2012 European CNS Targeted Drug Delivery Technology Innovation Award
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Frost & Sullivan’s Global Research Platform

Frost & Sullivan is in its 50th year in business with a global research organization of 1,800 analysts and consultants who monitor more than 300 industries and 250,000 companies. The company’s research philosophy originates with the CEO’s 360-Degree Perspective™, which serves as the foundation of its TEAM Research™ methodology. This unique approach enables us to determine how best-in-class companies worldwide manage growth, innovation and leadership. Based on the findings of this Best Practices research, Frost & Sullivan is proud to present the 2012 European Technology Innovation Award in CNS Targeted Drug Delivery Technology to-to-BBB.

Key Industry Challenges

Brain and CNS (central nervous system) disorders, both chronic and acute disease types are a major cause of mortality and debilitation. With increasing prevalence of neurodegenerative diseases and incidence of acute conditions like stroke, there is a need to develop effective therapies to tackle CNS related conditions. A number of tier one and mid-sized pharmaceutical and biotech companies have invested a significant portion of R&D spending for CNS drug discovery and development. Frost & Sullivan recognizes that in spite of the number of innovations, pharmaceutical and biotech companies are challenged because effective delivery to the brain is hindered by the presence of the neuroprotective Blood-Brain Barrier (BBB), the dynamic structure that forms a physical and biochemical barrier between the brain and systemic circulation. The BBB strictly regulates the entry and exit of molecules into the brain, and more than 95% of CNS therapeutics is unable to cross this structure in their free form. While it is a challenge for small molecules to enter the brain, biologicals are almost completely impermeable through the BBB.

With a better understanding of the BBB structure and function, a number of companies and academic organizations have developed strategies that can improve permeation across the BBB and result in improved therapeutic effects. Though a number of strategies have been developed for drug delivery across the BBB, very few have demonstrated the requisite safety and efficacy. Some of techniques are invasive and involve transient disruption of the BBB (via osmotic, biochemical methods) or direct delivery to the brain such as intracerebroventricular injections, intracerebral infusions or intrathecal mode of administration. Though these can effectively get the drug to the brain, safety and patient compliance are major concerns, and these delivery techniques are used only in critical conditions.

Pharmaceutical and biotech companies are in need of non-invasive delivery techniques that can deliver drugs across the BBB in a safe, specific manner with control on the pharmacokinetic and pharmacodynamic profile of the drugs. In addition to this, the drug delivery carriers should be easy to manufacture on a large scale and enable a quick entry to market, without too many manufacturing or regulatory hurdles. A number of receptor and carrier mediated delivery technologies, and peptide targeting techniques are being developed, and it is important to exploit suitable strategies that will be highly specific for the BBB, and can be used with existing drugs. In order to address the challenges of CNS targeted delivery, to-BBB, a Netherlands based company has developed a technology platform that uses already proven components such as PEGylated liposomes and
glutathione to deliver unmodified drug cargo across the BBB. Their G-Technology is widely applicable for a number of neurological conditions and has demonstrated to be one of the safest systems for CNS drug delivery. The in house lead candidate using this platform is currently in Phase 1/2a clinical trials.

**Impact of Technology Innovation Award**

The Frost & Sullivan Technology Innovation Award is a prestigious recognition of to-BBB’s accomplishments in the CNS Targeted Drug delivery. As an unbiased, third-party, Frost & Sullivan recognizes to-BBB for delivering excellence and best practices in their respective endeavors. The Technology Innovation Award is backed by extensive analysis; companies identified, and the uniqueness and impact of the technology are monitored and evaluated through primary analyst research. This stringent methodology positions to-BBB as a superior market participant.

**Key Benchmarking Criteria for Technology Innovation Award**

For the Technology Innovation Award, the following criteria were used to benchmark to-BBB’s performance against key competitors:

- **Uniqueness of Technology**
- **Impact on New Products/Applications**
- **Impact on Functionality**
- **Impact on Customer Value and Relevance of Innovation to Industry**

**Decision Support Matrix and Measurement Criteria**

To support its evaluation of best practices across multiple business performance categories, Frost & Sullivan employs a customized Decision Support Matrix (DSM). The DSM is an analytical tool that compares companies' performance relative to each other with an integration of quantitative and qualitative metrics. The DSM features criteria unique to each Award category and ranks importance by assigning weights to each criterion. The relative weighting reflects current market conditions and illustrates the associated importance of each criterion according to Frost & Sullivan. Fundamentally, each DSM is distinct for each market and Award category. The DSM allows our research and consulting teams to objectively analyze each company’s performance on each criterion relative to its top competitors and assign performance ratings on that basis. The DSM follows a 10-point scale that allows for nuances in performance evaluation; ratings guidelines are shown in Chart 2.

