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HACKING THE BLOOD-BRAIN BARRIER

By Bharat Kwatra

ABSTRACT*: The undermentioned method focuses on temporarily disrupting the tight junctions between the endothelial cells that form the blood-brain barrier, as well as temporarily permeabilising the cell membrane of the endothelial cells and the cells in the target tissue and in doing so, facilitating drug uptake into the target tissue.*

KEYWORDS: Blood brain Barrier, Microbubbles, permeabilising the cell membrane, Drug uptake, Neurosciences.

INTRODUCTION

For years the blood-brain barrier (BBB) has been a major problem for the pharmaceutical industry for it prohibits drugs from entering the brain and other parts of the central nervous system. Naturally, finding ways of crossing the BBB has been the subject of research of scientists ever since its discovery, but with little success.

Recently though, in vitro results of a several researches using a relatively new method for crossing the blood-brain barrier were published, and they seem to be very promising. So, next to our research of literature on BBB-related problems, I decided to set up some experiments.
The method focuses on temporarily disrupting the tight junctions between the endothelial cells that form the blood-brain barrier, as well as temporarily permeabilising the cell membrane of the endothelial cells and the cells in the target tissue and in doing so, facilitating drug uptake into the target tissue.

Although permeabilising the cell membrane of the endothelial cells isn't usually necessary (most diseases don't affect endothelium), it's an unavoidable incidental to do so since the disease approach will be from the side of the endothelium. This method takes advantage of the impact of the force that is created when oscillating micro bubbles "pop".

The proteins that form tight junctions should be forced apart under influence of this force, and in doing so they should leave a gap through which substances can easily pass. Besides, the shock that this "pop" provides should be enough to temporarily make the cell membrane porous, and thus to permeabilise it.

Experimental setup

In order to perform my experiments (and controls), I simulated a BBB by attaching endothelial and cancer cells to one side of a semi-permeable membrane.

The experiment was be conducted in two steps:

