The Discovery of Small Molecules for the Selective Inhibition of Pancreatic Cancer Metastasis

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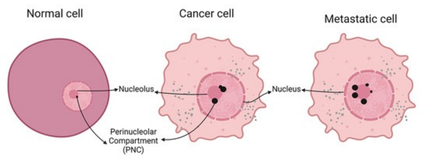
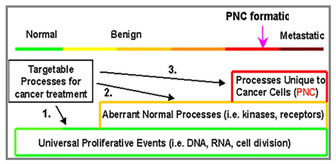
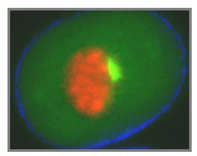
Metarrestin: Phenotypic Discovery to Clinical Agent



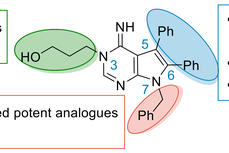
Perinucleolar compartment (PNC)
- Associated with the nucleolus
- **Present in metastatic tumor cells** not normal cells
- High PNC prevalence linked to poor patient outcome
- PNC integrity is dependent on RNA polymerase III
- DNA intercalation can disassemble the PNC
- We acknowledge support from NCI (R01 CA269967)

U.S. National Library of Medicine ClinicalTrials.gov
Metarrestin (ML-246) in Subjects With Metastatic Solid Tumors
clinicaltrials.gov, NCT04222413





- hydroxy, ether or amine afforded potent analogues
- appropriate constraint led to the highest potency



- unsubstituted phenyl groups preferred
- C-6 aryl critical for activity
- Aliphatic groups not active

- benzyl, phenethyl and 4-methoxybenzyl afforded potent analogues
- alkyl side chains were generally less potent

Figure 1 Initial mouse PK studies

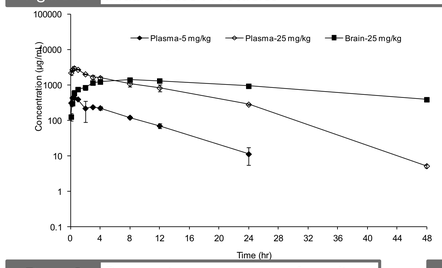
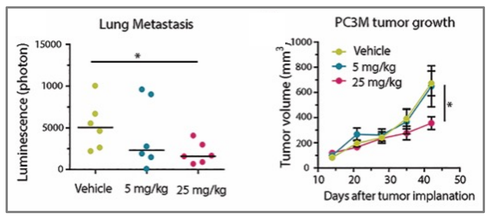


Figure 2 Xenograft animal studies (prostate cancer and a breast cancer patient-derived cell line)



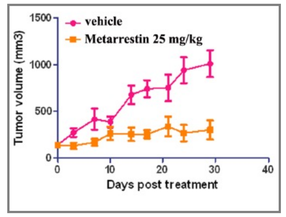


Figure 3 Pancreatic cancer xenograft studies

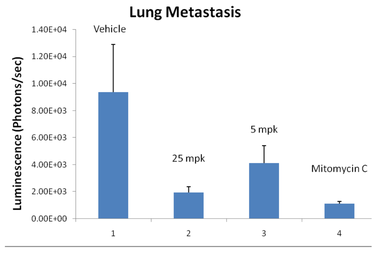


Figure 4 Autopsy organ comparison

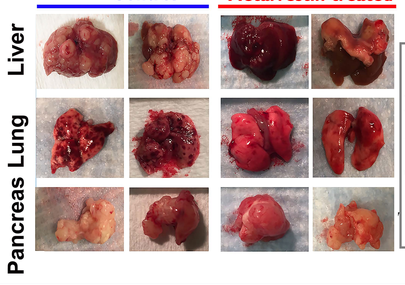
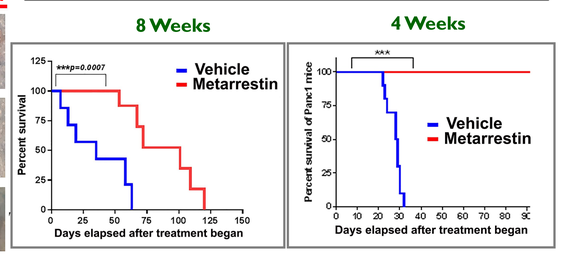


Figure 5 Pancreatic cancer mouse survival, treatment at 8 and 4 weeks



Alternative Scaffolds Identified from the High-Throughput Screen

Figure 6 New hit scaffolds identified from the high-throughput screen for metarrestin

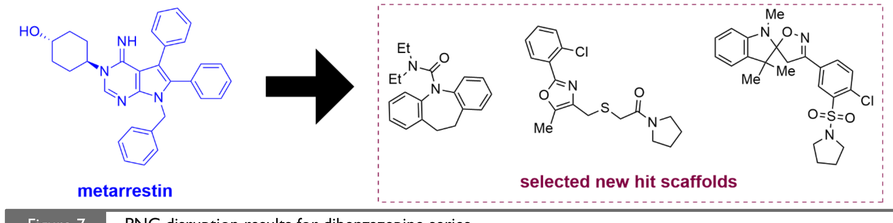
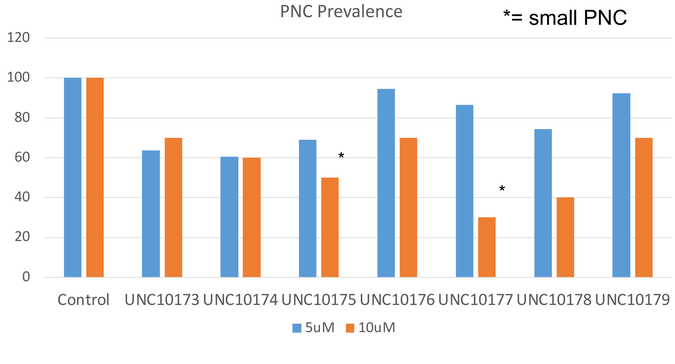
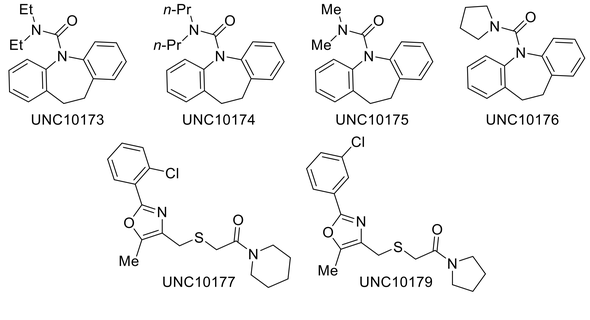


