Preclinical evaluation of the CNS penetration of a novel series of MTA-cooperative PRMT5 inhibitors including TNG456

EXTH-32

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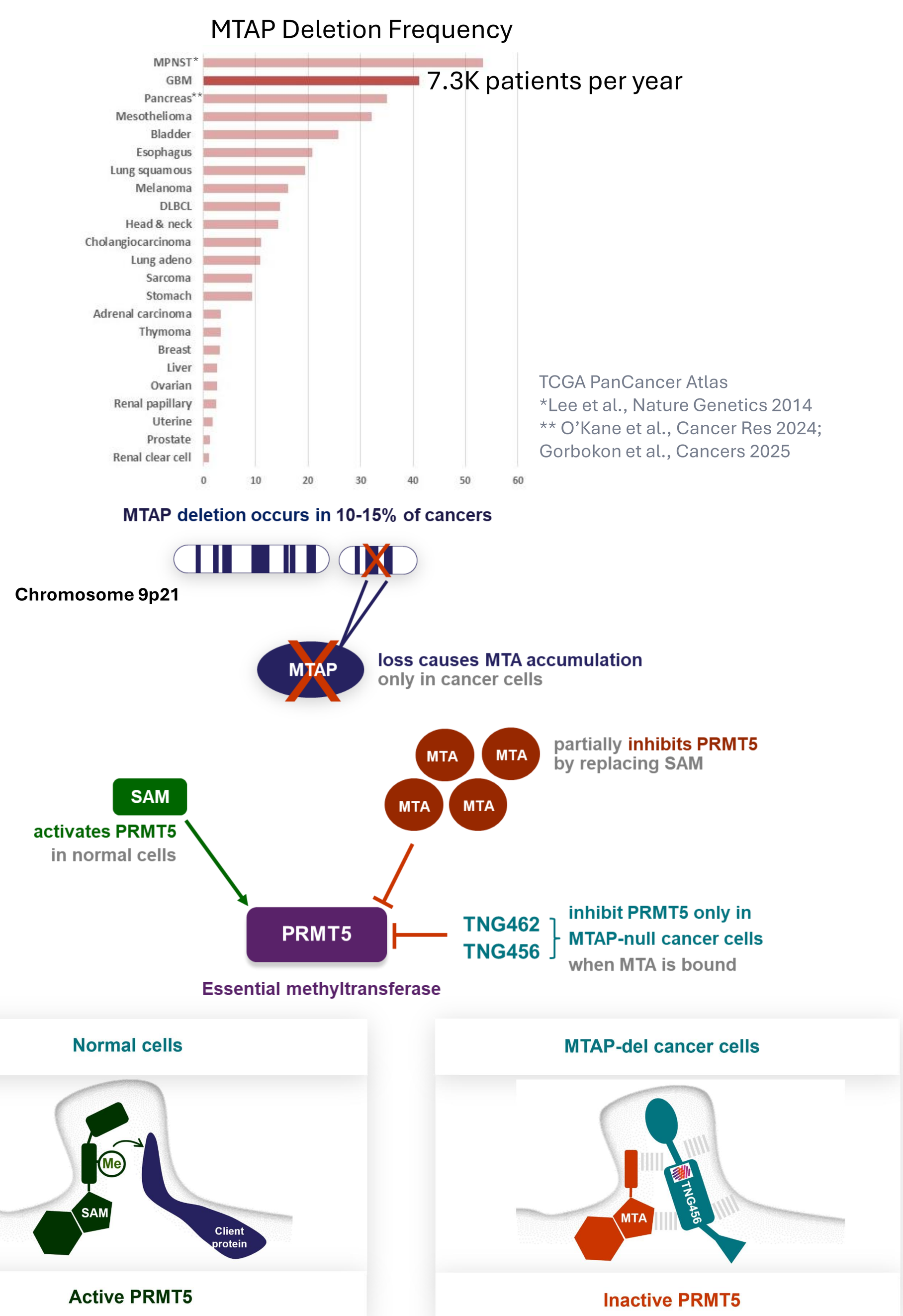
Abstract

The treatment of central nervous system (CNS) malignancies, including metastases, remains a significant unmet medical need. This is especially true for glioblastoma, where up to 50% of cases have loss of MTAP, which creates a dependency on PRMT5 and a susceptibility to MTA-cooperative PRMT5 inhibitors. Therefore, it is critical to establish preclinical drug discovery workflows that emphasize the importance of deriving free brain exposure to accurately predict drug exposure in the human CNS compartment.