1. I have injected a model drug into arranged setup.

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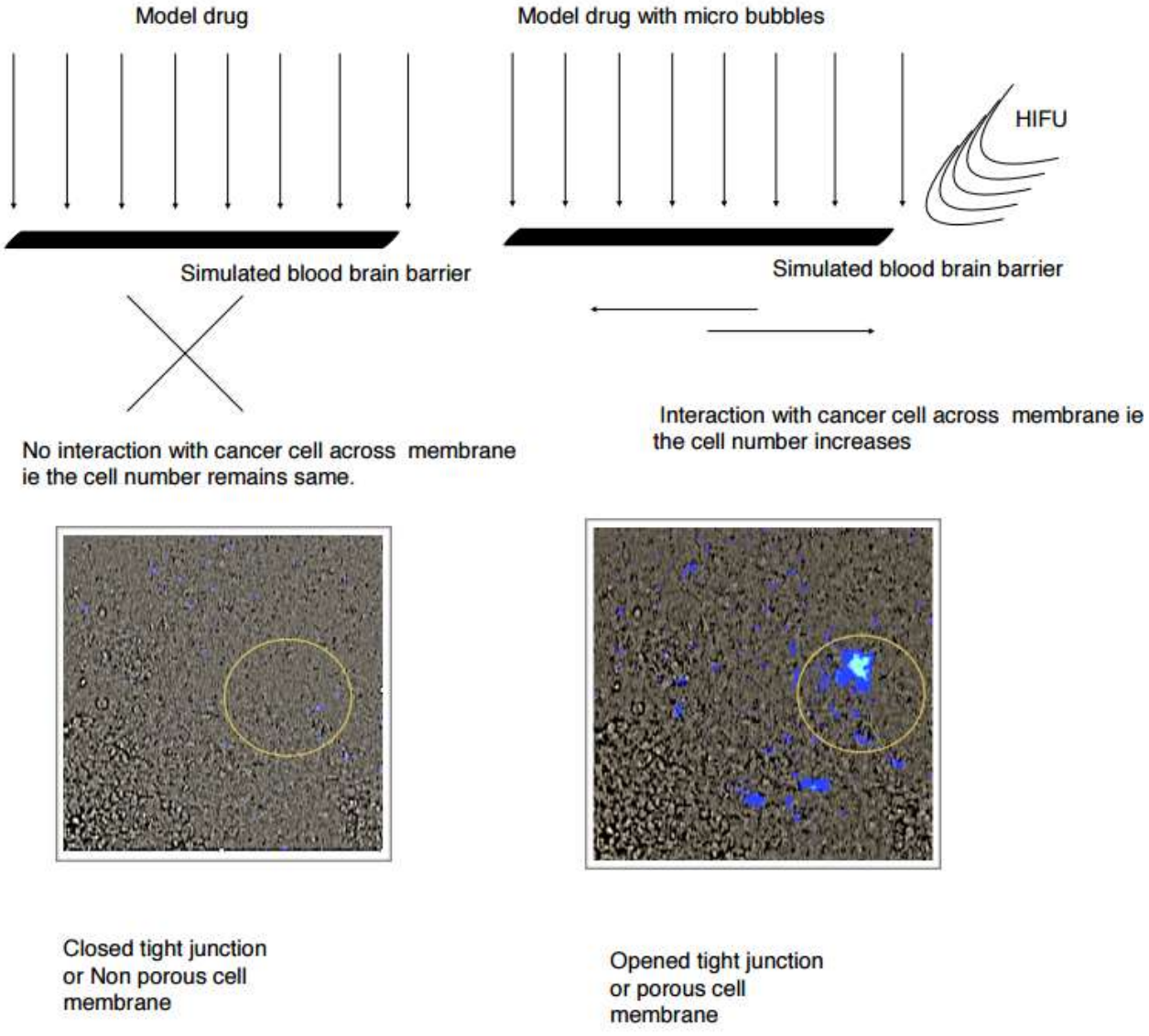
2. I have injected a model drug together with the micro-bubbles, get the bubbles to oscillate under influence of HIFU (High-Intensity Focused Ultrasound) into arranged setup.

Then Measure the amount of drug uptake and recovery in the different types of cells before and across the semi- permeable membrane, using a microscope with an optical fibre in both the cases.

The experiment was repeated six times in order to get accurate result.

To check the effect of micro bubbles on tight junction second step was repeated with stained epithelial, stain used was “Dapi”

