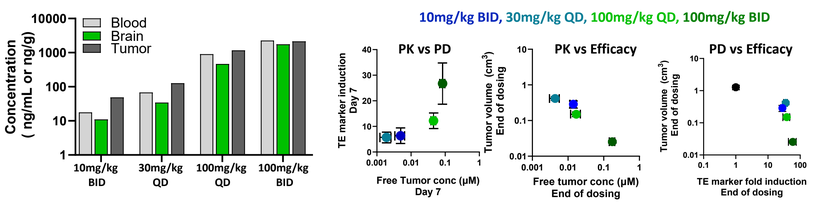
STM11315 is well tolerated



Target engagement is dose dependent

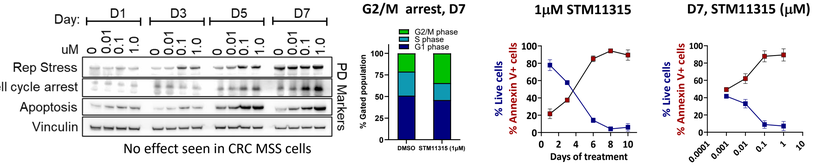


Tumor and brain penetration demonstrated. PK, PD and efficacy well correlated



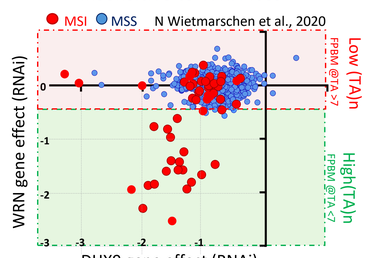
STM11315 Mechanism of action demonstrated as time- and dose- dependent

STM11315 induces PD response, cell cycle arrest and apoptosis in CRC MSI-H cells

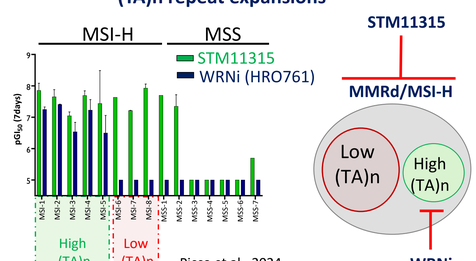


STM11315 induces selective anti-proliferative effects in a broader range of cancer cells than WRN inhibitor

DHX9 dependence in MSI-H cells insensitive to WRN loss



STM11315 activity in MSI-H cells is independent of (TA)n repeat expansions



Conclusions

- DHX9 is a compelling therapeutic target in cancers with genomic instability, high mutation burden or replication stress e.g. MMRd/MSI-H tumors.
- **STM11315 is a potent, selective** DHX9 inhibitor that induces anti-proliferative effects via increased replication stress, cell cycle arrest and apoptosis.
- STM11315 has an **excellent** oral **drug profile, no safety or CYP DDI liabilities** while demonstrating **brain penetration.**
- **Well tolerated *in vivo***, STM11315 achieves **complete, durable tumor regression** in a CRC CDX model, with **no tumor regrowth post treatment for >25 days.**
- Pharmacodynamic markers correlate with efficacy, confirming on-mechanism activity.
- With robust **selectivity, efficacy, PK/PD, safety profile, high potency** and **low human dose prediction,** the **STM11315 series** offers **best-in-class DHX9 inhibitor clinical candidates.**

Acknowledgements

- We thank the project team, consultants, CRO partners and colleagues for their valuable contributions

*Sygnature Discovery provided chemistry, DMPK, Hit-ID, *in vitro* screening, crystallography and *in vivo* support