*Chart 2: Performance-Based Ratings for Decision Support Matrix*
This exercise encompasses all criteria, leading to a weighted average ranking of each company. Researchers can then easily identify the company with the highest ranking. As a final step, the research team confirms the veracity of the model by ensuring that small changes to the ratings for a specific criterion do not lead to a significant change in the overall relative rankings of the companies.

**Chart 3: Frost & Sullivan’s 10-Step Process for Identifying Award Recipients**

**Best Practice Award Analysis for to-BBB**

The Decision Support Matrix, shown in Chart 4, illustrates the relative importance of each criterion for the Technology Innovation Award and the ratings for each company under evaluation. To remain unbiased while also protecting the interests of the other organizations reviewed, we have chosen to refer to the other key players as Competitor 1 and Competitor 2.

**Chart 4: Decision Support Matrix for Technology Innovation Award**

<table>
<thead>
<tr>
<th>Measurement of 1–10 (1 = lowest; 10 = highest)</th>
<th>Impact on Customer Value</th>
<th>Relevance of Innovation to Industry</th>
<th>Impact on Functionality</th>
<th>Impact on New Products/Applications</th>
<th>Uniqueness of Technology</th>
<th>Weighted Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Weight (%)</td>
<td>20%</td>
<td>25%</td>
<td>25%</td>
<td>30%</td>
<td>100%</td>
<td></td>
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<td>to-BBB</td>
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<td>9</td>
<td>9</td>
<td>10</td>
<td>9.3</td>
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</tr>
<tr>
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<td>9</td>
<td>8</td>
<td>8</td>
<td>8.25</td>
<td></td>
</tr>
<tr>
<td>Competitor 2</td>
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<td>8</td>
<td>8</td>
<td>8</td>
<td>7.8</td>
<td></td>
</tr>
</tbody>
</table>
Criterion 1: Uniqueness of Technology

Frost & Sullivan research shows that pharmaceutical and biotech companies struggle with the complexity of the Blood Brain Barrier (BBB) for effective drug delivery to the brain. Improving selective delivery to the brain without disrupting the BBB, causing immunogenicity or systemic toxicity is a challenge faced by many drug delivery technology developers.

Frost & Sullivan’s competitive analysis reveals that to-BBB’s G-Technology platform is based on glutathione mediated transport to the brain, which sets itself apart from competing technologies in terms of safety and ease of manufacture. These drug delivery carriers are basically nanoascale liposomes coated with PEG conjugated glutathione. Utilizing receptor mediated uptake of the endogenous tripeptide glutathione (antioxidant), drugs targeted for CNS diseases can be administered in a safe and effective manner, with high specificity. The drug is encapsulated in liposomes in an unmodified form, which is a key advantage of this delivery method. Though a number of companies are working on receptor mediated transport via insulin, transferring, and LRP receptors, the wide expression of these receptors on several other cells might result in non specific drug uptake. Other companies are working on vector-drug conjugates and fusion proteins, but these again might not have the same effect as the unmodified drug and are more complex to manufacture on a large scale.

The glutathione based targeting of drugs is highly specific as GSH (glutathione) transporters are present only in the CNS and BBB that can actively transport the molecule to the inside of the tissue. Since, glutathione is a potent endogenous anti-oxidant involved in cellular detoxifying mechanisms, and is also FDA GRAS approved substance for use in food and supportive therapy in cancer, HIV and Parkinson’s Disease, its safety profile is well established.

The G-Technology platform is a safe, effective and versatile approach for carrying different classes of drugs such as small molecules, peptides, proteins and nucleotides across the BBB, without the need for any drug modification. The PEGylation to the liposome enhances the circulation time of the drugs, and acts like a stealth mechanism to evade immune surveillance. The liposomal formulations can be tailor made for different drug moieties and the dosage and pharmacokinetics can be modified based on the application—chronic or acute disease. The company has a strong patent portfolio covering methods and use of GSH based delivery systems and the overall applications of G-Technology platform.