Observations



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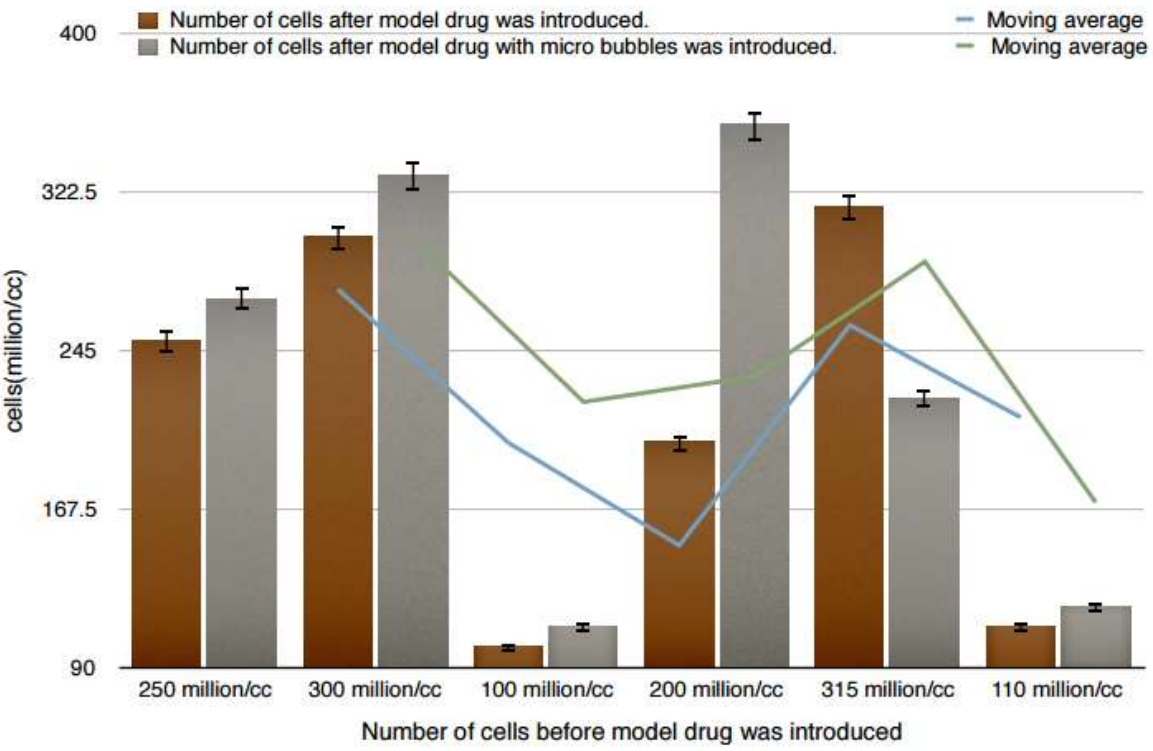
Number of cells before model drug was introduced.	Number of cells after model drug was introduced.	Number of cells after model drug with micro bubbles was introduced.	% increase in cell number
250 million/cc	250 million/cc	270 million/cc	8%
300 million/cc	300 million/cc	330 million/cc	10%
100 million/cc	100million/cc	110million/cc	10%
315 million/cc	315 million/cc	355 million/cc	12%
200 million/cc	200 million/cc	222 million/cc	11%
110 million/cc	110 million/cc	120 million/cc	9%



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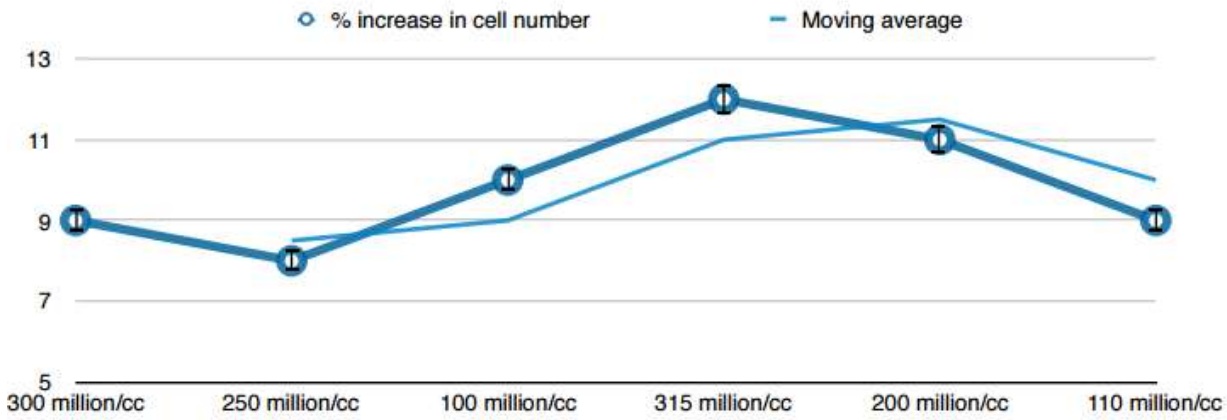

RESULTS

The results were gathered by two computer programs called ImageJ and MATLAB that, respectively, counted the amount of cells that had taken up the model drug over time and graphs were plotted:

These numbers and graph showed that indeed had been able to (safely) disrupt tight junctions and penetrate the cancer cells lying beyond the endothelium.

Besides, I found that endothelial could recover better from the shock than cancer cells and therefore had a much higher survival rate.

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