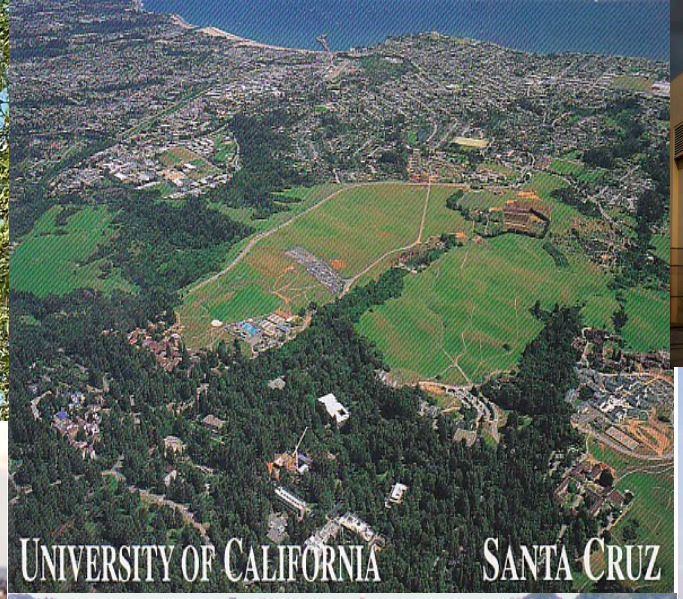
Innovation from a Neurosurgeon's Perspective

Michael Y. Oh, MD

Professor and Vice Chair

UCI Department of Neurosurgery


GLEN A. WILSON
HIGH SCHOOL
An International Baccalaureate School


UNIVERSITY OF CALIFORNIA
SANTA CRUZ


LA PUENTE
WARRIORS
INDIVIDUAL CHAMPS
WRESTLING CHAMPIONS
1980
SAL GOMEZ - PHOTOGRAPHY


University Hospital
N900UM

UCI Health

Innovation from a Neurosurgeon's Perspective

First in Human Trial

Date with a Scientist

From Innovation to Entrepreneurship

DBS for Obesity: Conducting a First-in-Human Study

A Big Problem

Swinging for a Home Run

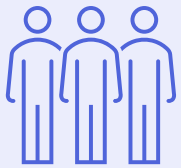
How to Conduct a First-in-Human Study

1. Isolate a problem
2. Propose a solution
3. Understand the system
4. Develop a protocol
5. Get approval
6. Secure funding
7. Identify patients
8. Conduct the study
9. Publish research

How to Conduct a First-in-Human Study

1. **Isolate a problem**
2. Propose a solution
3. Understand the system
4. Develop a protocol
5. Get approval
6. Secure funding
7. Identify patients
8. Conduct the study
9. Publish research

Obesity: An Epidemic



42% of the U.S. adult population is obese, including **9.2%** with severe obesity

There is an alarming rise of obesity in children, with **18.5%** suffering from obesity

Medications are largely ineffective, and only result in sustained weight loss in **~10%** of patients

How to Conduct a First-in-Human Study

1. Isolate a problem
2. **Propose a solution**
3. Understand the system
4. Develop a protocol
5. Get approval
6. Secure funding
7. Identify patients
8. Conduct the study
9. Publish research

Surgical Treatment for Obesity

Surgical treatment reserved for morbidly obese

Bypass, banding, intragastric balloon placement.

Morbidity as high as **~30%**.

Rife with complications: micronutrient deficiency, dumping syndrome, ulcers, hernias.

Success after surgery?

Despite “successful” bariatric surgery, many patients regain a significant amount of weight

Neurosurgery for Obesity

Ventromedial hypothalamus *(VMH, "satiety" center")* **and lateral hypothalamus** *(LH, "feeding" center)*

Lesioning studies in animals were first to suggest these functions of the hypothalamus

Clinical evidence from patients with tumors in these regions also corroborated findings in animal studies

Experiments have shown selective damage to LH neurons impairs food ingestion w/o affecting motor/swallowing functions

How to Conduct a First-in-Human Study

1. Isolate a problem
2. Propose a solution
3. **Understand the system**
4. Develop a protocol
5. Get approval
6. Secure funding
7. Identify patients
8. Conduct the study
9. Publish research

Biochemistry and Physiology

Leptin, ghrelin, and insulin

Three chemicals important in energy homeostasis.

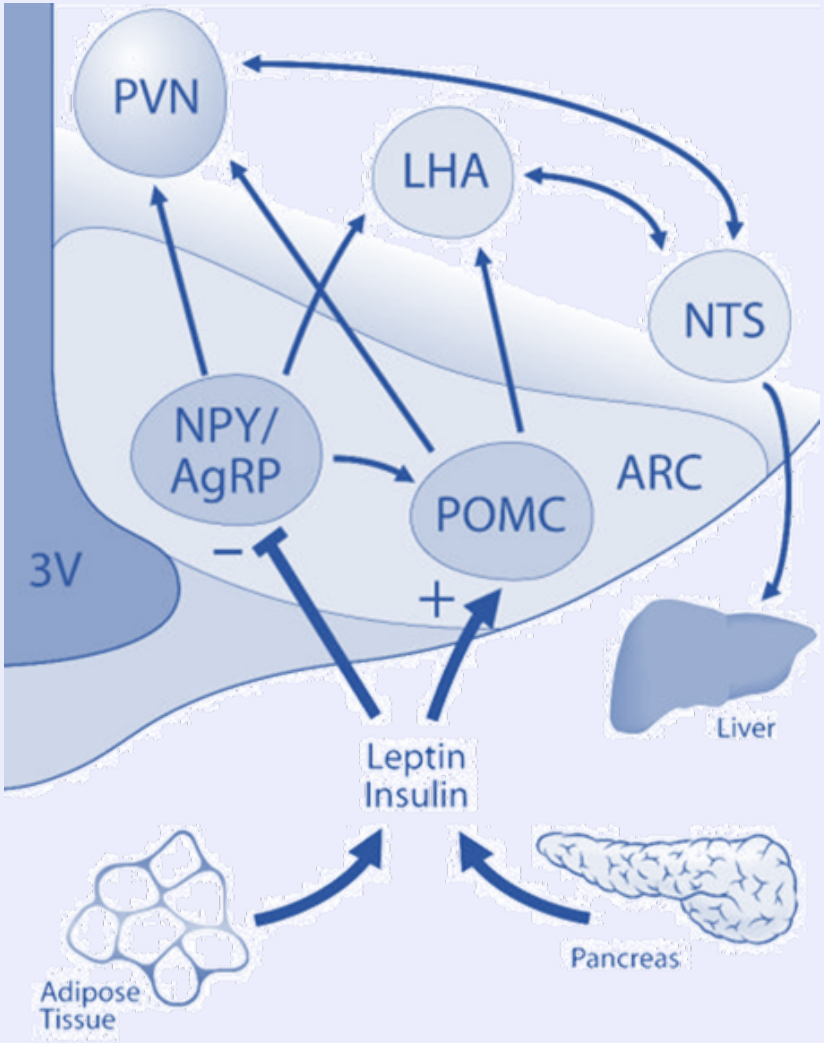
Experiments in animals have shown decrease in food intake with administration of exogenous leptin/insulin into the brain.

Leptin resistance

May be associated with obesity; analogous to insulin resistance.

DBS could be used to substitute the action of leptin on its receptors within the hypothalamus.

