Preclinical evaluation of CNS drug penetration of a novel series of MTAP-selective PRMT5 inhibitors including TNG456

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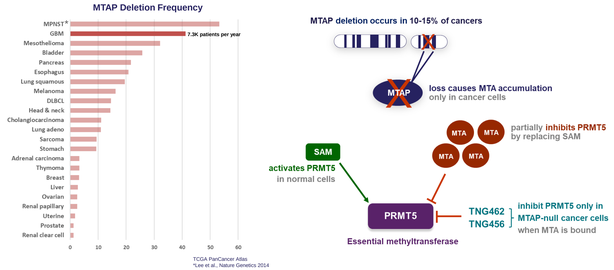
Poster #463

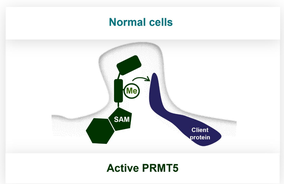
Abstract

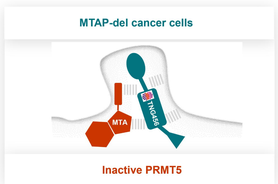
Treatment of brain tumors and brain metastases remains a significant unmet medical need. This is especially true for high-grade gliomas, where up to 50% of cases exhibit loss of MTAP, creating a dependency on PRMT5 and a susceptibility to MTA-cooperative PRMT5 inhibitors. For preclinical drug discovery, the accurate prediction of drug exposure in the human CNS compartment is therefore of critical importance.

This study evaluates the utility of preclinical models, specifically the monkey cerebrospinal fluid (CSF) model, alongside the physicochemical properties of compounds, including permeability and efflux characteristics, 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, as part of the 14-day terminal dose range finding toxicology studies, brain tissues were collected at necropsy 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, suggesting that incorporating these datapoints, in addition to optimizing permeability and efflux properties, enhances the reliability of CNS drug delivery predictions. This research highlights the importance of integrating non-terminal preclinical models and physicochemical analysis to improve the safety and efficacy of CNS-targeted therapeutics. In addition, utility of rodent terminal brain drug exposure models and the importance of deriving unbound free brain drug exposures will be discussed.

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

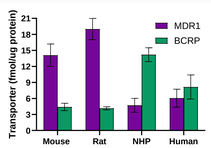






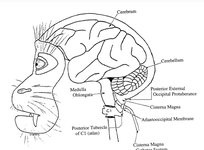
Non-human primate (NHP) CSF is an excellent model for human drug CNS penetration due to their BBB similarity

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]

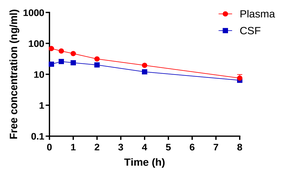
CSF Ported NHP model



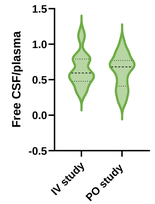
Surgically placed port at the cisterna magna allows for serial, noninvasive sampling of CSF without anesthesia[4]

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

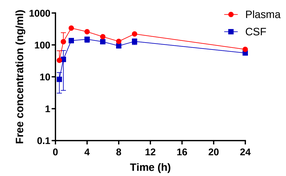
TNG456 in NHP following an intravenous dosing at 1 mg/kg



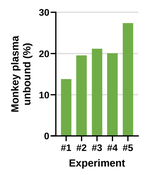
TNG456 CNS penetration



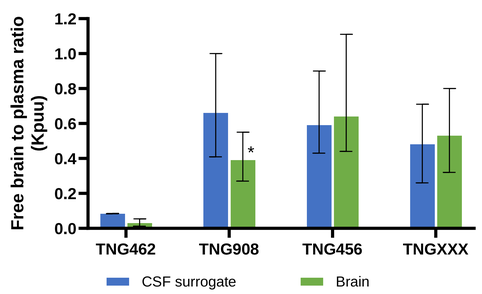
TNG456 in NHP following twice daily oral dosing of 10 mg/kg



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

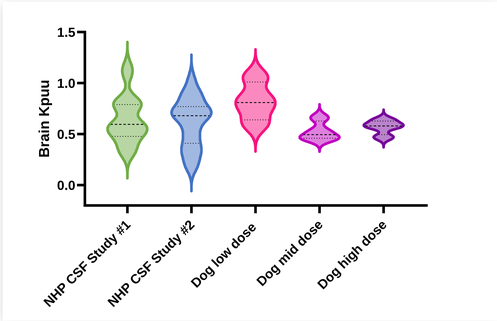
- Terminal brain and time-matched plasma samples were collected during the nonrodent DRF study
- NHP CSF serves as a robust surrogate for free drug brain exposure, predicting within a twofold range for highly permeable, low-efflux compounds (e.g., TNG908, Additional TNG, and TNG456)
- For efflux-prone small molecules (e.g., 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

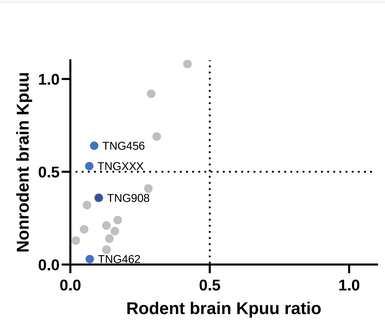
Parameter	TNG462	TNG908	TNG456	TNGXXX
Cellular activity GI_{50} (nM)	4	110	20	10
MTAP-null selectivity	45X	15X	55X	70X
fu, Brain	0.039	0.071	0.025	0.038
NHP fu, Plasma	0.254	0.165	0.204	0.255
n, (Range)	4, (0.247-0.250)	3, (0.118-0.243)	5, (0.138-0.274)	3, (0.247-0.265)
Dog fu, Plasma	0.175	0.126	0.111	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 tox study



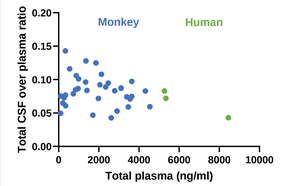
Rodent brain Kpuu is lower than nonrodent and lacks the dynamic range to distinguish moderate from low brain penetration



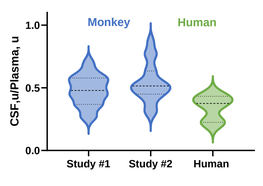
- Rodent CNS studies can serve as an initial screen to eliminate compounds with low CNS exposure[5]
- Collecting brain samples at the conclusion of terminal nonrodent toxicology studies offers valuable preclinical data for predicting human CNS exposure

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

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