Emerging Treatment Technologies: Beyond Brain Stimulation

Steven C. Schachter, M.D.
Chief Academic Officer and Director of NeuroTechnology, Center for Integration of Medicine and Innovative Technology (CIMIT)
Professor of Neurology, Harvard Medical School

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Outline

Emerging treatment technologies
- Focal brain cooling
- Silk-based brain implants
- Convection-enhanced drug delivery
- Optical neural control
- Laser ablation

Challenges for further development and clinical adoption
Focal brain cooling for seizure control

- Thermal energy (cooling) abates seizures at \( \sim 21^\circ C \)
- Compared to electrical currents (ECs), thermal energy:
  - A) Has a higher therapeutic ratio (cooling does not trigger seizures)
  - B) Relies only on one parameter (T), instead of many (frequency, amplitude, pulse width, pulse shape, etc.)
  - C) Is neuro-protective
Focal brain cooling for seizure control

- Thermal diffusivity is much lower than electrical and *rapid* intervention (within ~5 seconds of seizure onset) is key for efficacy
- Therefore, the rate of delivery of thermal energy must be enhanced for successful clinical applications
Focal brain cooling: Ivan Osorio

- Objective: To lower the temperature of amygdala and hippocampus (~1 cubic inch of brain tissue) to 16°C in 30 seconds maximum
- Strategy: To use a computer to design an optimal cooling probe (number and diameter of “needles”, inter-needle distance) such that the temperature of the brain tissue would drop as desired while minimizing tissue damage
Arrays of distributed probes deliver sufficient thermal energy to decrease the temperature of amygdala and hippocampus from $37^\circ\text{C}$ to $20^\circ\text{C}$ in 30s. Tissue disruption/loss caused by insertion of this probe is considerably less than that caused by ablative surgery.

The cooling probe is scalable.
Commercial status: Licensed by Cyberonics, Houston, TX

Selected Publications and Patents:


<table>
<thead>
<tr>
<th>Osorio I, et al.</th>
<th>Unitized Electrode with Three-Dimensional Multi-Site, Multi-Modal Capabilities for Detection and Control of Brain State Changes</th>
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<td>Gopalsami, N, Kulikov S, Osorio I, Raptis AP.</td>
<td>Surface Acoustic wave probe implant for prediction of epileptic seizures.</td>
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Focal brain cooling: Steven Rothman

- Objective: To lower the temperature of neocortical seizure focus
- Progress
  - Developed implantable fluid-based cooling and recording grid for use during invasive mapping
  - In dogs, the device was capable of cooling the cortical surface to the mid-20s°C
Progress

- Larger version of the device has been tested during craniotomies for epilepsy surgery at Washington University in St. Louis and cools human neocortex as expected

- In lab testing, newest version of device can run for over 2 weeks at high flow rates with no leakage; cools a brain phantom as expected
Focal brain cooling: Steven Rothman

Most recent version of cooling grid for use during invasive mapping. A. View from bottom; B. View from top. Fluid enters the central bladder and cools the cortex beneath the central 16 of 64 cortical contacts. Scale in A is 1 cm.
Status as of March 2011 (Rothman):

1. **Intellectual property** – covered by several patents on our specific physiological observations and others on the heat transfer technology that will eventually be needed for an implantable device.

2. **Industry** – fluid based cortical cooling grids were designed and fabricated by PMT in Chanhassen, MN (PMTcorp.com). Other FDA-approved devices that can be used with these grids are already commercially available.

3. **Plans** - over next 1-2 years, use the fluid based cooling grids to determine the temperature reduction necessary to prevent or terminate human neocortical seizures during invasive mapping; use this information to design an implantable, Peltier-based cooling device.

4. **Funding** – four centers (University of Minnesota, Washington University, University of Washington, Mayo Clinic) co-operatively applying for funding through Epilepsy Therapy Project and NINDS.

5. **Regulatory issues** – FDA application for Investigation Device Exemption will be submitted shortly.
Silk-based brain implants: Detlev Boison

- **Rationale**
  - Adenosine is an endogenous anticonvulsant of the brain that terminates seizures
  - Adenosine kinase is increased with astrogliosis and adenosine deficiency is a pathological hallmark of epilepsy (in rodents and humans)
  - Adenosine augmentation prevents pharmacoresistant seizures
Evidence of possible benefit when given locally

In the intrahippocampal KA model, seizures are not suppressed by CBZ, but are by the adenosine agonist CCPA or the adenosine kinase antagonist ITU.