Hypothalamic Neurocircuits Involved in Glucose Metabolism



Morton GJ 2007

An Energy Balance Problem

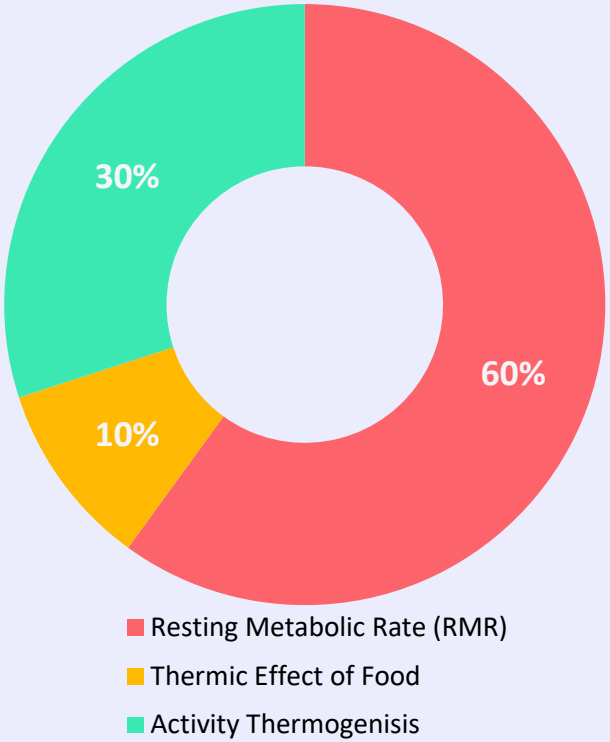
Energy in = food intake

Energy out = resting metabolic rate (RMR) + exercise + thermic effect of food

When energy in is greater than energy out, this causes obesity

DBS may be able to influence both sides of the energy equation

Resting Metabolic Rate



The lionshare of "energy out" is **resting metabolic rate** (RMR)

RMR contributes to obesity by acting as a buffer against weight loss – RMR decreases in response to caloric restriction

Previous efforts to increase RMR *(thyroid hormone, amphetamines)* for weight loss have had **significant side effects**

How to Conduct a First-in-Human Study

1. Isolate a problem
2. Propose a solution
3. Understand the system
4. **Develop a protocol**
5. Get approval
6. Secure funding
7. Identify patients
8. Conduct the study
9. Publish research

Deep Brain Stimulation?

Established Treatment

Well-established treatment for movement disorders and recently for psychiatric disease (OCD, Depression, Tourette's)

Proven Safety

Proven safety profile, both adjustable and reversible with the ability to modify parameters as needed

Unlike in movement disorders and psychiatric disease, effects on weight may not be readily apparent initially

Animal Studies of DBS for Obesity

Authors	Animal	Substance	Target	Laterality	Acute vs Chronic	Mode	Intensity (μA)	Frequency (Hz)	Pulse Width (μs)
Anand et al.	Cat	Standard Chow	VMH	Unilateral	Acute	Bipolar	NA*	5	200
Wyrwicka et al.	Goat	Standard Chow	VMH	Unilateral	Acute	Unipolar	NA*	50	NA
Morgane	Rat	Standard Chow	VMH	Unilateral	Acute	Bipolar	NA*	60	200
Brown et al.	Dog	Standard Chow	VMH	Unilateral	Acute	Bipolar	100	50	1,000
Ruffin et al.	Rat	Standard Chow	VMH	Unilateral	Acute	Bipolar	20 or 25**	NA	NA
Sani et al.	Rat	High-fat Diet	LH	Bilateral	Chronic	Bipolar	NA*	180-200	1,000

LH lateral hypothalamus, *VMH* ventromedial hypothalamus, *NA* not available

*Only voltage was reported in these studies: Morgane, 1.0-3.0 V; Anand et al., 2.0 V; Wyrwicka et al., 0.5-1.0 V; Sani et al., 2.0 V

** Constant current administered

Halpern 2011

Stimulation Targets for DBS in Obesity

Lateral Hypothalamus (LH)

- *Projects to:* cortex, basal ganglia, hypothalamic regions, PAG, reticular formation, and ventral horn of the spinal cord
- *Receives input from:* nucleus accumbens, amygdala, hippocampus, and nucleus of the solitary tract, and arcuate nucleus
  - Arcuate nucleus is outside BBB and hence could serve as a mediator of circulating hormones
  - It could influence the LH through direct projections
- Weight loss following LH stimulation is not related to decreased food intake or increased activity
  - Hypothesized to be due to increased metabolism (Sani et al. 2007)

Stimulation Targets for DBS in Obesity

Ventromedial Hypothalamus (VMH)

- High frequency stimulation leads to increased food intake
- Low frequency stimulation leads to decreased feeding

Nucleus Accumbens

- Obesity may result from a patient's desire for food that overrides normal satiety mechanisms
- Neuromodulation of the reward system may allow normal satiety mechanisms to achieve homeostasis

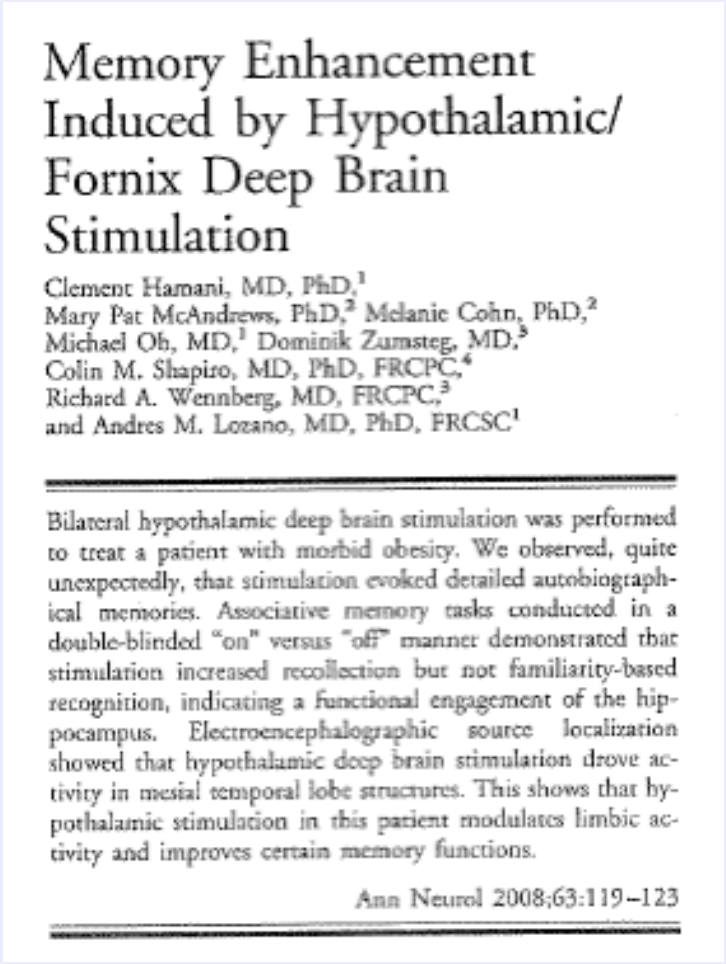
Leptin, Ghrelin, Neuropeptide Y, and GLP-1

- Shown to modulate reward system in addition to effects on energy and metabolism

How to Conduct a First-in-Human Study

1. Isolate a problem
2. Propose a solution
3. Understand the system
4. Develop a protocol
5. **Get approval**
6. Secure funding
7. Identify patients
8. Conduct the study
9. Publish research

Go to Canada! But Protect Your IP



Memory Enhancement Induced by Hypothalamic/ Fornix Deep Brain Stimulation

Clement Hamani, MD, PhD,[1]
Mary Pat McAndrews, PhD,[2] Melanie Cohn, PhD,[2]
Michael Oh, MD,[1] Dominik Zumsteg, MD,[3]
Colin M. Shapiro, MD, PhD, FRCPC,[4]
Richard A. Wennberg, MD, FRCPC,[3]
and Andres M. Lozano, MD, PhD, FRCSC[1]

Bilateral hypothalamic deep brain stimulation was performed to treat a patient with morbid obesity. We observed, quite unexpectedly, that stimulation evoked detailed autobiographical memories. Associative memory tasks conducted in a double-blinded "on" versus "off" manner demonstrated that stimulation increased recollection but not familiarity-based recognition, indicating a functional engagement of the hippocampus. Electroencephalographic source localization showed that hypothalamic deep brain stimulation drove activity in mesial temporal lobe structures. This shows that hypothalamic stimulation in this patient modulates limbic activity and improves certain memory functions.

