High CRBN expression in neuroendocrine cancer creates a vulnerability to GSPT1 molecular glue degraders: Target indication selection for CYRS1542 development

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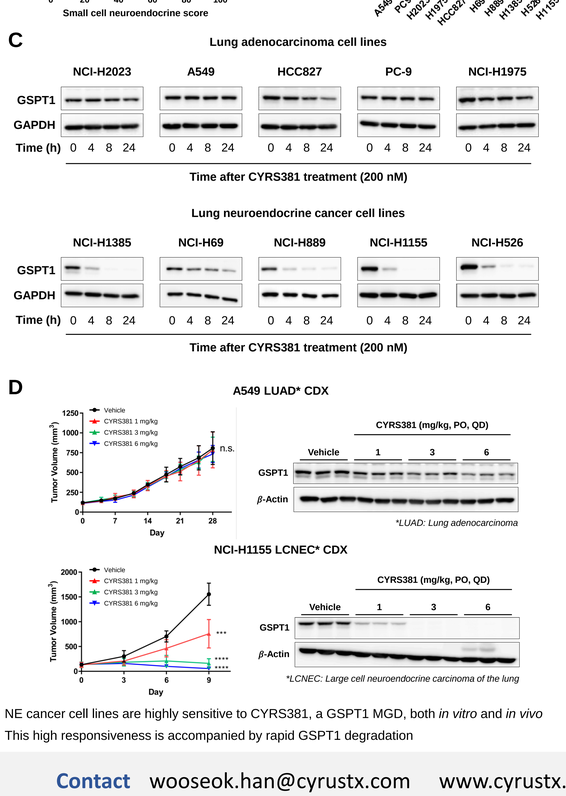
Introduction

- Multiple companies are developing GSPT1-targeted molecular glue degraders (MGDs) for neuroendocrine (NE) cancers, a rare and aggressive cancer type
- Our previous work identified CYRS1542, an optimized GSPT1 MGD with a superior therapeutic index, derived from CYRS381 (originally known as SJ6986) (Joo et al., AACR 2024)
- In this study, we investigated the mechanistic basis of GSPT1 MGD sensitivity in NE cancers, using CYRS381 as a tool compound to assess selective vulnerabilities

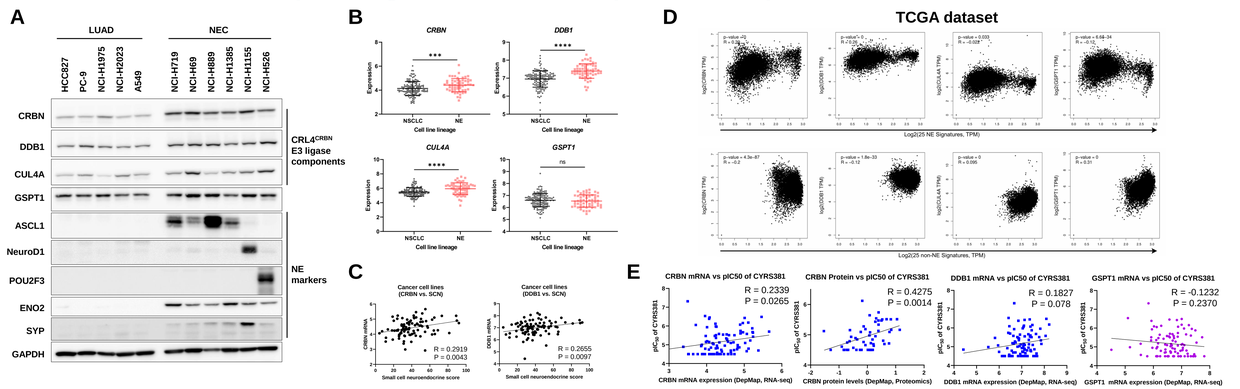
Results

Neuroendocrine cancers are preferentially sensitive to GSPT1 MGD



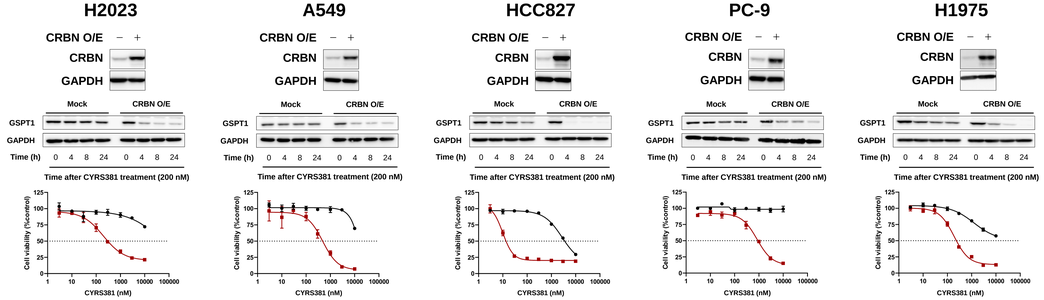
- NE cancer cell lines are highly sensitive to CYRS381, a GSPT1 MGD, both *in vitro* and *in vivo*
- This high responsiveness is accompanied by rapid GSPT1 degradation

Neuroendocrine cancers express higher CRBN-DDB1 expression compared to non-neuroendocrine cancers