Anti-ictogenic and anti-epileptogenic activity of silk-based adenosine delivery

Silk-based adenosine delivery

Infrahippocampal implantation into fully kindled rats ipsi to Kindling electrode: seizure suppression


Implantation before onset of kindling: suppression of kindling epileptogenesis

A  
Averaged daily adenosine release in vitro

B  
Seizure stage [0-5]

Days after implantation (6 stimulations / day)
Status as of March 2011 (Boison):

United States Patent 6110902
**Method for the inhibition of neuronal activity leading to a focal epileptic seizure by local delivery of adenosine**
Inventors: Mohler, Hanns; Boison, Detlev
Application Number: 08/881038
Publication Date: 08/29/2000

**Silk polymer-based adenosine release: therapeutic potential for epilepsy**
Inventors: Boison, Detlev; Kaplan, David L.
Application Number: PCT/US2009/044117
Publication Date: 11/19/2009
Filing Date: 05/15/2009

Timelines and Milestones:
• 2011: complete preclinical studies; demonstrate efficiency in different epilepsy models; compare efficacy with standard AEDs; determine therapeutic window.
• 2011: develop clinical grade polymers for focal adenosine delivery
• 2012: pilot studies in human patients with MTLE using transient adenosine infusions; dose-finding and safety studies; seek FDA approval for clinical studies
• 2013: Phase I clinical trials using silk-based adenosine releasing intrahippocampal implants
Potential advantages of this approach

• long-lasting therapeutic benefit (>3 months) in systemic KA rat model after short term (10 days) delivery from ventricular implants (unpublished data)
• avoidance of systemic and central side effects by focal application
• exploitation of novel pharmacological principle that is based on neurochemical rationale
• adenosine is already FDA approved (supraventricular tachycardia)
• silk is already FDA approved (e.g. for sutures)
• prior experience with I.T. infusion of adenosine to treat chronic pain
• safety, because adenosine is endogenous anticonvulsant subject to rapid metabolic clearance
• potential for the prevention of epileptogenesis
• silk-based adenosine delivery is also of potential use for other neurological and psychiatric disorders
Convection-enhanced drug delivery

- **Rationale**
  - Convection-enhanced delivery (CED) is a novel drug-delivery technique that uses positive hydrostatic pressure to deliver a fluid containing a therapeutic substance by bulk flow directly into the interstitial space within a localized region of the brain parenchyma.
Convection-enhanced drug delivery

- **Rationale**
  - CED circumvents the BBB and provides a wider, more homogenous distribution than bolus deposition (focal injection) or other diffusion-based delivery approaches
  - CED could represent an alternative to resective surgery in the treatment of focal epilepsies that are resistant to oral AEDs
Convection-Enhanced Delivery — An Alternative to Epilepsy Surgery?

In a possible application, the infusion catheter is fully implanted with a transdermal port that is internally sealed and filtered to prevent bacterial ingress. At the time of treatment, an infusion pump would be attached to the port (shown for the T1 catheter only). Multiple catheters are shown to illustrate possible trajectories. An individual patient would ordinarily have a single catheter, but more than one catheter might be necessary in some situations to achieve a sufficient distribution volume or for anatomically distinct foci.

Recent results

- A single, localized CED infusion of botulinum toxin B over a 20-minute period provided more than 2 months of seizure protection in the rat kindling model of epilepsy
- At therapeutic doses, no untoward toxicities were observed
Botulinum Toxins A and B Delivered by CED (20 min Infusion) into the Amygdala by CED Confer Prolonged Seizure Protection in the Rat Kindling Model
Convection-enhanced toxin delivery (Rogawski): Project status

- Preliminary animal research conducted at NINDS, NIH; funded by Epilepsy Therapy Project
- Developed collaboration with Medgenesis Therapeutix, a private specialty biopharmaceutical company founded in 2006 to develop CED treatments for brain tumors, Parkinson’s disease and epilepsy
- Patent filed (US 2009/0209937; Aug. 20, 2009)
- Additional POP animal studies conducted at
Convection-enhanced toxin delivery (Rogawski): Project status

- Developed 3-way agreement including Solstice Neuroscience as supplier of botulinum toxin B
- Animal (rat) safety studies with FDA-approved botulinum toxin B forms (native and stripped rimabotulinumtoxin B) underway at UC Davis
- Plan to undertake primate studies, if rat studies demonstrate adequate safety
- In preparation for first-in-man trial, pre-IND studies (tissue toxokinetics, systemic exposure) are planned
Convection-enhanced toxin delivery (Rogawski): Potential Advantages

- CED of peptide toxins can provide seizure protection for months
- Co-convection with gadolinium tracer allows region of brain perfused to be assessed in real time
- In clinical application, infusion would be done under EEG or MEG monitoring
- Patient would be re-infused at intervals
CED technical challenges

- Large-diameter delivery cannulas used today limit efficiency, have limited precision, and can cause mechanical trauma
- “Reflux” – movement of therapeutic away from the target back along the outside wall of the delivery cannula
Optimizing CED of drugs (Cunningham): The CED SYStem (CEDSYS) solution

- Array of multiple microcannulas strategically positioned to deliver therapeutic
  - Reflux is minimized by reducing the delivery cannula diameter 5-10x
  - Capable of simultaneous electrophysiological recording and delivering light

- Status
  - Stereotactic surgical planning software and instrumentation are near completion
Technology

1. Reflux is reduced by decreasing the delivery cannula from 1.0 mm to 0.2 mm.
   - Step design further reduces back-flow.

