Targeting DHX9 Inhibition as a Novel Therapeutic Modality in Microsatellite Instable Colorectal Cancer

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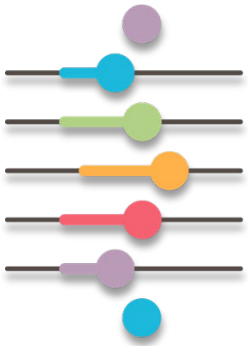
Disclosure Information

Presenter: Jennifer Castro (jcastro@accenttx.com)

I have the following relevant financial relationships to disclose:

Employee and shareholder of: Accent Therapeutics

I have no other financial relationships to disclose.



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RNA Helicase DHX9 Plays an Important Role in Maintaining Genome Stability

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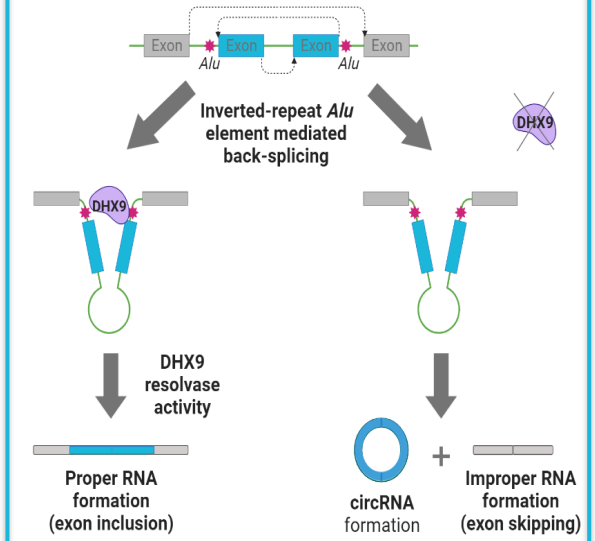
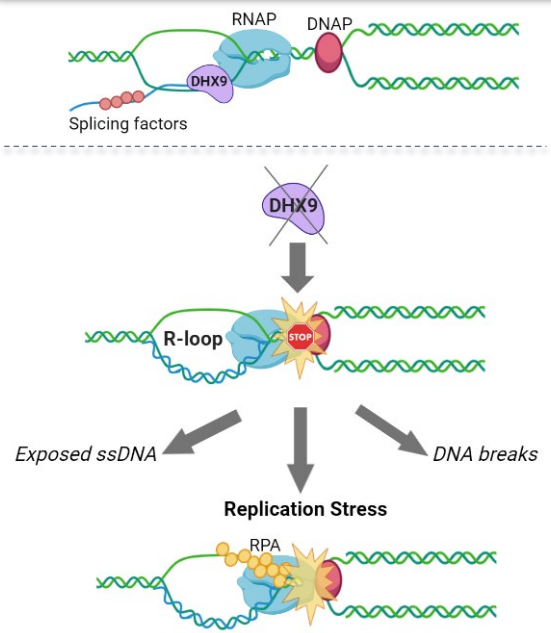
DHX9 (RNA Helicase A, RHA):

- Is a DEAH-box RNA helicase
- Unwinds double stranded DNA, RNA, and secondary RNA/DNA structures
  - Including R-loops, D-loops, circular RNA, and G-quadruplexes
- Plays important roles in replication, transcription, translation, RNA splicing and RNA processing

DHX9's Role in *Alu* Element Mediated circRNA Formation



DHX9's Role in R-loop Prevention



*Lee and Pelletier, Oncotarget (2016)
*Aktas et al, Nature (2017)
*Chakraborty et al, Nature (2018)
*Gulliver et al, Future Science (2020)

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DHX9 is a Novel Oncology Target with a Selective Dependency Profile in Microsatellite Instable Tumors