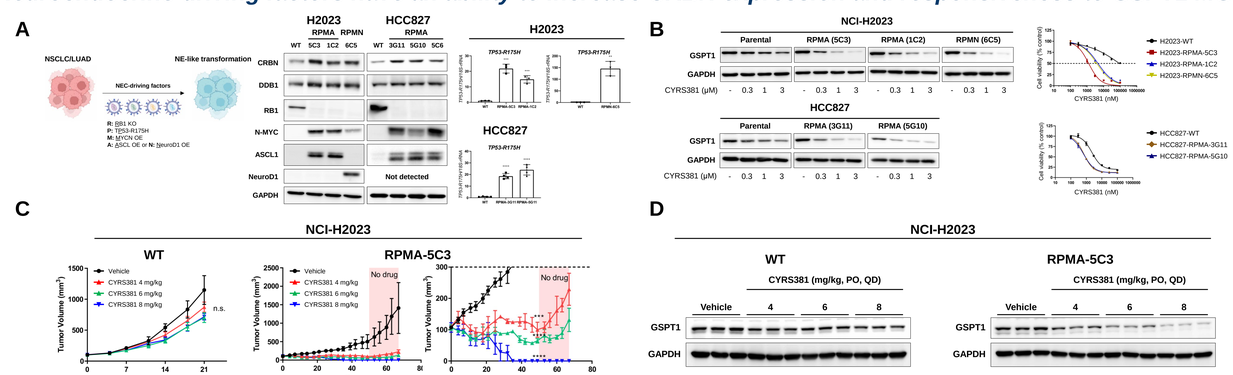
- NE cancer cell lines exhibit significantly elevated CRBN and DDB1 mRNA and protein expression compared to lung adenocarcinoma cell lines
- TCGA data reveal a significant correlation between CRBN expression and the NE cancer gene signature in human tumor tissues
- In a panel of cancer cell lines, CRBN expression is strongly correlated with sensitivity to GSPT1 MGD, but not with GSPT1 expression

Overexpression of CRBN is sufficient to confer cellular vulnerability to GSPT1 MGD



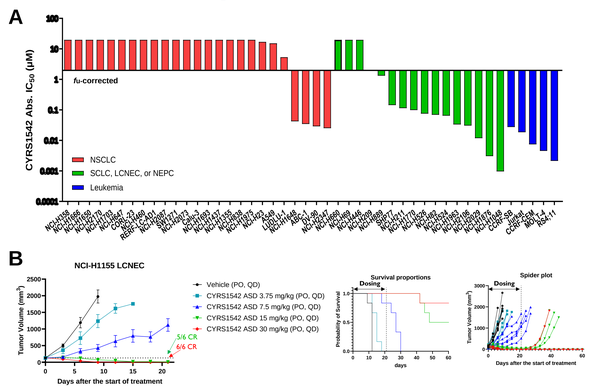
- CRBN overexpression in lung adenocarcinoma cell lines facilitates GSPT1 degradation induced by GSPT1 MGD
- Lung adenocarcinoma cell lines with CRBN overexpression exhibit extremely increased sensitivity to GSPT1 MGD

Neuroendocrine-driving factors have an ability to increase CRBN expression and responsiveness to GSPT1 MGD



- The ectopic expression of RPMA or RPMN in lung adenocarcinoma cell lines consistently increased CRBN and DDB1 expression across all clones, regardless of the parental cell line (i.e., H2023 and HCC827)
- The increased CRBN expression induced by RPMA or RPMN ectopic expression resulted in enhanced cellular responsiveness to CYRS381, a GSPT1 MGD, both *in vitro* and *in vivo*

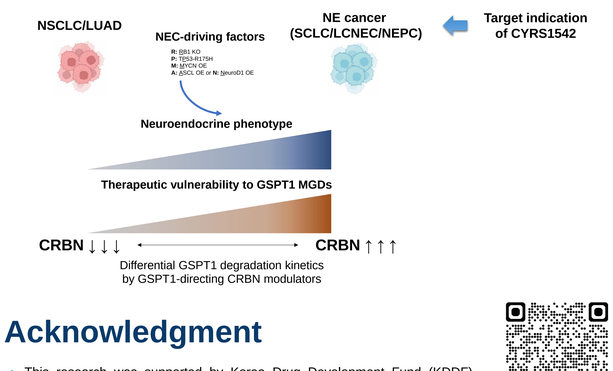
CYRS1542 is similarly active in neuroendocrine cancer



- CYRS1542, a clinical development candidate originating from CYRS381, demonstrates preferential activity against NE cancer *in vitro* and *in vivo*
- CYRS1542 significantly reduced tumor volume in a PDX model of SCLC with a NE phenotype

Conclusion

- Here, we present the mechanistic basis underlying the heightened vulnerability of NE cancers to GSPT1 MGDs
- Based on this mechanistic understanding, NE solid cancers were selected as the target indication for CYRS1542, a potential best-in-class GSPT1 MGD for the treatment of patients with these cancers
- The IND submission to the FDA for CYRS1542 has been completed, enabling a Phase 1 clinical trial to evaluate this hypothesis – An IND submission to the MFDS is being prepared



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