TRANSIL^{XL}
Brain Absorption Kit

A Fast High-Throughput Assay for Brain Tissue Binding and Brain Disposition

FEATURES AND BENEFITS

- Fast, requires only 20 minutes total assay time
- Measures brain tissue binding, and predicts blood-brain barrier penetration
- Ready-to-use format in 96-well plate format generating highly reproducible results
- Rapid compound quantification due to immoblized brain membranes
- Kit includes a spreadsheet for calculation of final results and traffic light system for data quality rating

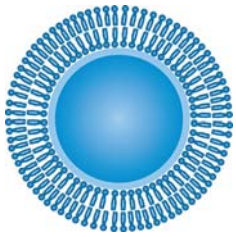

Fig. 1: Illustration of a TRANSIL Brain Absorption bead with a single lipid bilayer reconstituted from porcine brain lipids.

TECHNICAL DESCRIPTION

The TRANSIL^{XL} Brain Absorption kit estimates the binding of drugs to brain tissue and predicts the disposition of drugs into brain. It measures the affinity of drugs to reconstituted porcine brain membranes. The brain membrane affinity is used to estimate the brain tissue binding and to predict the brain-to-plasma distribution via a hybrid model that also incorporates the drug's polar surface area and it's plasma protein binding.

The kit consists of ready-to-use 96-well microtiter plates. One plate can be used for measuring brain tissue binding and brain disposition of up to 12 compounds. The assay requires only 5 steps: (i) addition of drug candidate, (ii) mixing and incubation for 12 minutes, (iii) removal of beads by centrifugation, (iv) sampling of supernatant, and (v) quantification of drug candidate.

CAPABILITIES

- Detection systems
  - LC/MS/MS
  - Scintillation counting
  - Others
- Parameters estimated and predicted
  - Unbound fraction of drug in brain
  - Brain-to-plasma distribution

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CORRELATION WITH DIALYSIS AND IN VIVO DATA

A strong correlation (r^2=0.93, n=65) is observed between the brain free fraction obtained with equilibrium dialysis and brain free fraction determined using the TRANSIL^{XL} Brain Absorption kit (fig. 2). The compound set represents a wide range of chemical structures with a range of logP from 0.6 to 6.2, a range of polar surface area from 3 to 26, and a range of H-bond donors from 0 to 4 and brain free fractions from 0.05% to 63%. Hence, the TRANSIL method yields comparable results to equilibrium dialysis. Likewise, a good correlation (r^2=0.86, n=36) was observed between the predicted brain-to-plasma distribution coefficient (logBB) and the in vivo determined logBB of drugs passively diffusing across the blood-brain barrier (fig. 3).

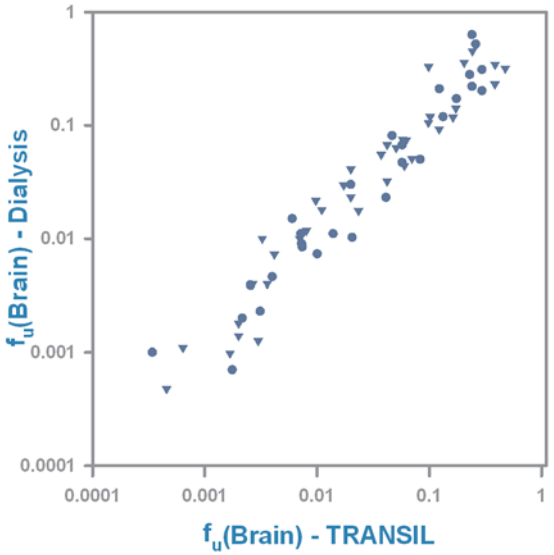

Fig. 2: Correlation of brain tissue binding estimates obtained from the TRANSIL^{XL} Brain Absorption kit and equilibrium dialysis (r^2=0.93).

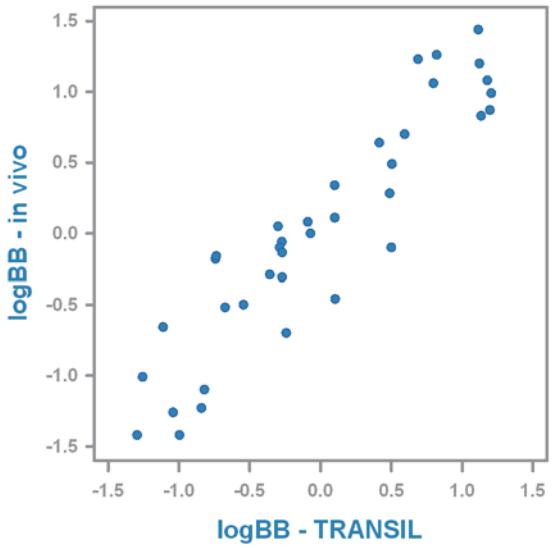

Fig. 3: Correlation of brain disposition estimates obtained from the TRANSIL^{XL} Brain Absorption kit and *in vivo* experiments (r^2=0.86).

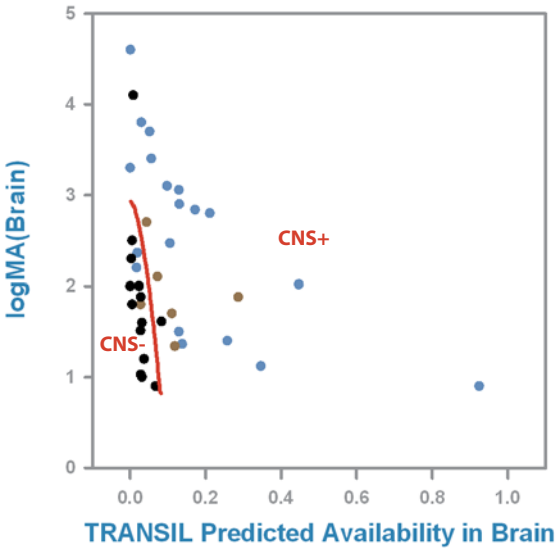

Fig. 4: Classification of CNS (blue), non-CNS (black) and drugs with CNS side effects (brown) using the TRANSIL^{XL} Brain Absorption kit using a computed classifier (red line).

CLASSIFICATION OF CNS VS NON-CNS DRUGS

Rate and extent are considered critical for brain penetration. The rate can be estimated by the log transform of the affinity to brain membranes (logMA). The best estimate for the extent is the free concentration of a drug candidate in the brain. The free concentration of a drug in brain is proportional to the product of the B/P ratio and the drug's free fraction in the brain, called brain availability. Using the rate and extent estimates from the TRANSIL^{XL} Brain Absorption kit yields a reliable classification of compounds suitable as CNS drugs (CNS+) and compounds primarily targeting other organ systems (CNS-) compounds (fig. 4). The classifier has astrong performance with a rate of correct classified compounds exceeding 82%.

PRODUCT INFORMATION

Order Number	Name
TMP-0110-2096	TRANSIL^{XL} Brain Absorption kit

V008.12.08.27

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