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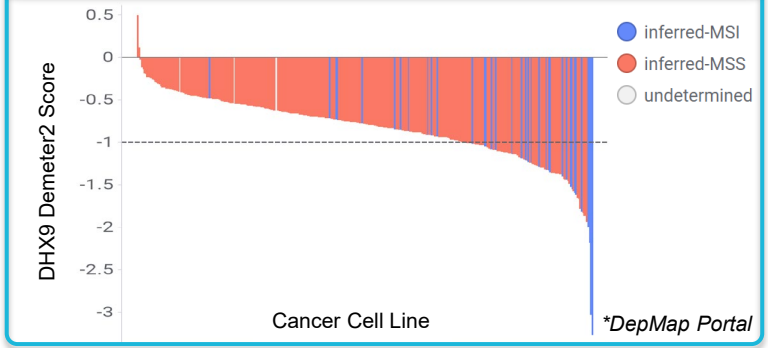
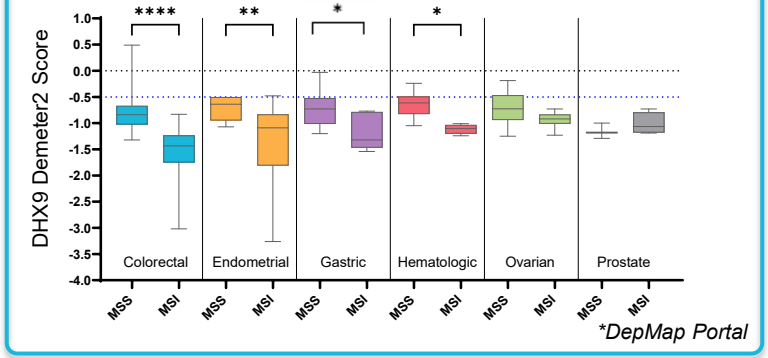
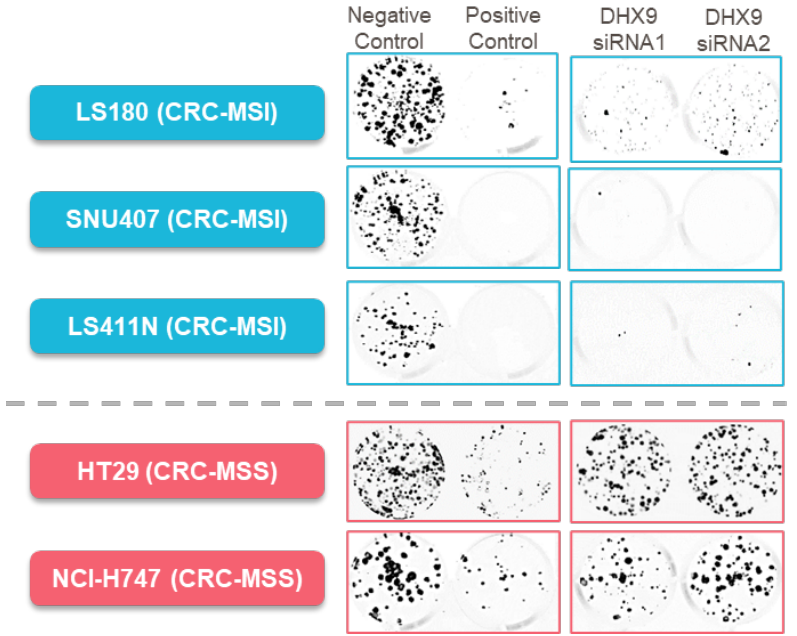
DHX9 Dependency in RNAi Screens



DHX9 Dependency in Relationship to MSI Status





Tumors with underlying mutations in the MMR pathway (e.g.: CRC-MSI) are likely vulnerable to increased replication stress

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DHX9 Knockdown Leads to Replication Stress, Cell Cycle Arrest and Apoptosis in CRC-MSI

