

## to-BBB

to-BBB is a private biotechnology company focusing on enhanced drug delivery across the blood-brain barrier

## Vision

The treatment of currently unserved brain diseases will be best achieved by safely enhancing the blood-to-brain delivery of drugs.

## Mission

The company is developing novel treatments for devastating brain disorders by combining existing drugs with the G-Technology<sup>®</sup>, to-BBB's proprietary brain drug delivery platform.

***"No other technology is able to enhance the brain delivery of drugs with the favorable pharmacokinetic and safety profile of the G-Technology<sup>®</sup>"***

## Contact

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## Opportunities in CNS drug development

In attempts to cure diseases of the central nervous system (CNS), many promising active compounds (mainly biopharmaceuticals) have shown potential therapeutic effect, however over 95% never reach the brain in therapeutically relevant concentrations. These compounds are denied access to the brain by the neuroprotective blood-brain barrier (BBB).

This sophisticated physiological system regulates the selective uptake of essential nutrients and metabolites and is in place to keep out foreign and potentially harmful substances. While this is life-supporting protection for the brain, it caused resignation in past drug development, as many promising therapeutic compounds were doomed to failure due to dose-limiting toxicity.

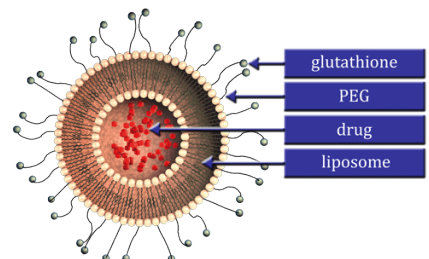
- ✓ The blood-brain barrier blocks most modern medicines
- ✓ to-BBB provides the safest proprietary brain drug delivery platform
- ✓ to-BBB aims to become the leading brain drug delivery company by enabling successful development of novel treatments for patients with devastating brain diseases

## to-BBB's platform technologies

Where the blood-brain barrier blocks many modern medicines, to-BBB is enabling successful development of new treatments for patients with devastating brain diseases. to-BBB's technology platforms open new gateways to treat devastating brain disorders like brain tumors, Alzheimer's disease and lysosomal storage diseases by combining with established and marketed drugs. The future of getting drugs into the brain in a safe way is to hijack the endogenous uptake-machinery of the BBB by associating the drug with compounds that are naturally transported into the brain. to-BBB's platform technologies utilize an endogenous receptor-targeted mechanism in combination with nanosized drug-loaded liposomes. This approach is unique in that it does not require drug modification and at the same time gives rise to metabolic protection during transport and increased bioavailability at the target site.

## G-Technology<sup>®</sup>

to-BBB provides the safest proprietary brain drug delivery platform. This G-Technology is the company's core platform and stands for liposomes coated with glutathione-conjugated PEG to mediate safe targeting and enhance the delivery of drugs to the brain.



Intravenous injections of PEGylated liposomes are already on the market (Caelyx<sup>®</sup>), and high dosages of glutathione in supportive therapy in cancer as well. Glutathione, a natural anti-oxidant, is found at high levels in the brain and its receptor is abundantly expressed at the blood-brain barrier. Therefore, glutathione uniquely minimizes common risks like adverse immunological reactions or interference with life-essential physiological pathways.

## Important features of the G-Technology

- ✓ Proof-of-concept studies with peptides and small molecules in pain, brain tumors and viral encephalitis strengthen the evidence that the G-Technology is effectively and safely enhancing the delivery of drugs to the brain.
- ✓ A technological and mechanistic validation has shown that the higher the amount of glutathione coating of the brain-targeted liposomes, the more free drug was actually delivered to the brain.

## Partnering opportunities

In addition to current ongoing collaborations and internal programs, to-BBB wants to enable multiple value adding industrial collaborations for specific compound - disease combinations using the unique G-Technology platform.

## Science Collaborations

NKI, the Netherlands; Industrial Technology Research Institute (ITRI), Taiwan; VUmc, the Netherlands; University of Uppsala, Sweden; University of Padua, Italy; Joanneum Research, Austria; Leiden University, the Netherlands

## Industry Collaborations

MedImmune (AstraZeneca); Shire; Genzyme; Lundbeck; two undisclosed Top 10 pharma companies; GSK R&D China; Janssen; Abbott; Ablynx; NeuroVive; Synageva

## Investors

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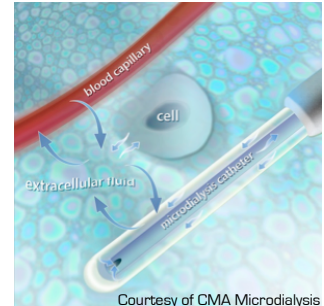
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Head of Finances

## Glutathione-dependent enhanced brain drug delivery

Using a technological validation approach that is also representative for a therapeutic route of administration, to-BBB has shown that the higher the amount of glutathione coating of the liposomes, the more free drug was actually delivered to the brain. The different amounts of glutathione on the surface of the liposomes did not change plasma levels and half-life of the different liposomes.

On the other hand, the plasma level of the liposomal drug was greatly enhanced (500 times compared to the free drug), while the liposomal formulation did reduce the dose-limiting toxicity associated with the free drug. Using a brain microdialysis technique (see figure), the free drug in the extracellular fluid of the brain was measured, which indicates that the drug was actually released from the intravenously administered liposomes. The apparent maximum increase for this particular composition, dose and timeframe was estimated to be as much as 500% of that of non-targeted liposomes.



Courtesy of CMA Microdialysis

## G-Technology proof-of-concept

In addition to the technological validation, initial proof-of-concept was obtained using bio-imaging technologies, pain inhibition using analgesic peptides, brain antiviral activity using antiviral drugs and anti-brain tumor activity using anticancer drugs. Although the ultimate brain uptake and efficacy of any encapsulated compound will depend on the compound as well as the disease, to-BBB will be able to test and optimize the G-Technology for almost every specific situation.

## 2B3-101: to-BBB's lead compound

to-BBB's lead compound is glutathione pegylated liposomal doxorubicin hydrochloride (2B3-101), which is based on the already marketed pegylated liposomal doxorubicin (Caelyx) that does not effectively cross the blood-brain barrier. Studies in an experimental brain cancer model have shown that 2B3-101 reduces brain tumor growth more efficaciously than Caelyx, and, prolongs survival up to 60% when given at the maximum tolerated dose. Extensive GLP toxicity, safety and toxicokinetic evaluations have shown equal or less severe findings for 2B3-101 as compared to Caelyx, possibly driven by the PK profile; the half-life of 2B3-101 in plasma was about 25 hr vs. 28 hr for Caelyx. to-BBB obtained clinical scale batches of 2B3-101, produced according to cGMP by TTY Biopharm (Taiwan). to-BBB has received approval to start treating patients with brain metastases in a Phase I/II clinical trial in June 2011.

## Pipeline

to-BBB is currently in the preclinical development of their second product 2B3-201 for neuroinflammation. Based on available proof-of-concept animal data, to-BBB is considering the development of other product candidates in the disease areas of Alzheimer's disease, MS, lysosomal storage diseases, Parkinson's disease and ALS. In addition to the internal development, the company is exploring specific proprietary product indication combinations in several industrial collaborations.

	Indication	Discov.	Optim.	Preclin.	I/II	IIIb
2B3-101	Brain Cancer	[Progress bar]		[Progress bar]	[Progress bar]	
2B3-201	Neuroinflammation	[Progress bar]		[Progress bar]		
2B3-XXX	Other candidates	[Progress bar]		[Progress bar]		

[Legend] Situation in 12 months from now