Ann Neurol 2008;63:119–123

Quaade F, Vaernet K, Larsson S: Stereotaxic stimulation and electrocoagulation of the lateral hypothalamus in obese humans. Acta Neurochir (Wien) 30:111–117, 1974

Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Sha- piro CM, et al: Memory enhancement induced by hypotha- lamic/fornix deep brain stimulation. Ann Neurol 63:119–123, 2008

Approvals

IRB Approval

- Safety and Stature
- Join the Committee

FDA Approval

- Early Feasibility Study
- First in Human Study
- Traditional Feasibility Study
- Pivotal Study

Right of Reference Letter

- Ask and You Shall Receive (*as long as you are a high volume clinician*)

Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

---

Guidance for Industry and Food and Drug Administration Staff

Document issued on: October 1, 2013

The draft of this document was issued on November 10, 2011.

For questions regarding this document, contact CDRH's Andrew Farb, 301-796-6343, Andrew.Farb@fda.hhs.gov or Dorothy Abel, 301-796-6366, Dorothy.Abel@fda.hhs.gov, or CBER's Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

How to Conduct a First-in-Human Study

1. Isolate a problem
2. Propose a solution
3. Understand the system
4. Develop a protocol
5. Get approval
6. **Secure funding**
7. Identify patients
8. Conduct the study
9. Publish research

Secure Funding

- Intramural
  - Department
  - Medical School
  - University
  - Philanthropy
- Extramural
  - State
  - Societies
  - Foundations
  - NIH
  - $250,000-$500,000
- Industry

How to Conduct a First-in-Human Study

1. Isolate a problem
2. Propose a solution
3. Understand the system
4. Develop a protocol
5. Get approval
6. Secure funding
7. **Identify patients**
8. Conduct the study
9. Publish research

Inclusion Criteria

1. Male and female patients age ≥ 18 years.
2. BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with a comorbid condition.
3. Failure of bariatric surgery (gastric banding or bypass.
4. Chronic obesity diagnosed by an eating disorder specialist with expertise in the treatment of obesity.
5. Stable at present body weight for a 6-month period.
6. Psychiatric evaluation.
7. Karnofsky Performance Score > 60.

Patient Demographics and Treatment History

Case No.	Age (yrs)	Sex	Pre-DBS Body Weight (lbs)	Pre-DBS Body Weight (BMI)	Prior Surgical Weight Loss Treatment	Co-morbidities
1	60	F	278.7	49.4	Gastric Bypass 2001	HTN
2	50	F	326	48.1	Gastric Bypass 2001	Sleep Apnea, DM2, HTN, Migraine
3	45	M	314	45.0	Gastric Bypass 2003	Lower Extremity Edema

HTN Hypertension, *DM2* Type 2 Diabetes Mellitus

How to Conduct a First-in-Human Study

1. Isolate a problem
2. Propose a solution
3. Understand the system
4. Develop a protocol
5. Get approval
6. Secure funding
7. Identify patients
8. **Conduct the study**
9. Publish research

LH Targeting

- CRW frame
- Indirect targeting *(6.5mm lateral to AC-PC line, 4.5mm post to AC, 3mm below AC-PC line)*
- CT / MRI fusion
- MER, microstimulation, macrostimulation
- Postoperative MRI