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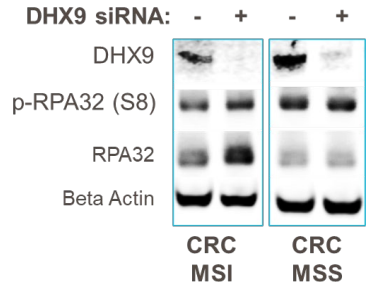
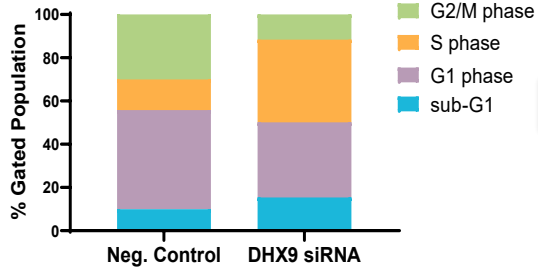
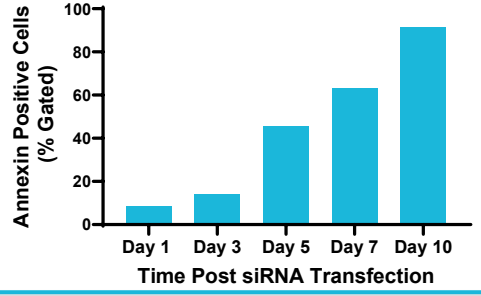
RPA Accumulation in CRC-MSI 3 Days Post DHX9 KD



S-phase Cell Cycle Arrest in CRC-MSI 5 Days Post DHX9 KD



Late Onset of Apoptosis in CRC-MSI Upon DHX9 KD Over Time



- DHX9 siRNA knockdown leads to an accumulation of RPA in CRC-MSI cells, but not CRC-MSS cells, indicating increased replication stress
- Cell cycle arrest in S-phase observed at 5 days post transfection
- Increase of Annexin positive cells over time upon DHX9 knockdown, consistent with timing of cell cycle arrest

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Accent's DHX9 Drug Discovery Program is Enabled by Proprietary Crystal Structure and a Robust Assay Suite

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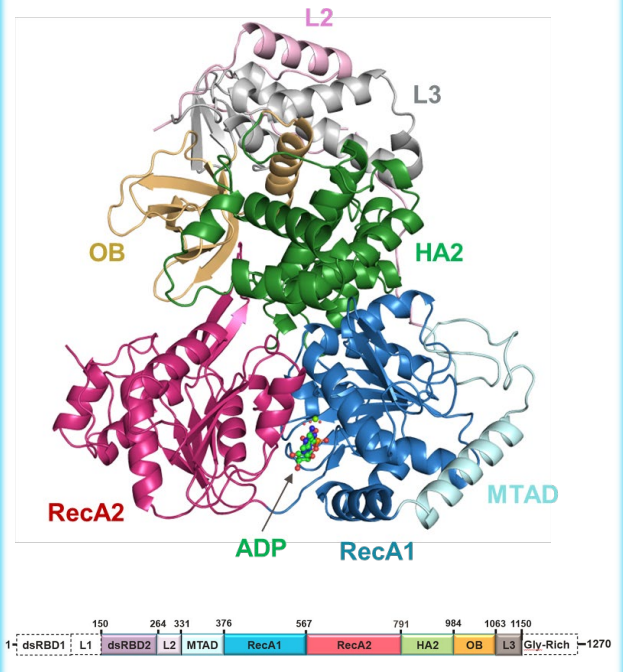
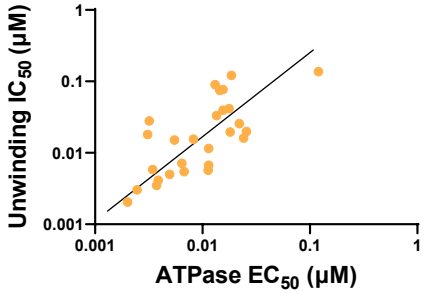
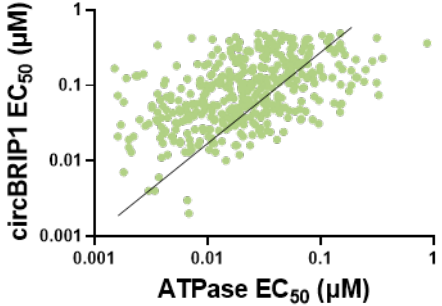
Crystal Structure of Human DHX9 (2.62 Å)