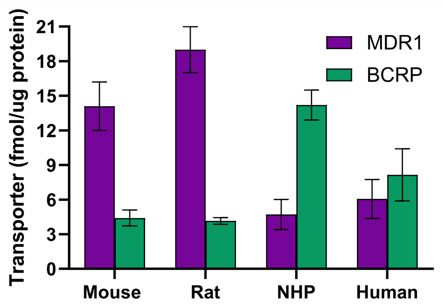
This study evaluates the utility of preclinical methods, which include a monkey cerebrospinal fluid (CSF) model and characterization of physicochemical properties of compounds, such as permeability and efflux potential, to predict free brain drug exposure in humans. The non-terminal monkey CSF model permits assessment of CNS penetration with minimal invasiveness. Complementary to this survival study, terminal brain tissues were collected from 14-day terminal dose range finding (DRF) toxicology studies to verify and correlate predicted brain penetration with actual exposure levels. Our findings demonstrate a strong correlation between CSF concentrations in the monkey model and free brain drug exposure. In contrast, rodent terminal brain drug exposure models had limited utility. These data highlight the importance of integrating non-terminal preclinical models and physicochemical analysis to improve the safety and efficacy of CNS-targeted therapeutics.

MTA-cooperative PRMT5 inhibitors are synthetic lethal with MTAP deletion which occurs at high prevalence in CNS tumors



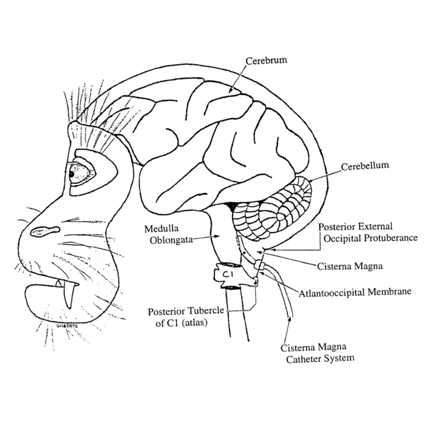
Non-human primate (NHP) CSF is an excellent model for human drug CNS penetration due to their BBB similarity

Efflux transporters expression levels at BBB



MDR1 and BCRP contributes to ~90% and 10% of efflux cross BBB. NHP closer to human vs rodents[1,2,3]

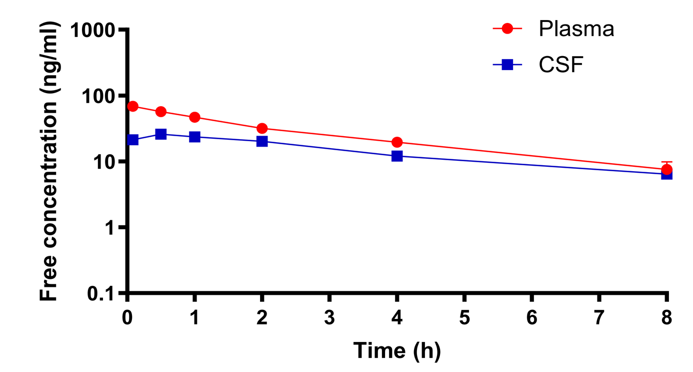
CSF ported NHP model



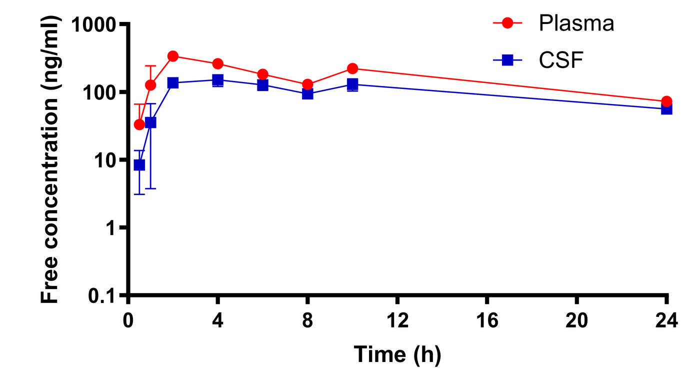
Surgically placed port at the cisterna magna allows for serial, noninvasive sampling of CSF without anesthesia[4]

TNG456 exhibited CNS penetration in two independent NHP studies, as evidenced by CSF sampling

