## BLOOD BRAIN BARRIER DISRUPTING AGENTS AND USES THEREOF (Tel Hashomer)

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### Background

Most therapeutic agents are BBB impermeable. Their arrival from blood to brain i.e. to suppress brain tumors is currently an unachievable task.

We found in an in vitro BBB reflecting model that cationized and/or neutralized albumins disrupt the BBB and enable the blood to brain entry of impermeable therapeutic agents in sufficient quantities. Peripherally administered cationized albumin however cannot be used as those derivatives are heavily taken by kidneys and liver as well and may therefore cause hepatic and glomerular toxicity. Therefore, convection-enhanced delivery (CED) was applied in a glioma rat model to deliver the BBB-opening agent and methotrexate. This approach (CED) yields drug distribution orders of magnitude above that obtained by peripheral administration while fully avoiding systemic toxicity. We further found that non-cationized ("neutralized") analogue HSA-$(CONH\text{-}C_2H_5)_{85}$ (termed EA-HSA) is advantageous in terms of efficacy and the lack of neurotoxicity.

### The Need

One of the major obstacles in treating brain tumors is the BBB that restricts the penetration of most drugs into the tissue. Consequently, high doses of chemotherapeutics are administrated systemically to obtain desired brain concentration, causing systemic toxicity and serious adverse effects. Although the BBB is compromised to some extent under the conditions of malignant gliomas, making it more permeable for drugs, this disruption is not enough to enable therapeutic doses of systemically administered drugs to reach the tumor tissues. Moreover, the BBB in the tumor's periphery remains intact restricting the administration of drugs to these regions. For treatment to be effective, it should access the entire tumor since survival of even a few cells could result in cancer reoccurrence as typically takes place with high-grade gliomas. Our research results and future plans address these problems.

### The Technology

We developed a family of human serum albumin (HSA) derivatives which disrupt BBB following intracranial administration by convection-enhanced delivery (CED) and permit the blood to brain penetration of methotrexate (and probably other chemotherapeutic agents). Co-administration of such derivative i.e. HSA-$(CONH\text{-}C_2H$

### The Market

The global glioblastoma treatment market, by drugs was valued at USD 341.4 million in 2013 and is

anticipated to reach USD 910.9 million by 2022, expanding at a CAGR of 11.4% from 2014 to 2022. Factors such as rising geriatric population, various organizations generating awareness coupled with introduction of novel therapies are driving the growth of this market. In addition, rising awareness against various types of brain tumors, development in drug delivery technologies and combination of modern diagnostic techniques are also supporting the growth of the market.

As per statistics published by the WHO in 2012, more than14 million new cases of cancer and about 8.2 million deaths were reported; thus alerting the healthcare fraternity to the augmenting growth of the disease. Furthermore, it stated that morbidity is expected to increase by about 70.0% over the next two decades. Similar data was published by the Global Health Observatory (GHO) in 2015, which stated that the number of premature deaths due to cancer is expected to increase by 44.0% by 2030.

As per the National Cancer Institute estimates, 23,770 new cases of brain tumor were diagnosed in 2016, in the United States itself. The statistics estimate that more than 4,000 children and teens were diagnosed with brain tumor. The National Cancer Institute, USA, states that at least 33.8% such patients survive for five years.

**Key players in the brain tumor treatment market are Genetech U.S.A, Bristol Myers Squibb, Hoffmann- La Roche, AstraZeneca plc, Pfizer, Inc., Novartis AG, Antisense Pharma, Merck & Co, Macleods Pharmaceutical Limited, Mankind Pharma, Dr. Reddys Laboratories Ltd.**

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