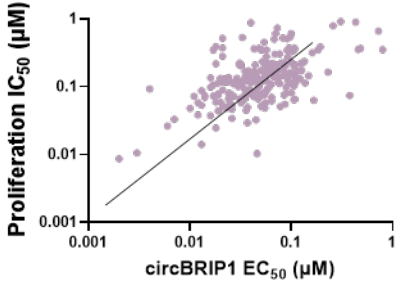
DHX9 ATPase Biochemical Activity Correlates to Unwinding Inhibition



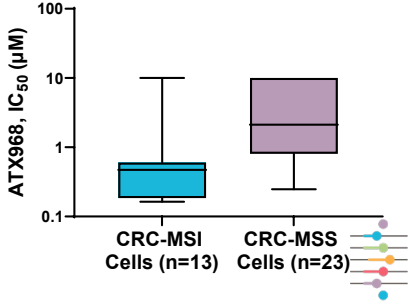
DHX9 Biochemical Activity Correlates to Cellular Target Engagement



Cellular Target Engagement Correlates to Anti-Proliferative Activity



CRC Focused Cell Panel Proliferation Screen Confirms MSI Selectivity



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DHX9 Inhibitor ATX968 is Well Tolerated *in vivo* and Exhibits Robust and Durable Tumor Regression Selective to CRC-MSI

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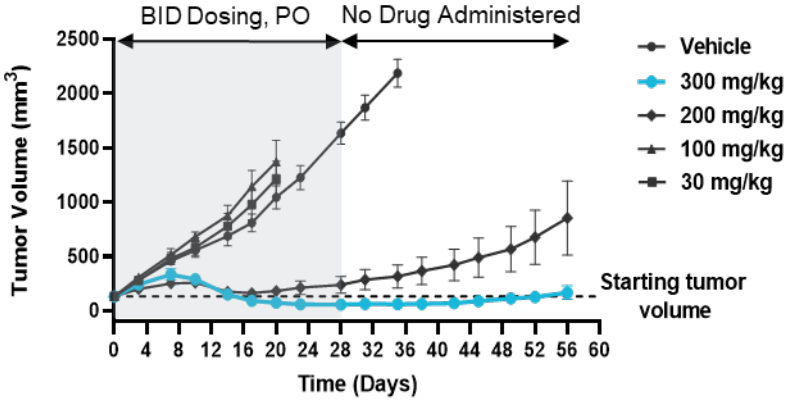
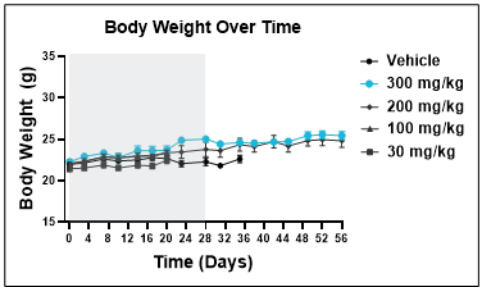
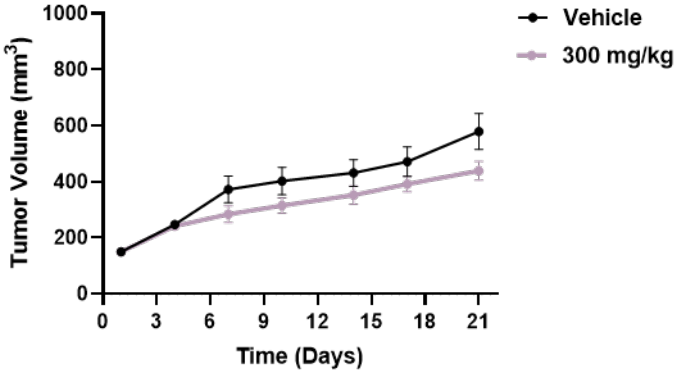
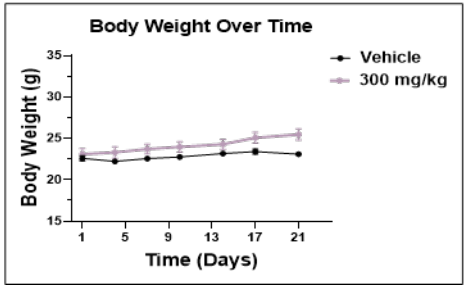
CRC-MSI LS411N Xenograft Efficacy Study ATX968, BID PO





