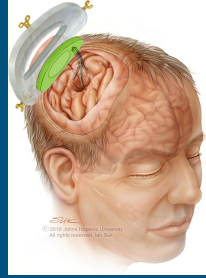
MRI-Compatible Skull-Embedded Implant for Direct Medicine Delivery

Paper Critique

Oh S, Odland R, Wilson SR, et al. Improved distribution of small molecules and viral vectors in the murine brain using a hollow fiber catheter. J Neurosurg. 2007;107(3):568-577.

By Vivian Looi (Group 16)

Project Summary



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- Problem: The **stagnancy** **in patient standard of care** for Glioblastoma Multiforme (GBM).

- Overall goal: Develop a skull-embedded implant with the **first** **chronic** **infusion of medicine** **directly** **into the brain.**

- My goal:
  - Implement code for the **pumps**.
  - Develop **Bluetooth connectivity** of the implant device for real-time interaction between the device, cellular devices, and the monitoring network.

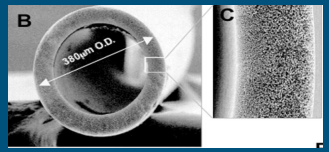
Paper Selection

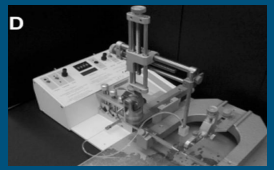
Oh S, Odland R, Wilson SR, et al. Improved distribution of small molecules and viral vectors in the murine brain using a hollow fiber catheter. J Neurosurg. 2007;107(3):568-577.

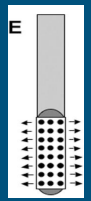
- Improve my understanding on the **fundamental mechanism of drug infusion** to brain tumor tissue by the device, which is the **primary motivation** for the initiation of this project.
- The choice of catheter imposes **physical constraints** to the delivery rate of drugs, which is relevant to the setting of **limits for the pumping rate**, which I am involved in for this project.

Summary and Key Result

- Design and develop a **hollow fiber catheter** for convection-enhanced delivery (CED) to increase the flow rate and decrease the total infusion time for treatments of brain tumor.
- Compare the **distribution and efficacy** of drug therapy and gene therapy delivered using the newly designed hollow fiber catheter and a conventional needle used in standard clinical CED procedures.







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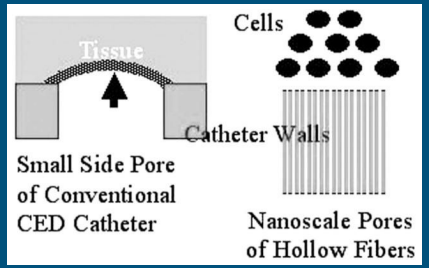
⇒ Using a hollow fiber catheter **improves the distribution and efficacy** of CED-mediated drug therapy and gene therapy.

Significance

- Provides the solution to the problem of **impedance mismatch**
  - Increased impedance in the catheter (pore connectedness) [9]
  - Increased surface area (> 25 times)
  - Reduced potential for generation of the tissue-deforming force (generate 874,000 times less deforming force)
  - Uniform drug delivery along the length of the catheter

⇒ Increases **rate of delivery** at nominal flow velocities



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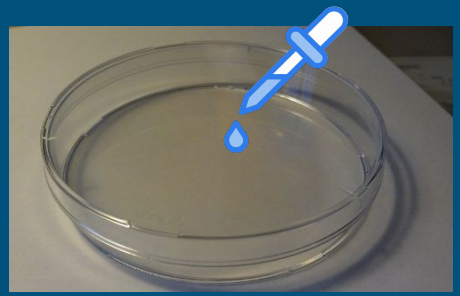
Background

- Convection-Enhanced Delivery (CED)
- Problem of CED method for GBM treatment
- Recombinant adenoviral vectors
- Firefly luciferase
- GFP (Green fluorescent protein)

Experiments

Study 1: Dye infusion into Agarose Gel (in vitro)



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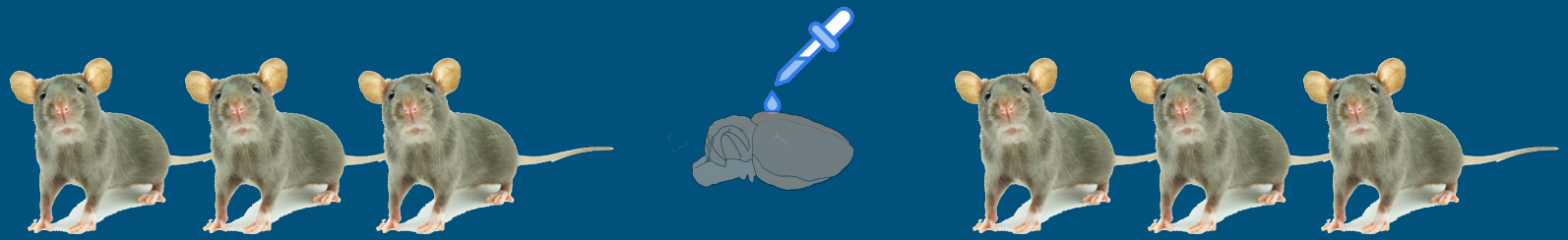
Experiments

Study 2: Dye infusion into mice brain (in vivo)



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Experiments

Study 3a: Adenoviral-mediated Gene Transfer (Gene transfer and expression)
⇒ vivo bioluminescent imaging

RAdLUC (firefly luciferase)

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Experiments

Study 3b: Adenoviral-mediated Gene Transfer (Gene transfer and expression)

⇒ vitro activity assay

RAdLUC (firefly luciferase)

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Experiments

Study 4: Adenoviral Vector Infusion (Distribution of gene transfer)

RAdGFP (GFP)