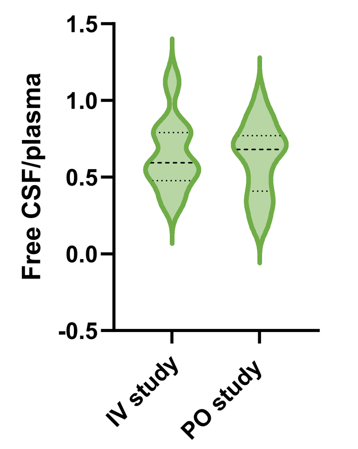
TNG456 in NHP following an intravenous dosing at 1 mg/kg



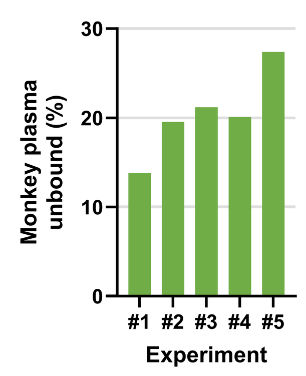
TNG456 in NHP following twice daily oral dosing of 10 mg/kg



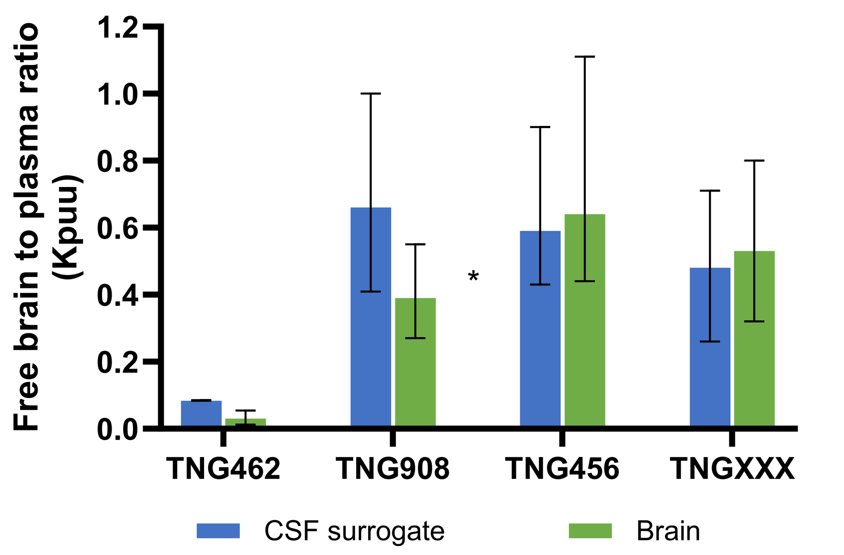
TNG456 CNS penetration



The unbound fraction of TNG456 fluctuates by up to twofold across experiments



NHP CSF is a robust surrogate for free drug brain exposure, as confirmed by direct brain measurements



*TNG908 brain kpuu calculated based on extrapolated plasma concentration

Terminal brain and time-matched plasma samples were collected during the nonrodent DRF study

NHP CSF serves as a robust surrogate for free drug brain exposure, predicting within a twofold range for highly permeable, low-efflux compounds (e.g., TNG908, Additional TNG, and TNG456)

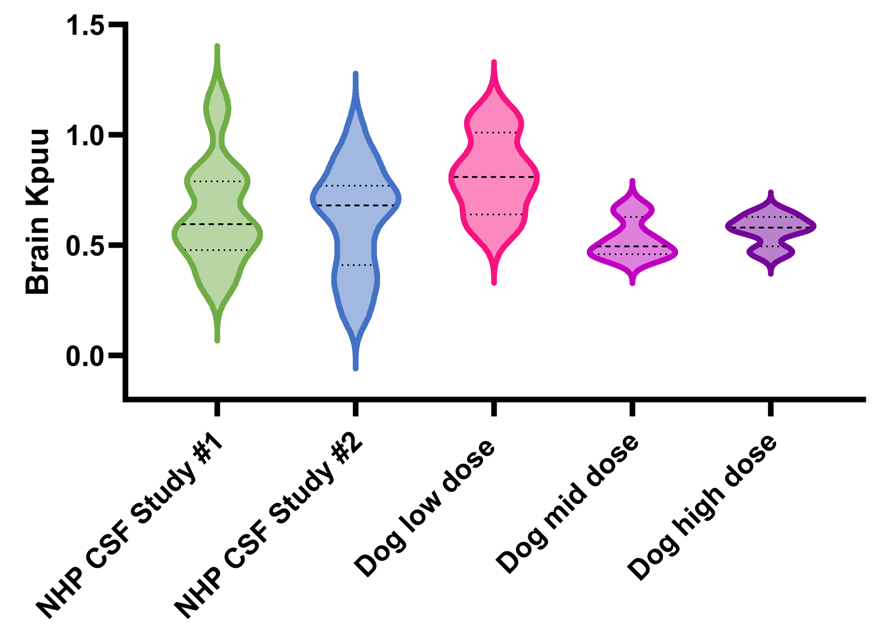
For efflux-prone small molecules (e.g., Vopimetostat (TNG462)), NHP CSF overestimates free brain exposure by 2.7-fold