CRC-MSS SW480 Xenograft Efficacy Study ATX968, BID PO





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ATX968 Achieved Dose Dependent Intra-tumoral circBRIP1 PD with a Well Correlated PK/PD/Efficacy Relationship

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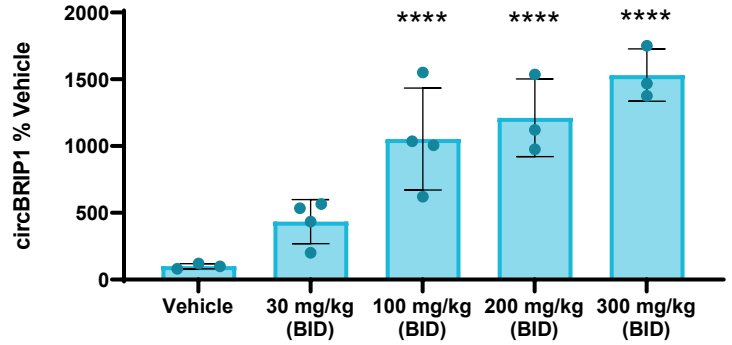
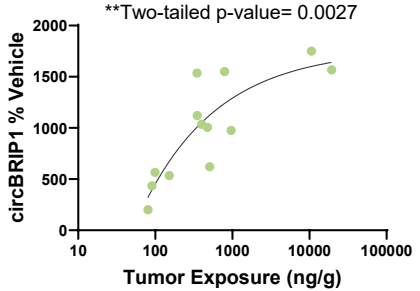
circBRIP1 Induction in LS411N Tumors



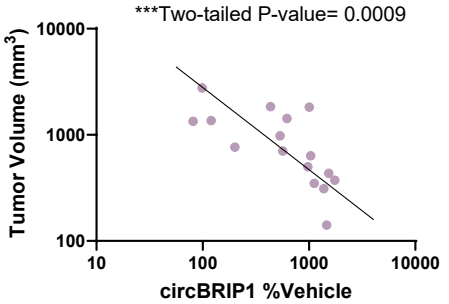
**** *Statistically Significant by 2way ANOVA p-value= <0.0001*

DHX9 inhibition leads to dose dependent circBRIP1 induction in all cells/tumors, including human PBMCs

Tumor Exposure Correlates to Intra-tumoral circBRIP1 PD



Tumor Volume Correlates to Intra-tumoral circBRIP1 PD



*Data shown are from tumor samples collected at day 21, 12 hours post last dose

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DHX9 Inhibitors: Candidate Novel Therapeutics for Tumors with MSI or Defective DNA Repair Pathways

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Summary of Presentation

- DHX9 is an RNA helicase with important roles in maintaining genome stability, including prevention of R-loops and replication stress
- Novel inhibitors of DHX9 demonstrate selective anti-proliferative activity in CRC-MSI cells with defective mismatch repair
- Oral dosing of mice bearing human CRC-MSI tumors with ATX968 results in robust and durable tumor regression with correlated intra-tumoral induction of the PD biomarker circBRIP1
- PD biomarker circBRIP1 can also be measured in human PBMC, making circBRIP1 a potential non-invasive PD biomarker for clinical applications
- Sensitivity of other tumor types to DHX9 inhibition is currently under investigation

Acknowledgements

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THANK YOU!

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