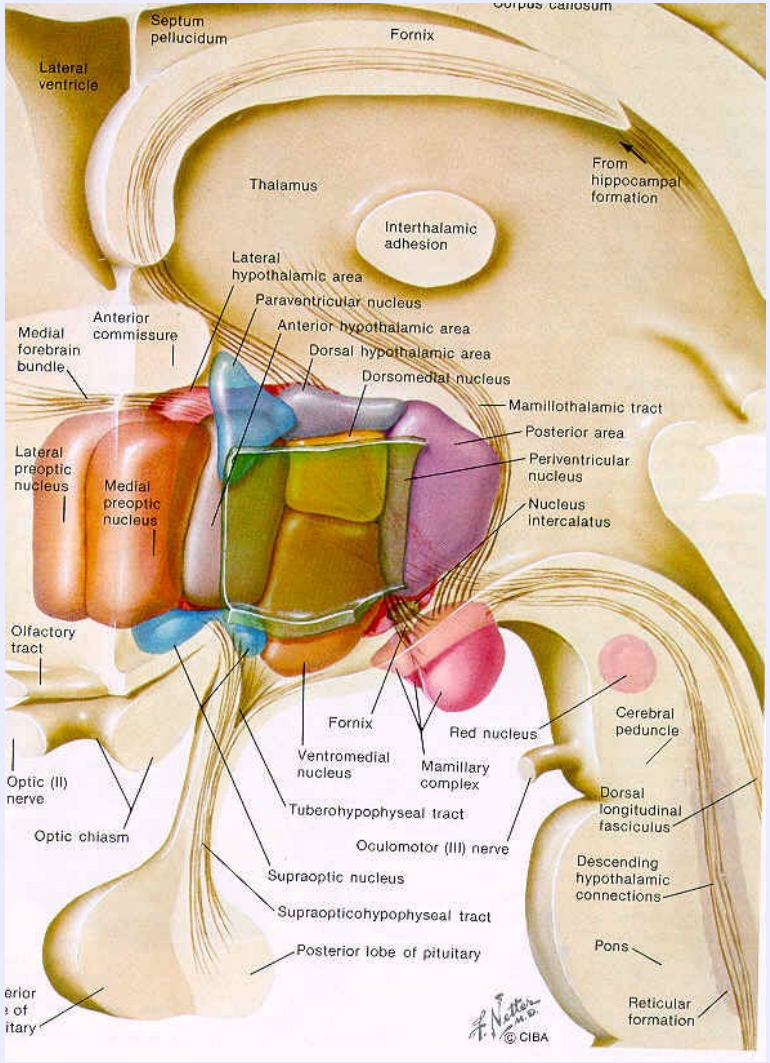
Microstimulation Evoked Responses

Evoked responses more useful than MER for guiding electrode placement

Within LH: nausea and thermal sensations

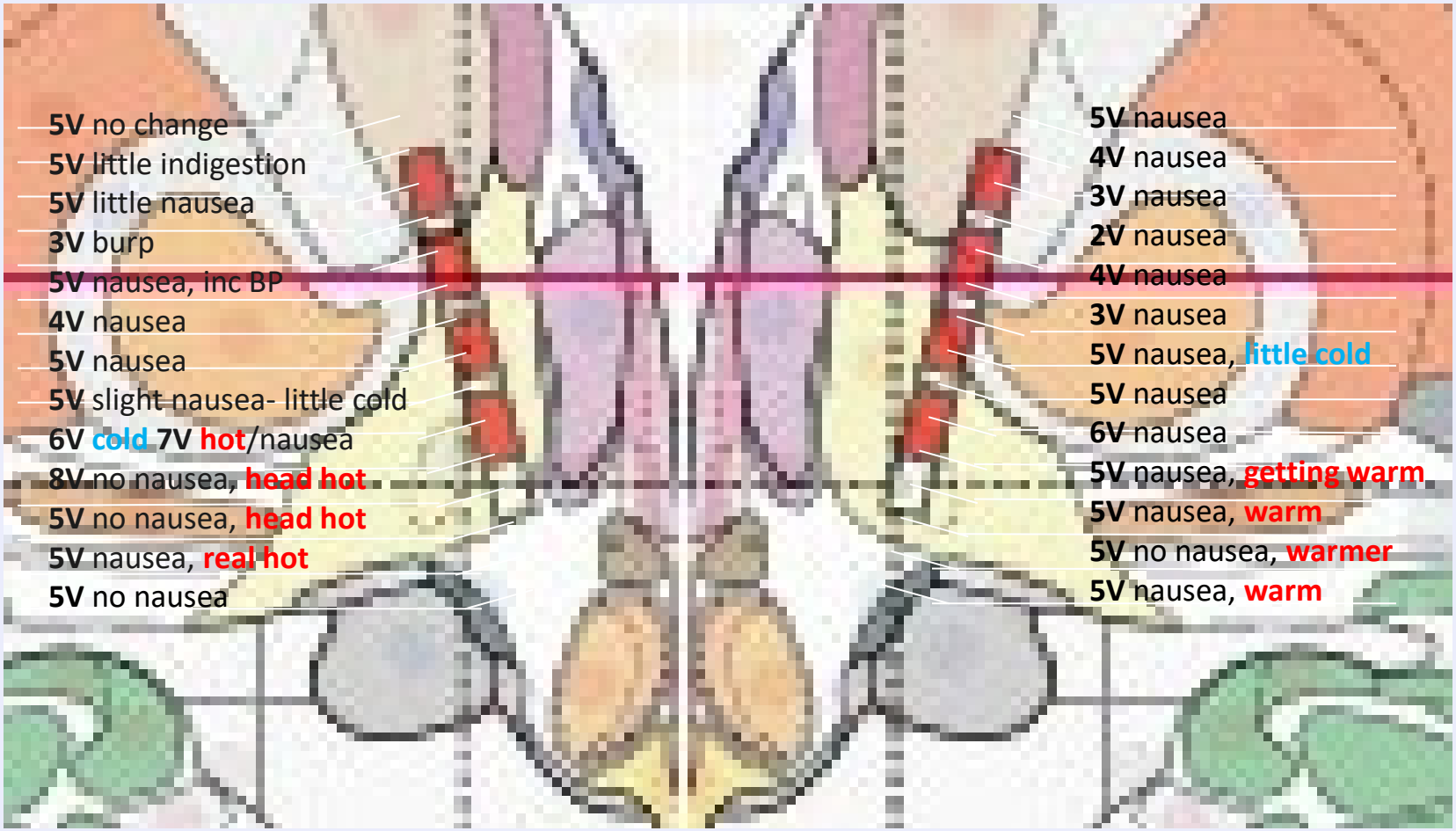
Lateral to LH: paresthesias

Ventromedial to LH: anxiety



Wilent et al. 2011

Intra-Operative Macrostimulation



Metabolic Chamber

Airtight room

Records oxygen consumption and carbon dioxide production minute-to-minute

Records spontaneous physical activity by a microwave detector

Once a month, the accuracy and precision of the chamber is assessed by propane combustion tests

Calculates resting metabolic rate (RMR) in kcal/min

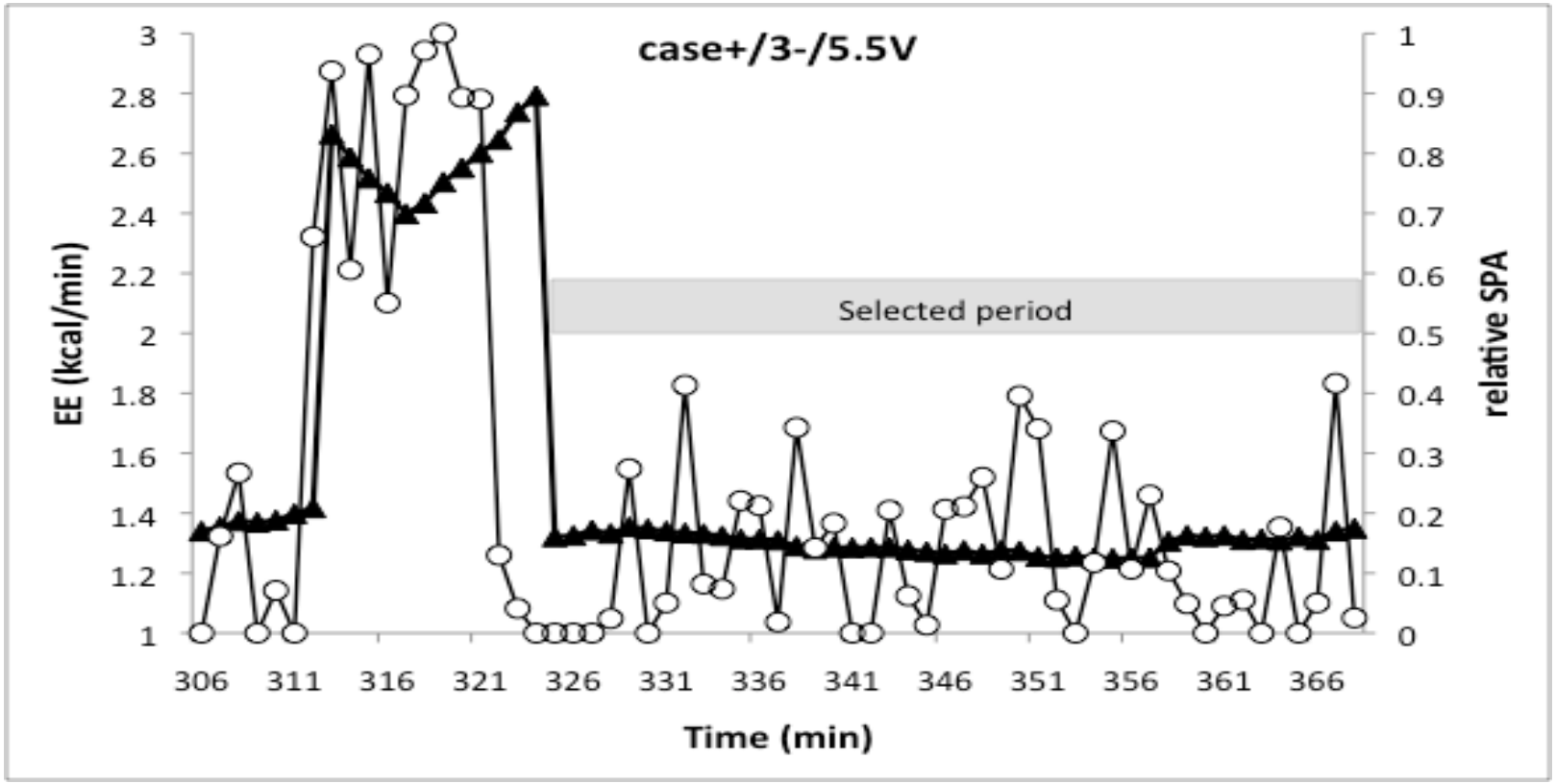
Metabolic Chamber

Louisiana State University

Pennington Biomedical Research Center

Baton Rouge, LA

RMR Calculated Over Periods with Minimal Spontaneous Activity



Psychological Metrics

Gormally Binge Scale

Patient #1 had improved such that her Binge Scale score was within the normal range while the other 2 participants continued to score in the moderate binge eating range.

Cognitive Restraint Subscale

Patient #1 improved into the high range while the other 2 patients remained in the low range.

Hunger Subscale

Patient #1 had a Hunger score of 0 at post-operative follow-up and commented that “this was the first time in her life that she didn’t have to fight constant hunger.”

Body Shape Questionnaire

Patient #2 and #3 had increase to normal.

Impact of Weight on QOL

Pre- and post-op testing revealed that DBS did not worsen a participants QOL.

Biochemical Analysis

- Serial blood testing of the following nutritional studies, pituitary hormones, and neuroendocrine/neuropeptide studies did not reveal significant changes with LH DBS stimulation:
- fasting glucose, hemoglobin A1C, serum calcium, serum magnesium, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, serum iron, TSH, free T4, total T4, T3, FSH, LH, serum cortisol, folate, vitamin B12, ACTH, fasting insulin, insulin-like growth factor, growth hormone, leptin, ghrelin, AGRP, NPY, PYY, and adiponectin.