Criterion 2: Impact on New Products/Applications

Frost & Sullivan expects that the simplicity and versatility of G-Technology will enable the drug carriers to be applied to already existing drugs in the market to improve the performance and safety and can also be explored for peptides, antibodies and nucleotide based drugs (RNAi). The platform is broadly applicable for a number of CNS disorders and diseases with CNS manifestations, and to-BBB is developing formulations for both chronic and acute diseases, that include neurodegenerative disorders, lysosomal storage disorders, stroke, and brain tumors.

to-BBB has entered into a number of research collaborations with tier one pharmaceutical companies such as Abbott, Genzyme, Shire, and MedImmune to leverage their technical expertise in drug delivery for more effective delivery of their CNS drugs. In addition, the company also has its own pipeline of drugs, with its lead candidate 2B3-101 in Phase 1/2a of clinical trials. The drug candidate is a formulation of glutathione pegylated liposomal
doxorubicin hydrochloride (2B3-101), which is based on the pegylated liposomal doxorubicin (Caelyx) that is already available in the market. Limited efficacy of Caelyx in crossing the BBB prompted to-BBB to explore its delivery carrier for delivery of doxorubicin in brain cancer. Frost & Sullivan finds that proof of concept studies in experimental brain cancer animal models have demonstrated that 2B3-101 is more effective in reducing the tumor growth and can extend survival up to 60%, when used at maximum tolerated dose. In 2011, the company started treating patients with solid tumors and brain metastases and glioma in a clinical phase I/IIa trials, in order to assess the dosage, and results have been positive till date with no dose limiting toxicity observed. The company’s other candidate 2B3-201 is currently in preclinical development for neuro inflammation.

Using the G-Technology platform, to-BBB is planning to initiate studies on inherited retinal diseases such as Retinitis Pigmentosa, Lebers Congenital Amaurosis and Achromatopsia. The similarity between the BBB and BRB (brain retinal barrier) in terms of cell surface receptors on both the membranes will be exploited for these applications.

Though delivery of antibodies is not a mainstream application of liposomal delivery system due to the reduced half-life, the company is also investigating several antibodies developed by partners to evaluate their efficacy when delivered via the G-Technology platform.

**Criterion 3: Impact on Functionality**

In Frost & Sullivan’s opinion, an ideal drug delivery carrier should be tunable to incorporate different drug moieties, and should be a safe and selective carrier system. The glutathione transporter exploited by to-BBB has a good safety profile in humans, since the normal physiological plasma and brain concentrations of glutathione are quite high (millimolar range). In spite of glutathione being taken up by many cells via facilitated transport, the uptake via transporters is highly specific as these are only present in the CNS and BBB.

Combining the receptor-mediated targeting with liposomal encapsulation and PEGylation, the pharmacokinetic and biodistribution properties of the drugs can be effectively controlled. Frost & Sullivan believes that the main advantage of using this system is that targeted CNS delivery through endogenous GSH transporters ensure that the BBB is not disrupted and remains fully functional. Different liposomal formulations can be developed to enable either a chronic or acute treatment of the disease. Since glutathione transporters are conserved in mice and humans, assessment of animal models can be easily translated in human trials. The company has completed proof of concept studies successfully with small molecules and peptides in animal models of pain, brain tumors and viral encephalitis, which demonstrates the safety and targeted delivery potential of G-Technology. Pharmaceutical and biotech companies, which could be potential partners for to-BBB, could use these studies as a positive starting point to advance drug candidates in these areas.

**Criterion 4: Impact on Customer Value and Relevance of Innovation**

Safety, effective drug targeting and cost effectiveness are some of the key features that will impact the customer’s decision on adoption of a particular drug delivery carrier. Frost & Sullivan notes that pharmaceutical companies can collaborate with to-BBB to expand the possible therapeutic outcomes of their already existing drug pipeline which targets CNS diseases. Depending on the desired PK/PD profile, to-BBB can optimize different formulations.
The use of two safe and well accepted systems—liposomes and glutathione in this drug delivery approach will make it easier for drugs delivered via these carriers to face less regulatory hurdles. Since pharmaceutical companies can leverage to-BBB’s delivery platform without any modification to the parent drug compound, there are minimal risks associated with the use of this technology platform. to-BBB has entered into a number of research collaborations with Tier 1 pharmaceutical and biotech companies to jointly develop effective therapies for several CNS indications.