Enhancing permeability & reducing efflux improves brain penetration: evidence from NHP CSF and nonclinical brain studies

Parameter	TNG462	TNG908	TNG456	TNGXXX
Cellular activity GI_{50} (nM)	4	110	20	10
MTAP-null selectivity	45X	15X	55X	70X
fu, Brain	0.039	0.071	0.025	0.038
NHP fu, Plasma	0.254	0.165	0.204	0.255
n, (Range)	4, (0.247-0.250)	3, (0.118-0.243)	5, (0.138-0.274)	3, (0.247-0.265)
Dog fu, Plasma	0.175	0.126	0.111	0.144
n, (Range)	4, (0.139-0.268)	3, (0.081-0.203)	5, (0.077-0.145)	3, (0.139-0.154)
NHP CSF/Plasma	0.02	0.12, 0.10	0.12, 0.12	0.18, 0.07
NHP CSF,u/Plasma,u	0.08	0.72, 0.60	0.57, 0.61	0.69, 0.27
NHP Brain Kp		0.82		
Dog Brain Kp	0.135		2.85	2.03
NHP or Dog Brain Kpuu	0.03	0.36	0.64	0.53
n, (Range)	21, (0.013-0.054)	3, (0.24-0.50)	12, (0.44-1.1)	12, (0.32-0.80)
MDCKII Permeability (cm/s)	2.3×10^{-6}	16.4×10^{-6}	12.9×10^{-6}	11.6×10^{-6}
MDR1 ER	81	3.2	2.6	2.4
BCRP ER	1.2	<2	1.1	1.0

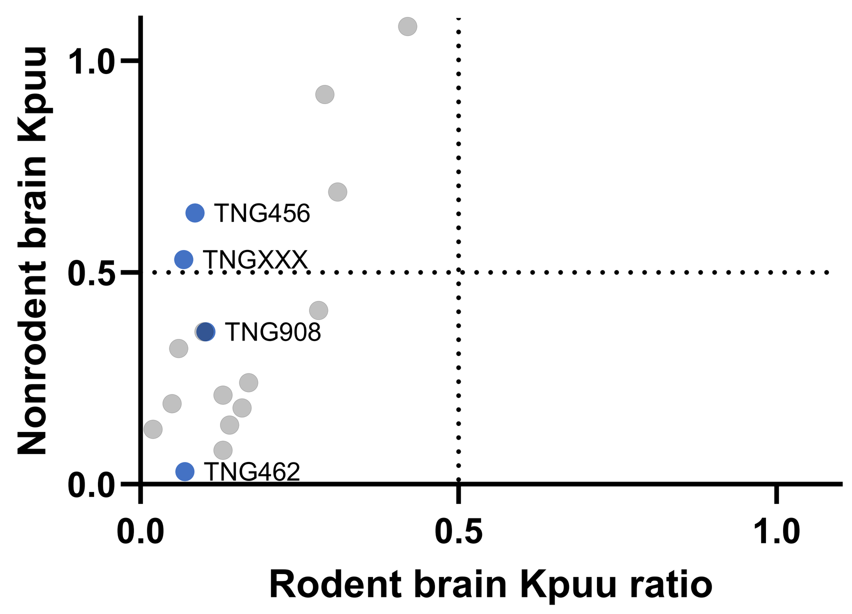
BCRP: breast cancer resistance protein; CSF: cerebrospinal fluid; ER: efflux ratio; Fu: unbound fraction; Kp: total tissue to total plasma ratio; Kpuu: free tissue to free plasma ratio; MDCKII: Madin-Darby canine kidney type II; MDR1: multidrug resistance 1; NHP: nonhuman primate.