Summary of average resting metabolic rate (RMR) changes with bilateral monopolar stimulation of individual DBS contacts during metabolic chamber experiments in three patients undergoing LH DBS

Case No.	Contact 0	Contact 1	Contact 2	Contact 3
1	No Change	**28% increase at 5.5 volts**	Indeterminate	No change at 0-5 volts; Indeterminate at >5 volts
2	Indeterminate	Indeterminate	Indeterminate	**15% increase at >5 volts**
3	Indeterminate	**9% increase at >4 volts**	Indeterminate	**21% increase at >4 volts**

- Stimulation was performed in monopolar mode with the case or pulse generator always acting as the anode (positive contact)
- Pulse width (90 microseconds) and frequency (185 Hz) were kept constant during all stimulation settings
- Calculations were deemed indeterminate when patient motion made it difficult to ascertain whether RMR changes were due to stimulation or motion

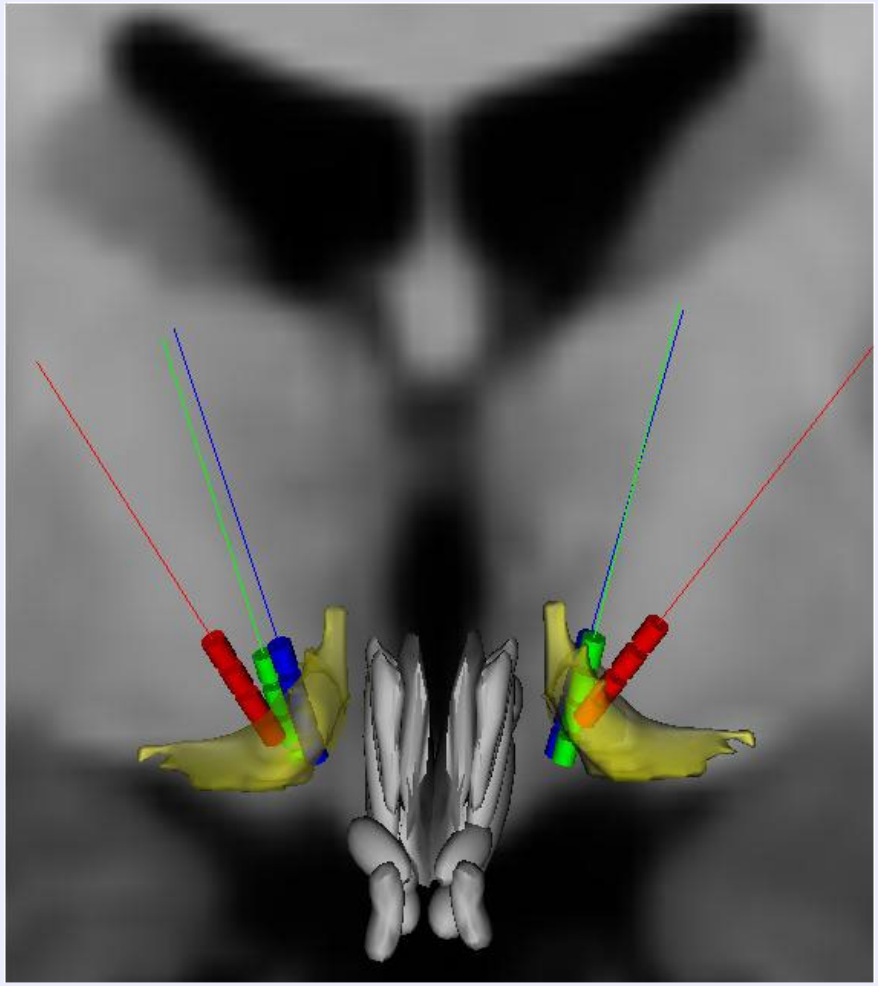
3D LH stereotactic anatomy

LH reconstructed from Mai stereotactic atlas with superimposed electrode contact locations from all 3 patients

Patient 1 (**red**)

Patient 2 (**green**)

Patient 3 (**blue**)

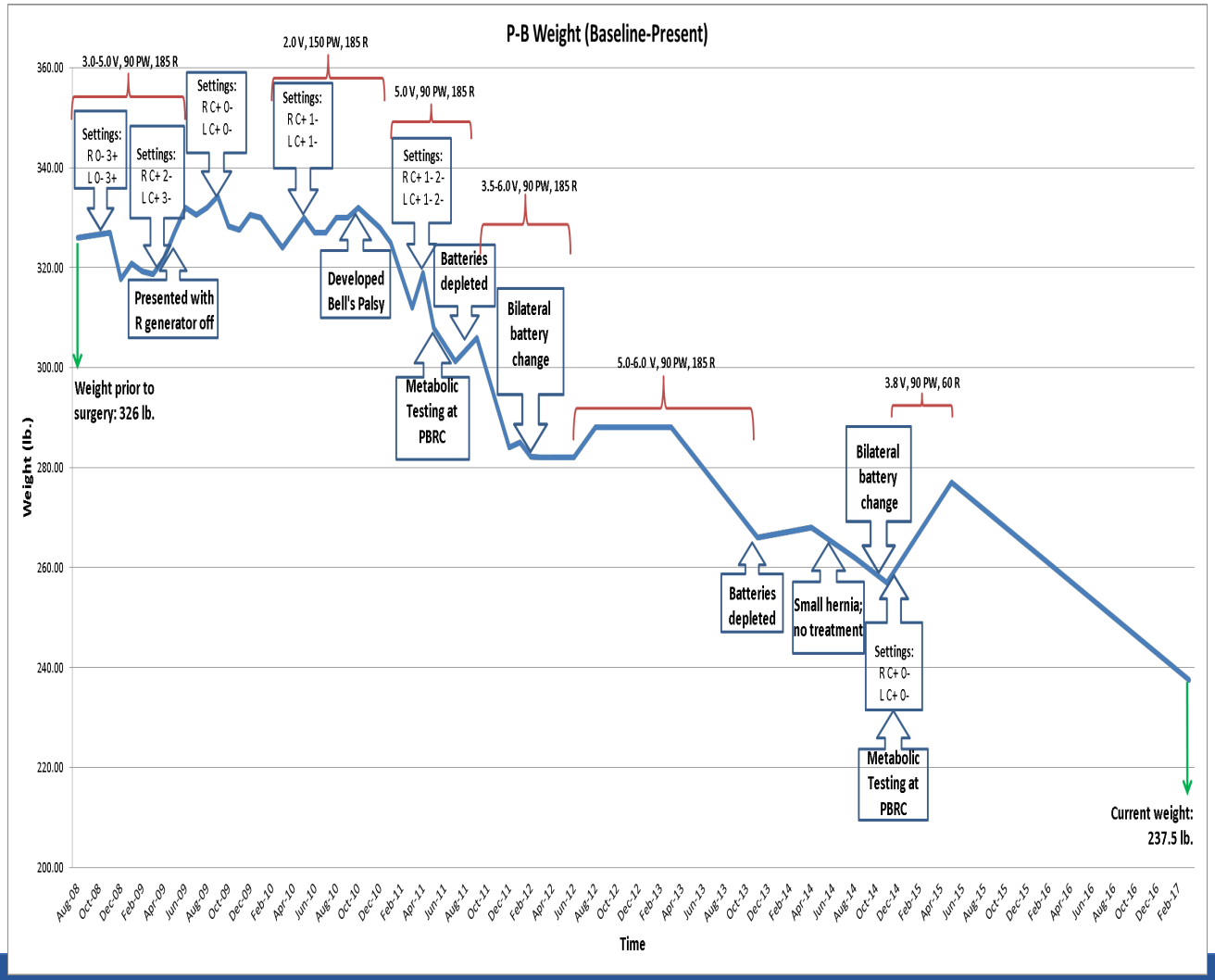


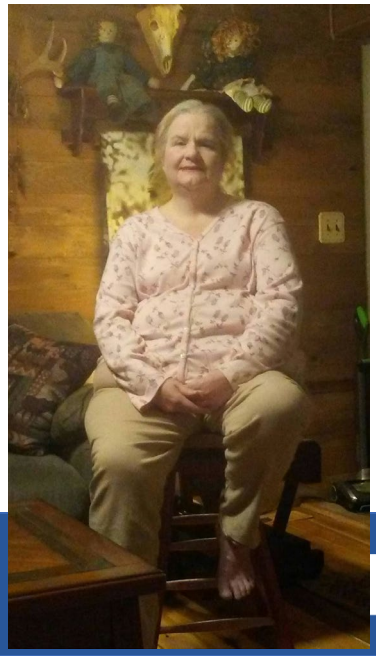
Images courtesy of Kirk W. Finnis Phd, Medtronic Neuromodulation