The company has won several awards and private funding to advance its technology platform. In December 2011, the company was awarded a €600,000 grant through the “International Innoveren” program of the Dutch government agency Agentschap NL that will enable the company to accelerate its drug development programs and support research partnerships with top pharmaceutical companies. Another €1 million grant through the Eureka Eurostars™ program was awarded to NeuroVive Pharmaceutical AB and to-BBB for the collaborative development of effective therapies for stroke and other acute neurological conditions. From Frost & Sullivan’s perspective, the versatility of the company’s technology is clearly indicated by such awards and collaborations, and the most recent example would be €1.25 million by the European Commission’s 7th Framework Programme that will exploit the company’s technology platform for preclinical development of treatments for inherited retinal degenerative diseases. The company has established a fully owned subsidiary in Taiwan (to-BBB Taiwan Ltd.), and is looking to establish its presence in Asia. to-BBB has developed a number of agreements with Taiwanese organizations such as ITRI, TTY Biopharm and also investors.

**Conclusion**

to-BBB has developed a CNS targeted drug delivery platform that can be used with a wide range of drug moieties for effective and safe delivery to the brain. Frost & Sullivan research clearly shows that being a BBB specific method and ease of scale up, this technology stands apart from competing platforms in terms of its safety profile and ability to develop formulations for both chronic and acute conditions. to-BBB’s G-Technology has garnered interest from pharmaceutical/ biotech companies and government agencies, which Frost & Sullivan firmly believes indicates the potential of this technology platform. In recognition of to-BBB’s contribution to CNS targeted drug delivery, Frost & Sullivan is proud to present the 2012 Technology Innovation Award to to-BBB.
The CEO 360-Degree Perspective™ - Visionary Platform for Growth Strategies

The CEO 360-Degree Perspective™ model provides a clear illustration of the complex business universe in which CEOs and their management teams live today. It represents the foundation of Frost & Sullivan’s global research organization and provides the basis on which companies can gain a visionary and strategic understanding of the market. The CEO 360-Degree Perspective™ is also a “must-have” requirement for the identification and analysis of best-practice performance by industry leaders.

The CEO 360-Degree Perspective™ model enables our clients to gain a comprehensive, action-oriented understanding of market evolution and its implications for their companies’ growth strategies. As illustrated in Chart 5 below, the following six-step process outlines how our researchers and consultants embed the CEO 360-Degree Perspective™ into their analyses and recommendations.

Chart 5: The CEO’s 360-Degree Perspective™ Model
Critical Importance of TEAM Research

Frost & Sullivan’s TEAM Research methodology represents the analytical rigor of our research process. It offers a 360-degree view of industry challenges, trends, and issues by integrating all seven of Frost & Sullivan’s research methodologies. Our experience has shown over the years that companies too often make important growth decisions based on a narrow understanding of their environment, leading to errors of both omission and commission. Frost & Sullivan contends that successful growth strategies are founded on a thorough understanding of market, technical, economic, financial, customer, best practices, and demographic analyses. In that vein, the letters T, E, A and M reflect our core technical, economic, applied (financial and best practices) and market analyses. The integration of these research disciplines into the TEAM Research methodology provides an evaluation platform for benchmarking industry players and for creating high-potential growth strategies for our clients.

**Chart 6: Benchmarking Performance with TEAM Research**

About Frost & Sullivan

Frost & Sullivan, the Growth Partnership Company, enables clients to accelerate growth and achieve best-in-class positions in growth, innovation and leadership. The company’s Growth Partnership Service provides the CEO and the CEO’s Growth Team with disciplined research and best-practice models to drive the generation, evaluation and implementation of powerful growth strategies. Frost & Sullivan leverages 50 years of experience in partnering with Global 1000 companies, emerging businesses and the investment community from more than 40 offices on six continents. To join our Growth Partnership, please visit [http://www.frost.com](http://www.frost.com).