2. CEDSYS is capable of delivering light.
   - Implications for photodynamic therapy, optogenetics, etc.

3. Custom microcannulas are capable of simultaneous electrophysiological recording.
   - Porcine substantia nigra mapped and injected with surrogate therapeutic (microspheres, Bjarkam et al., 2009)

4. FDA-approved FHC microTargeting™ Platform in position for CEDSYS applications.
   - CEDSYS technique allows strategic placement of multiple, flexible microcannulas within the diseased brain region.
Glioblastoma multiforme

SEDYS Strategy: Miles Cunningham

Conventional Delivery Cannula  CEDSYS microcannula array
CEDSYS: Status

- Cunningham and Frederick Haer and Company (FHC) collaborating on developing CEDSYS
  - Merging CEDSYS with FHC microTargeting™ Platform
  - Presently preparing studies for IRB approval
  - SBIR pending with mid-20’s score
  - CIMIT application for epilepsy study in preparation
- Patent pending; undergoing first office action
  - Inventor: Miles Cunningham; Owner: McLean Hosp
Optical neural control: Ed Boyden

- Objective: Transiently silence specific targeted cells, or drive specific neurons, using light to halt seizures while minimizing side effects
- Concept: Genes from bacteria, plants, and fungi that encode for light-activated proteins which in turn control membrane ion channels to produce hyperpolarization or depolarization are delivered to target neurons by viral vectors
- Different proteins respond to different light colors
- Naturally occurring channelrhodopsins in retinal photoreceptors work by similar mechanism.
Results to date

I. Invented optogenetics – drive/silence neurons with light


Halo


ChR2

Boyden et al. (2005) Nature Neuroscience 8(9):1263-8

II. Began primate testing – no cell death or immune reaction

Han et al., 2009 Neuron 62(2):191-198; new manuscript in preparation.

III. Created wirelessly-powered prosthetics for safe, long-term light delivery

Plans for coming year: Ed Boyden

I. In collaboration with experts in the field - closing the loop, to detect and perturb seizures – get to proof of concept

II. Funding
NIH Director’s New Innovator Award
Paul Allen Distinguished Investigator In Neuroscience
Will seek more collaborative NIH funding with experts in the field

III. IP status
MIT has filed 14 patents directly related to optical neural control

IV. Industrial involvement
Seeking industrial collaborators
Already a startup (Eos) working on blindness (Boyden, science advisor)
Minimally Invasive MRI-guided Laser Ablation of Epileptogenic Foci

Bill Hoffman. CEO.
Visualase, Inc.
713-275-2063
bhoffman@visualaseinc.com

Visualase is FDA cleared for use in soft tissue. 
It is not FDA approved for treating any specific disease or condition.
Laser Ablation Procedure, in Neurosurgery

1. Laser fiber is placed in target tissue. Placement confirmed with MR.

2. Laser energy is delivered under MR thermography visualization.

3. Post-Tx MR confirms ablation zone.

Tissue at 60°C dies instantaneously. To protect tissue, temp is kept below 50°C.

Swelling typically occurs for ~2 weeks, treated with steroids.

Visualase is FDA cleared for use in soft tissue. It is not FDA approved for treating any specific disease or condition.
# Current Status

**IP:** 6 Patents issued, 10 patents pending. 400k lines of proprietary code (software)

**Regulatory:** 510(K) Clearance for soft tissue ablation in neurosurgery (and other specialties)

**Development:** Product is fully developed and has been safely used to ablate ~100 brain tumors and, under IRB, to ablate Epileptogenic foci in two patients

**Reimbursement:** Significant reimbursement already exists.

## Clinical:

- **General:** multiple peer reviewed animal studies
- **Brain:** early clinical experience in brain mets, NEUROSURGERY, July 2008. Follow up study submitted for publication, mid-2011
- **Prostate:** several early case reports published in European Urology, several studies ongoing, multi-center trial to commence in 2011
- **Epileptogenic foci ablation:** Several investigators have submitted protocols to IRB

## Financial:

- Visualase is venture funded
- Adequate funds through early-mid 2012, Series B funding late 2011, strategic partners and VC
Challenges for further development
Challenges for further development and clinical adoption

- Networking with IT and materials scientists, engineers from numerous disciplines
- Assembling development teams
  - Clinical expertise
  - Technology
  - Patient input
- Early financial support (for example, Epilepsy Research Foundation or CIMIT (www.cimit.org))
Challenges for further development and clinical adoption

PRE-CLEARANCE
- Strategies for demonstrating proof of principle
- Conducting controlled trials; ?blinding ?placebo effects
- Selection of appropriate candidates for trials
- ? Need for multiple therapeutic indications/uses to attract investment

POST-CLEARANCE
- Demonstrating favorable cost:benefit to payors
- Patient acceptance
- Physician adoption
Summary

- A variety of technologies other than brain stimulation are emerging as potential treatments for epilepsy in the 21st century
- Challenges are most likely to be solved by the engineering, medical and commercial development communities working together
Acknowledgements

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- Ivan Osorio, University of Kansas Medical Center (iosorio@kumc.edu)
- Michael Rogawski, University of California, Davis (rogawski@ucdavis.edu)
- Steven Rothman, University of Minnesota Medical School (srothman@umn.edu)