Body Weight Before and After Metabolically Optimized LH DBS Settings

Case No.	Body Weight (lbs) Prior to Optimized Settings	Body Weight (lbs) at Last Follow-up	Months at Optimized Settings	Percentage Change in Body Weight (%)
1	305	302	16	0.9% Decrease
2	325	285	11	12.3% Decrease
3	359	300	9	16.4% Decrease

Promising Results





How to Conduct a First-in-Human Study

1. Isolate a problem
2. Propose a solution
3. Understand the system
4. Develop a protocol
5. Get approval
6. Secure funding
7. Identify patients
8. Conduct the study
9. **Publish research**

A Multidisciplinary Endeavor

Title

Lateral hypothalamic area deep brain stimulation for refractory obesity: A pilot study with preliminary data on safety, body weight, and energy metabolism

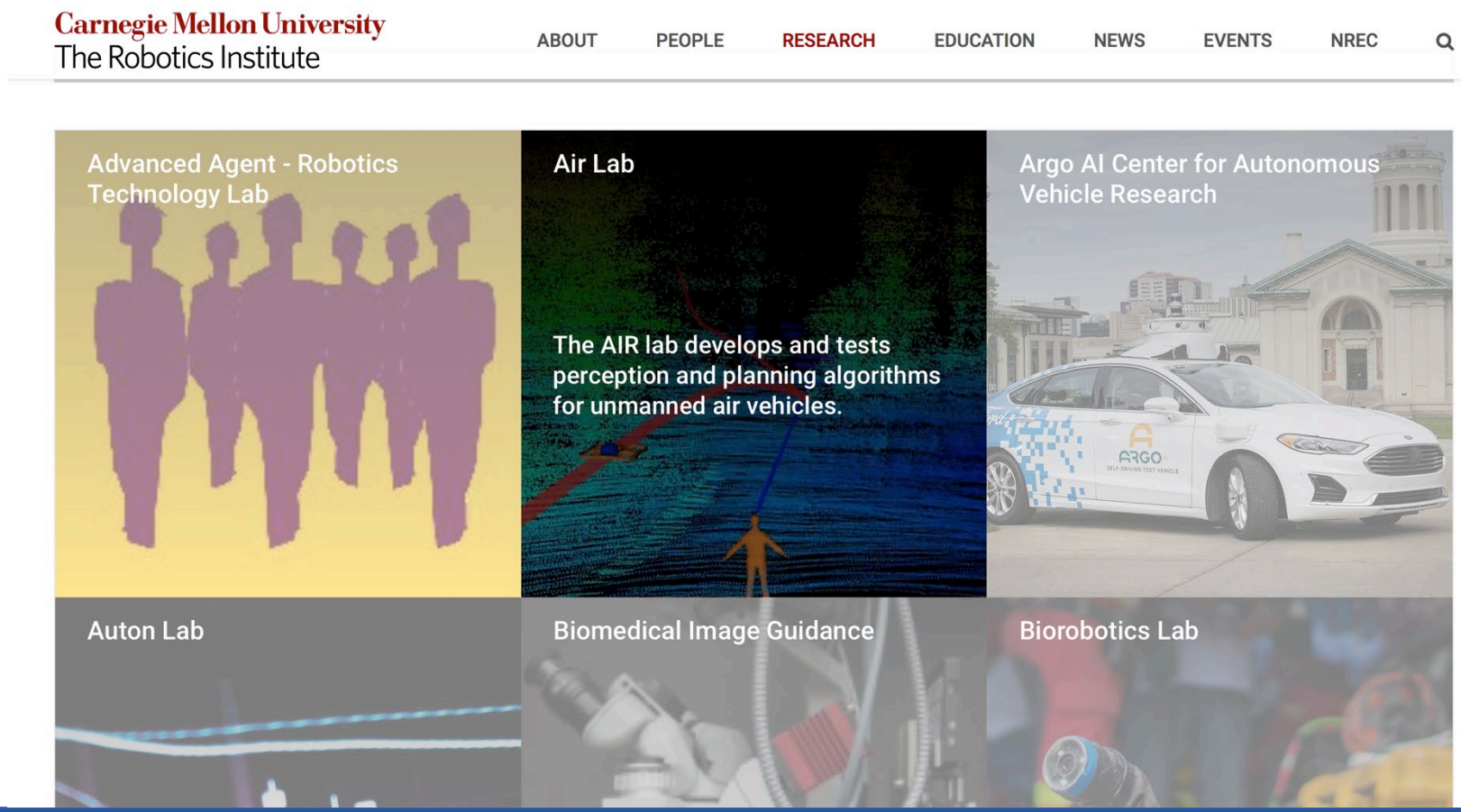
Authors

Donald M. Whiting M.D., Nestor D. Tomycz M.D., Julian Bailes M.D., Lilian de Jonge Ph.D. , Virgile Lecoultre Ph.D., Bryan Wilent Ph.D., Dunbar Alcindor M.D., E. Richard Prostko M.D., Boyle Cheng Ph.D., Cynthia Angle R.N., Diane Cantella R.N., Benjamin B. Whiting, J. Scott Mizes Ph.D., Kirk W. Finnis Ph.D., Eric Ravussin Ph.D. and Michael Y. Oh M.D.

Published

Journal of Neurosurgery: April 5, 2013

Date Night with a Scientist



Smith and Nephew Buys BBT

Navio™

The Navio surgical system is smaller, smart instrumentation that offers surgeons and patients a big advantage in precision bone cutting.

Smart instrumentation
Intelligence that you can hold in your hand, Navio smart instrumentation combines intraoperative navigation, powerful CT-free implant planning features and instrumentation that helps reproduce accurate results time and time again.

Robotics-assisted precision
Precision instrumentation that doesn't push back, handheld tools provide ease of access to the incision site and take advantage of the surgeon's skilled hands.

Smaller footprint
Operating Room space is at a premium and the small footprint of the Navio system allows for easy integration into existing OR workflows. By staying small and nimble, Navio provides flexibility to the nursing staff and leverages minimal setup and maintenance.

Patient-specific, CT-free procedure
A CT-free approach does not require pre-operative imaging beyond normal x-ray film. Based on a patient-reconstructed kinematic reference frame and acquired key anatomic landmark points and surface maps, Navio provides the opportunity to plan the placement of the implant and balance of the joint to each patient's specific needs.

Precision Freehand Sculpting
The computer-controlled cutting tool always knows where it is in space and adjusts exposure beyond the protective guard to achieve precise bone preparation.

Navio delivers the precision of robotics in a handheld, smart instrument. Precision Freehand Sculpting, the core technology, allows the system to deliver accurate and reproducible results in an efficient and ergonomic package that avoids the traditional pitfalls of large industrial-style robotic equipment.

with minimal soft-tissue impact, Navio enabled procedures are becoming very attractive to potential patients suffering on the sidelines with knee pain.

Surgeons can approach their partial knee replacements with the confidence that robotics-assisted surgical systems provide a consistent platform to optimally orient an

External Ventricular Drainage

inTRAvent MEDICAL PARTNERS

HOME ABOUT TECHNOLOGY CLINICAL NEWS CONTACT

inTRAvent Medical Partners' Bedside Neuro-Navigation Device Obtains FDA 510(k) Clearance