TNG456 monkey free CSF/plasma brain levels in NHP closely align with dog brain exposure data from the DRF toxicology study



Terminal brain and time-matched plasma samples were collected during the nonrodent dog DRF toxicology study

Rodent brain Kpuu is lower than nonrodent and lacks the dynamic range to distinguish moderate from low brain penetration

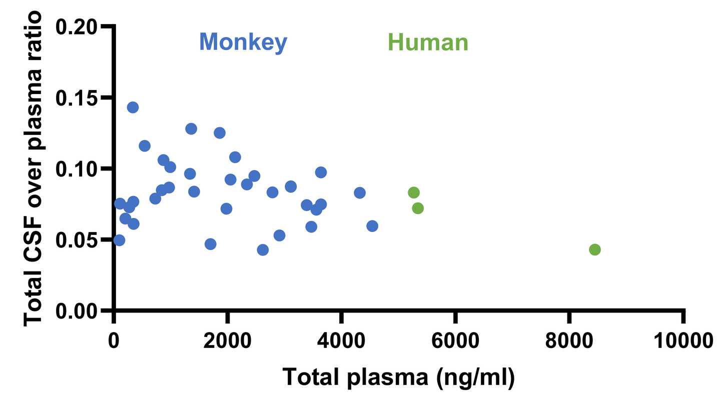


Rodent CNS studies can serve as an initial screen to eliminate compounds with low CNS exposure[5]

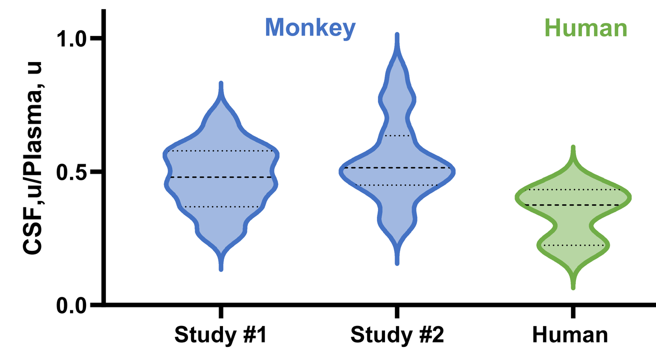
Collecting brain samples at the conclusion of terminal nonrodent toxicology studies offers valuable preclinical data for predicting human CNS exposure

The CSF levels of TNG908 in humans and NHPs are closely aligned, differing by less than twofold

Total TNG908 CSF/Plasma ratio



TNG908 Free CSF/Plasma ratio



Summary

- **MTAP Deletion in Cancer:** present in 10-15% of all human cancers, frequently observed in CNS malignancies (>40% glioblastomas) and brain-metastasizing tumors (15% NSCLC, 16% melanoma)
- **NHP CSF as a CNS Model:** due to BBB similarity, nonhuman primate CSF serves as a strong model for human drug CNS penetration
- **Predictive Value of NHP CSF:** validated by preclinical brain studies as a reliable predictor of free drug brain exposure
- **Optimizing Brain Penetration:** enhancing permeability and reducing efflux improves CNS exposure, as shown in NHP CSF and terminal brain studies
- **Rodent Model Limitations:** the rodent Kpuu model has a narrower dynamic range and struggles to distinguish moderate from poor brain-penetrant compounds
- **TNG908 Translational Consistency:** human CSF data align within a twofold range of monkey CSF data, supporting its predictive validity
- **CNS Penetration:** TNG456 demonstrates excellent brain penetration in preclinical studies and is predicted to be brain-penetrant in humans
- **CNS Efficacy:** TNG456 is expected to be clinically active in GBM due to improved selectivity and therapeutic index (vs TNG908) coupled with CNS penetration
- **Clinical Development:** TNG456 monotherapy is currently enrolling patients in a Phase 1/2 clinical trial (NCT06810544)

Acknowledgements

We sincerely thank our DMPK colleagues at Wuxi AppTec and Pharmaron, our Toxicology colleagues at WuXi, and our toxicology consultants at Akkeri, Kenjie Amemiya, Stephene Ford, and Ewa Budzynski, for their invaluable contributions to this poster.

We also extend our deepest gratitude to the TNG908-C101 clinical trial team, all the participating sites, investigators, patients and caregivers. Special thank you goes to Dr. Capucine Baldini at Gustave Roussy in France, and her patients who generously provided their CSF samples for the TNG908 analyses.

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