

Controlled Opening of the Blood-Brain Barrier to Enable Effective Therapeutic Access to Breast Cancer Brain Metastases

Background – The Medical Problem: The spread of cancer cells throughout the body represents the greatest threat to the survival of breast cancer (BC) patients, especially when such cells have entered the brain. These brain seeds are particularly difficult to treat. Many treatments, such as small-molecule chemotherapeutic drugs like Adriamycin or much larger molecules such as Herceptin antibodies, generally do not reach the brain lesions at high enough concentrations, because the blood-brain barrier (BBB) prevents their effective passage from the blood vessels into the brain. This problem is exacerbated because BC sometimes spreads to the brain already at early stages of the disease and goes unrecognized, providing the seeds for recurrence with poor prognosis.

The controlled, reversible opening of the BBB could be a means to allow all currently used BC therapeutics to effectively enter the brain and unfold their therapeutic impact as effectively inside the brain as they do throughout the rest of the body. It would end the protected sanctuary status for brain metastases. However, currently available methods to open the BBB are complicated and associated with significant risks, and therefore not widely available in standard clinical practice.

Our Novel Approach: We are developing a novel method to open the BBB in a controlled, safe, and fully reversible fashion that is relatively easy to perform and could be widely used to treat BC patients who present with brain metastases. We are using NEO100, a highly purified version of perillyl alcohol, a natural compound related to limonene present in the essential oils of citrus fruit peel. Using mice as a model, we discovered that arterial injections of NEO100 resulted in reversible opening of the BBB, without noticeable detrimental effects on the animals. The BBB of these mice remained open for about 2-4 hours and made the brain accessible to any and all therapeutics circulating in the bloodstream. For example, when we injected Herceptin antibodies into the tail vein of mice, we were able to detect their presence in mouse brain—but only after prior arterial injection of NEO100, not in the absence of NEO100. More importantly, with the use of mice harboring HER2-positive metastatic BC in their brains, we could demonstrate that BBB opening with NEO100 enabled therapeutic activity of Herceptin; that is, mice receiving a single dose of Herceptin along with NEO100-mediated BBB opening survived much longer than mice receiving Herceptin without BBB opening. In fact, in the absence of BBB opening with NEO100, Herceptin was not active at all, which is consistent with the well-known problem that most therapeutics have a hard time entering the brain and reaching the malignant lesions.

Our Proposed Project: We have solidly established the impressive therapeutic benefit of our novel procedure with different types of mouse tumor models and have published the results. We now seek to bring it to the clinic, so women with brain-metastatic BC can benefit from it. The all-important next step in this translational process is to obtain IND (investigational new drug) approval from the FDA. Without it, clinical trials are not possible. As with all new drugs and procedures, the FDA requires demonstration of safety (and ideally, efficacy as well) in a larger animal model between small rodents and human patients. We therefore propose to use rabbits as a suitable stepping stone from mice to humans in order to perform the experiments that are required for an IND application. Towards the end of this project, we will be able to submit a complete IND application with all the necessary documentation and paperwork. Once IND is granted, we have the appropriate expertise and infrastructure in place to promptly initiate clinical trials.

Specific Aims: In our prior mouse models, we performed arterial injections of NEO100 directly into the mouse heart. Naturally, this cannot be done in patients; rather, the equivalent procedure for humans is insertion of a catheter through the femoral ('groin') artery with selective threading toward the arteries of the brain. This is a commonly used clinical procedure that is rather safe. We will apply this "human" procedure to rabbits, followed by injection of NEO100 to open the BBB. **Aim 1:** Demonstrate that 'groin' injections of NEO100 are safe (EEG, vital signs, etc.). **Aim 2:** Demonstrate that BBB opening with NEO100 supports greater amounts of Adriamycin (as a representative of a small-molecule BC drug) and Enhertu (as a representative of a large antibody used for BC) to enter the brain. **Aim 3:** Establish that BBB opening with NEO100 enables Adriamycin and Enhertu to become therapeutically active in rabbits with brain tumor lesions. These three specific aims will be accompanied and complemented by the assembly of essential IND paperwork that is required for clinical trials.

Ultimate Applicability: Effective opening of the BBB should make it possible to treat brain metastases as effectively as the underlying systemic disease; most, if not all, therapeutics will be enabled to become effective in the brain as well. This new method therefore has the potential to substantially reduce morbidity and mortality, and potentially even result in cures for more of these patients.