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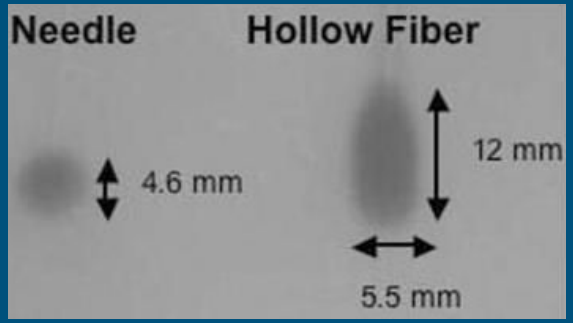
Results

Study 1: Dye infusion into Agarose Gel (in vitro)



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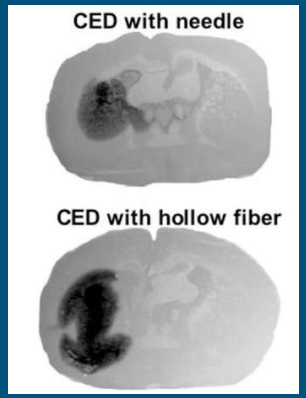
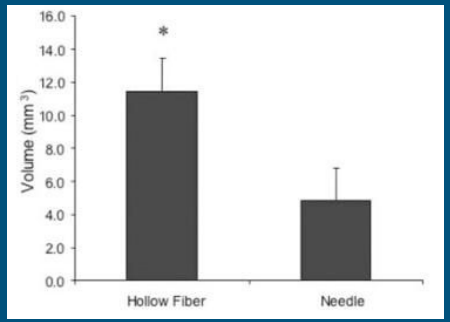
Results

Study 2: Dye infusion into mice brain (in vivo)





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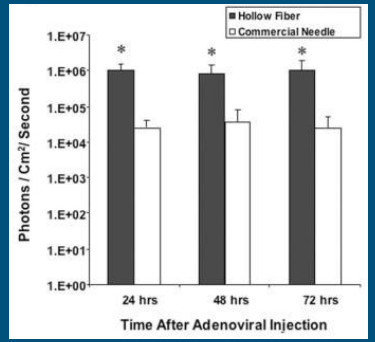
Results

Study 3a: Adenoviral-mediated Gene Transfer (Gene transfer and expression)

⇒ vivo bioluminescent imaging



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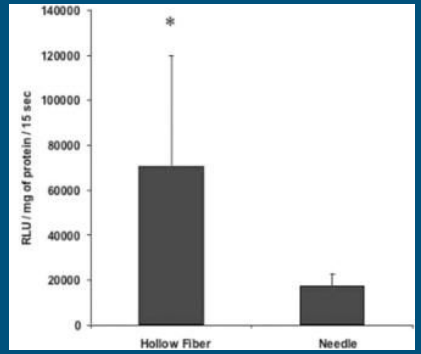
Results

Study 3b: Adenoviral-mediated Gene Transfer (Gene transfer and expression)

⇒ vitro activity assay



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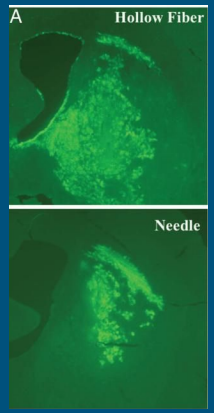
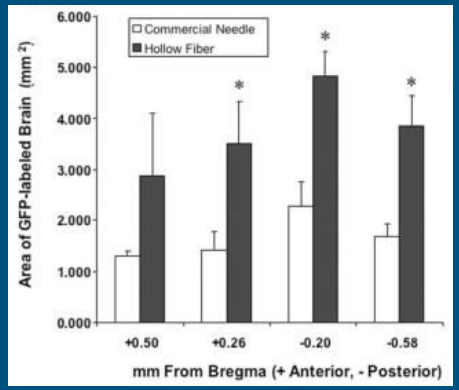
Results

Study 4: Adenoviral Vector Infusion (Distribution of gene transfer)





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Integrating the results from 4 studies…

Compared with single-lumen catheters, hollow fiber catheter

- significantly increased the distribution of Evans blue dye
- significantly increased total luciferase expression
- significantly increased the distribution of GFP

⇒ May improve the **distribution of CED-mediated drug delivery**, as well as **gene distribution and expression for gene therapy** in the CNS.

Assessment (paper)

- Good
  - Very rich **background information about CED** is provided.
  - The **design of the hollow fiber catheter** is described in detail in the paper, such that it could be reproduced by other researchers to conduct other studies to propagate their findings.
  - **Photographs and the plots** provided summarized the key results effectively, which makes the results of this paper accessible and understandable.

Assessment (paper)

- Bad
  - **Not enough background information** provided for the materials and methods used in the study.
  - The paragraphs in the Materials and Methods section **can be more organized**.
  - No reasonings given for increased **gene expression**.
  - There is a **typo** for the flow rate in the catheter that is optimal for current CED methods (the flow rate should have been <= 0.5 µl/minute instead of >= 0.5 µl/minute).

Assessment (research)

- Comprehensive
- Appropriate choice of infusate and models
- Possible future directions:
  - Repeat the four studies using **primate brains**.
  - Repeat the four studies on **brain tumor tissues**.
  - Repeat the four studies to compare hollow fiber catheter and **other existing methods** that also increase the drug delivery rate in CED.

Conclusion

This paper produced a successful prototype of the hollow fiber catheter to be used in CED to **improve the distribution and efficacy of drug therapy and gene therapy.**

Personal Relevance

- Gained much more insights into the principles behind CED, and hence a **greater motivation** to participate in this project.
- Realized the limitations of single-lumen catheters, and hence will consider **implementing code in the pump to avoid breaking constraints** to inflict harm in brain tissue.

Thank you!