Figure 7 PNC disruption results for dibenzazepine series





Scaffold Synthesis

Figure 8 UNC11204 and UNC11205 Analog synthesis from commercial precursor

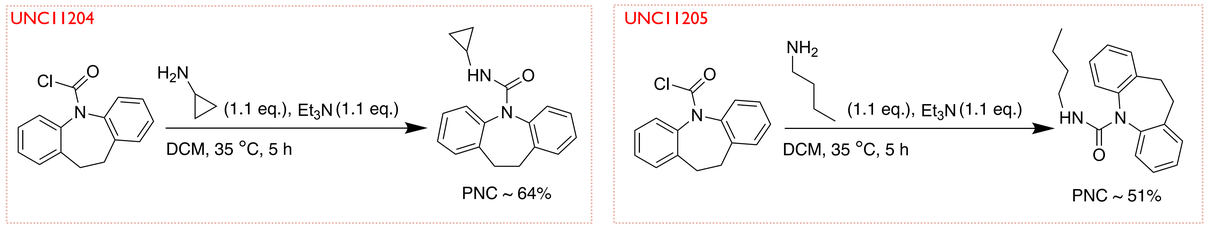
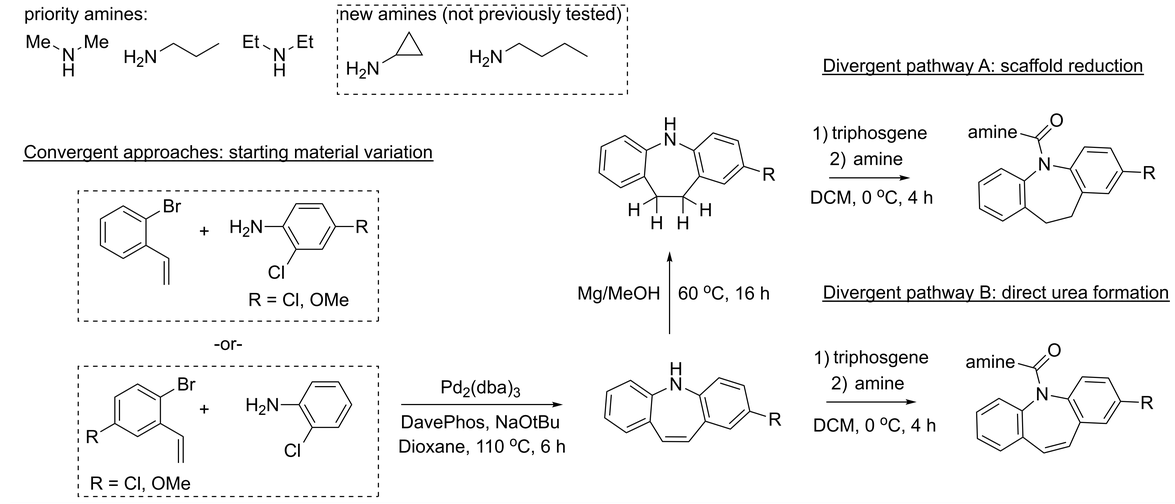
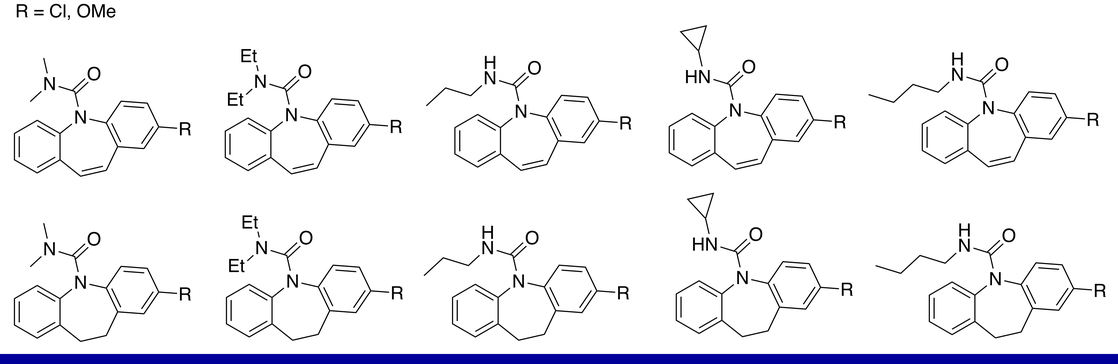


Figure 9 Synthetic routes of target structures



Target Structures

Figure 10 Structures of selected new analogues to validate the HTS scaffolds and probe molecular features critical for PNC disruption activity



Conclusion

- The analogs synthesized by substituting different amines showed promising inhibition of PNC.
- Future efforts will focus on synthesizing additional analogs that incorporate a methoxy and chlorine on the para position of the aromatic ring.

References

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