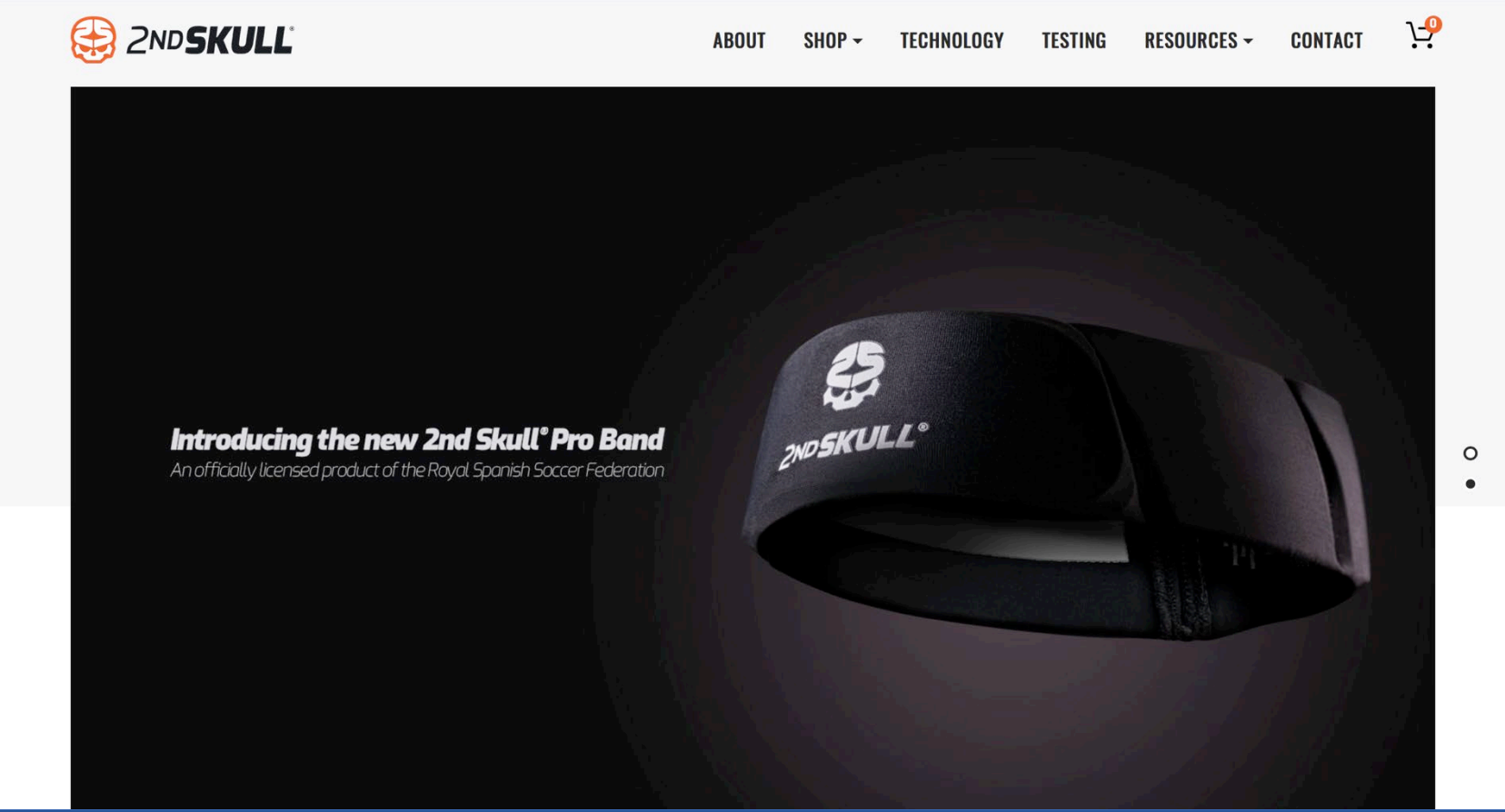
SOLOPASS® is designed to provide imaging and guidance to improve the placement of external ventricular drains, one of the most common procedures in neurointensive care.

CLICK HERE TO READ PRESS RELEASE

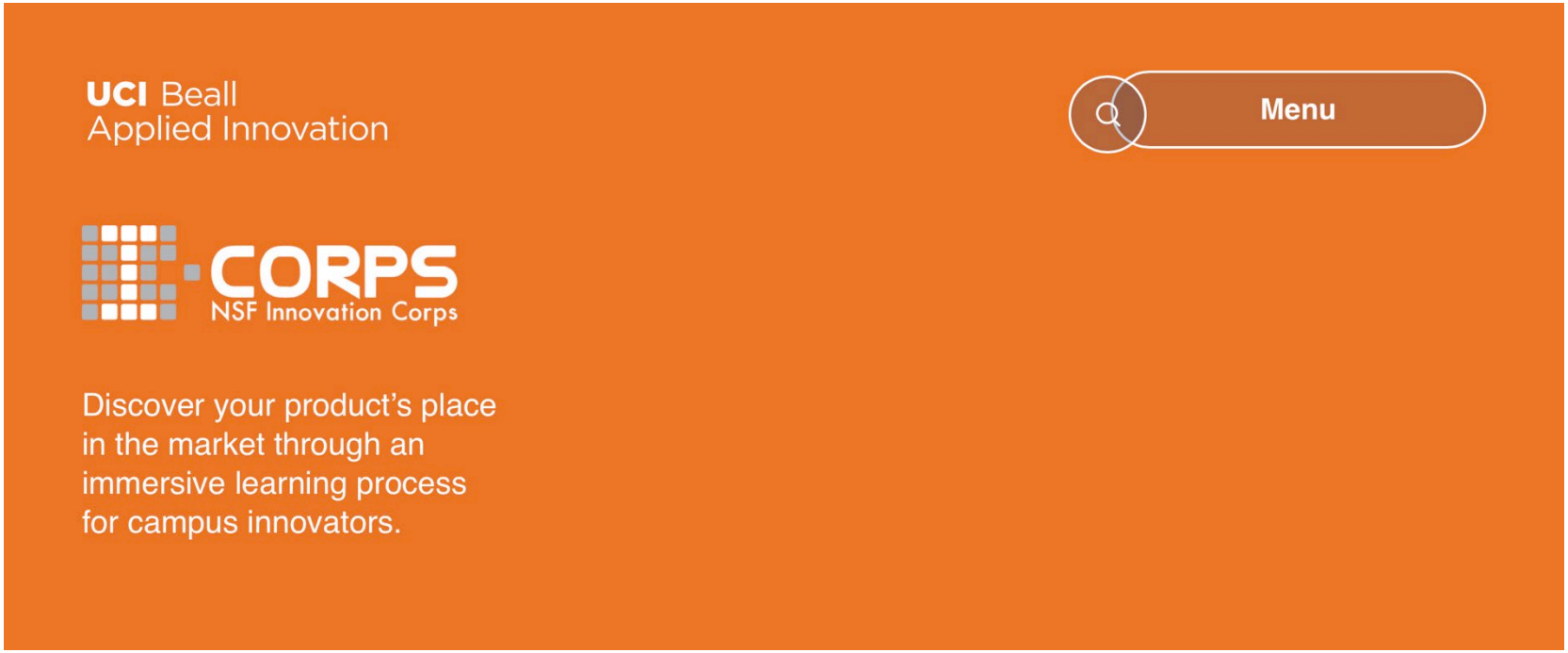
SOLOPASS®

UCI Health

Steelers Fan



I-Corps and Dural Repair



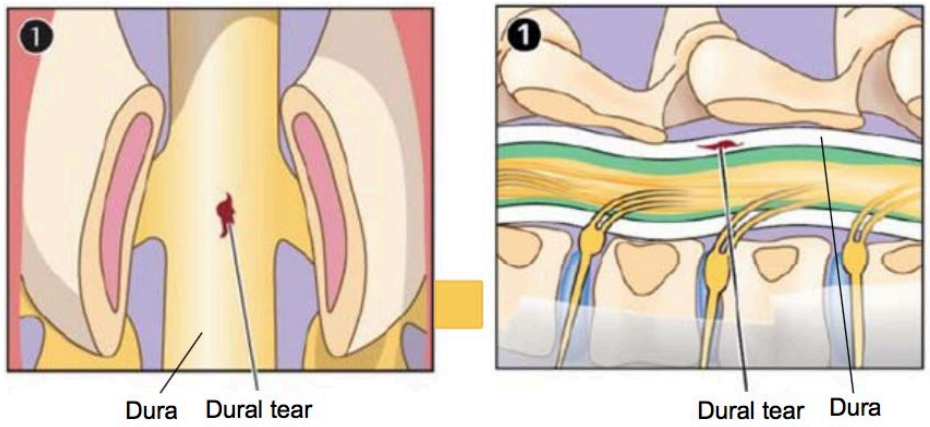

1
Dura
Dural tear
1
Dural tear
Dura

FIG. 6A

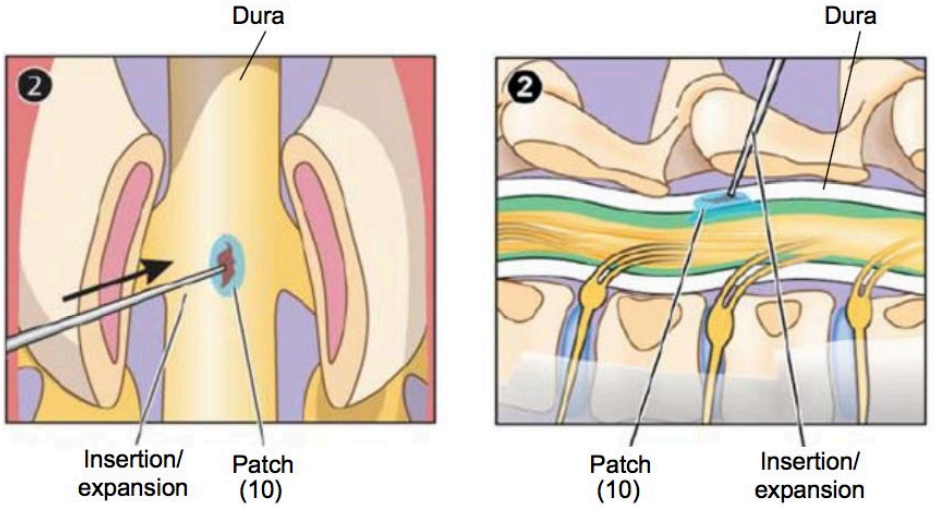

Dura
2
Insertion/
expansion
Patch
(10)
Dura
2
Patch
(10)
Insertion/
expansion

FIG. 6B

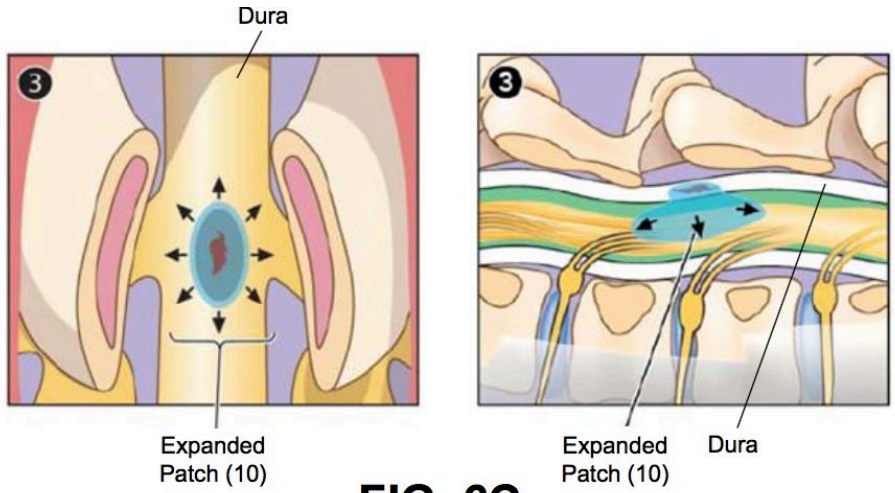


FIG. 6C

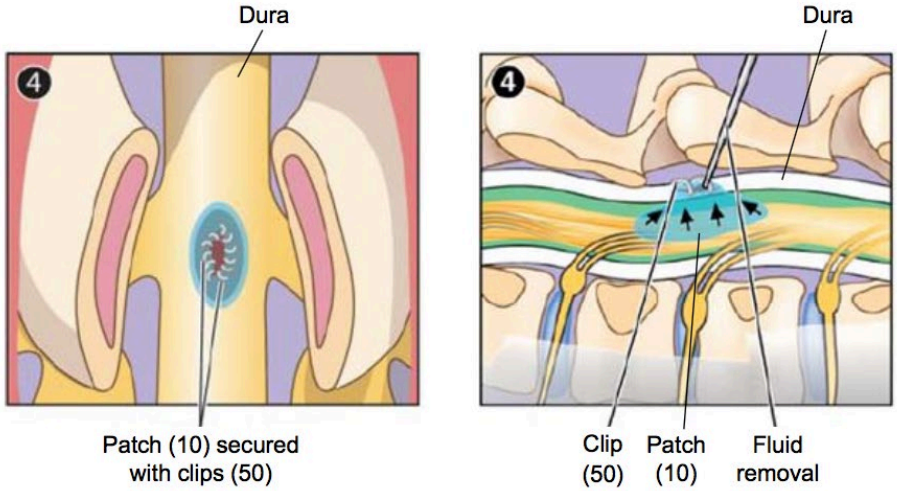
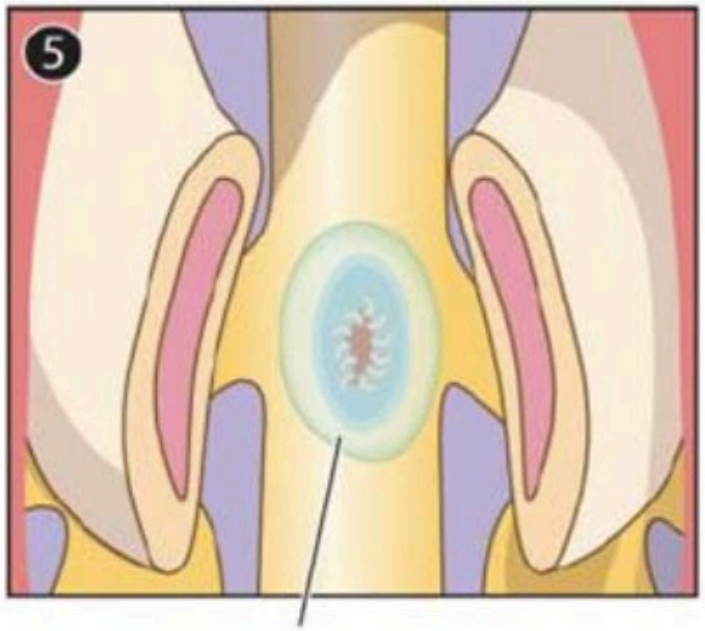
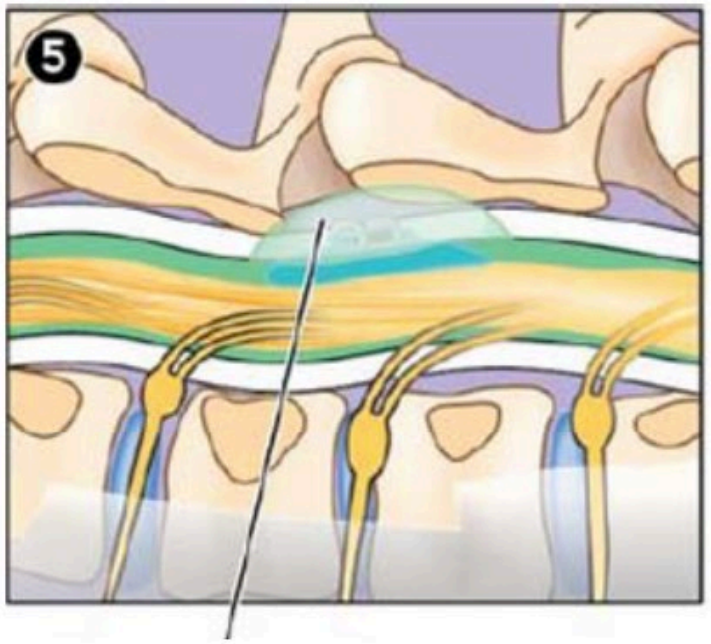


FIG. 6D

UCI Tech Transfer Office



Patch (10)/dura/clips (50)
covered in sealant



Patch (10)/dura/clips (50)
covered in sealant

FIG. 6E

Innovation from a Neurosurgeon's Perspective

First in Human Trial

Date with a Scientist

From Innovation to Entrepreneurship

Closing Thoughts on Innovation

You can't do this alone

Build your team

Be patient!

This is a long process

Plan for disappointment

Home runs are only in baseball