What is it and how does it work?

Eric Grigsby, MD, MBA
Founder and CEO, Neurovations
A Patient Care and Innovation Company

Ricardo Vallejo, MD, PhD
Director of Research, National Spine and Pain Centers
Research Professor, Psychology Department, Illinois Wesleyan University
Patient Care & Innovation Since 1992

1989-90
Inaugural Napa Pain Conference
Dr. Grigsby starts one of the first university pain management clinics in the US at UC Davis.

1991-94
Napa Pain Institute
Dr. Grigsby is certified in the first cohort of pain management by the Board of Anesthesiology.

1997-98
Clinical Research
Leveraging Mayo Clinic training, Dr. Grigsby becomes Principal Investigator in early stage trials with active involvement in clinical and translational patient care.

2005
Neurovations!
Research and education combine to become Neurovations—a patient care and innovation company.

2010-11
N3 Laboratories
Neuromodulation: The Science debuts focused on science and innovation of neuromodulation.

2013-14
Spine and Pain Center of Kaua'i
The Kauai Clinic is established in part to handle an underserved clientele. Kauai Pain Conference debuts to an international audience.

2016
Redwood Pain Institute
Redwood Pain Institute opens in partnership with St. Joseph's Health.

2018-19
Neurovations Center for Hope
The Neurovations Center for Hope begins research and development phase with 5 patients.

Clinics which do clinical research
An innovation company which also provides medical services
What is it and how does it work?

Ricardo Vallejo, MD., PhD
Director of Research
National Spine and Pain Centers
Disclosures

• Speaker's Bureau: Avanos & Medtronic
• Advisory Board: Medtronic
• CEO SGX Medical (No commercial interest)
• Product Royalties: N/A
• Equity: SGX Medical
• Company employee: National Spine and Pain Centers

Any off label uses of devices or products will be disclosed and discussed in a balanced manner: N/A
No commercial company or product names or logos will be used in this presentation: Agree

‘Doctors put drugs of which they know little into bodies of which they know less for diseases of which they know nothing at all.’

Voltaire

• Drugs = Electrical Signal AKA: Waveform
• Body = Spinal Cord
• Disease = Pain

‘Doctors put drugs of which they know little into bodies of which they know less for diseases of which they know nothing at all.’

Voltaire
Pain is the Disease

- How pain transition from acute to chronic
- Role of Neuroinflammation

“Doctors put drugs of which they know little into bodies of which they know less for diseases of which they know nothing at all.”

• Voltaire

Glial cells greatly outnumber neurons in the spinal cord

Outnumber Neurons 12:1

- SCS electrical pulses reach glial cells in addition to neurons
Doctors put drugs of which they know little into bodies of which they know less for diseases of which they know nothing at all.

- Voltaire

What are the effects of the Electrical Signal on the neural tissue?

We can do the same!!

- Burst pulse = 47, 57, 57
- PW = 600 to 1,000 μsec

Glial Cells Respond to Electrical Stimuli...

[Diagram showing effects of electrical stimuli on glial cells]
Molecular Mechanisms of SCS for pain: Transcriptomics, Proteomics and Cell Functionality

- Previous MoA studies focused on neurons and their AP
- MoA should account for biological processes affected by the electric fields (beyond gate theory)
- Chronic pain results as an unbalance of key Neuro-Glia I teractions
- ELECTRICAL FIELD, APPLIED IN THE RIGHT WAY, MAY BE USED TO HELP TO BALANCE IT

Transcriptomics – Rodent Models in SCS

Despite differences in models and designs, both studies concluded that:
- SCS at low frequency involves modulation of gene expression associated with immune and inflammatory response and synaptic signaling.
- Glial cells are involved.

MECHANICAL HYPERSENSITIVITY
Last bullet rephrased slightly

M, 6/25/2019
**Invitro**

- Immune function → Gfap
- Synaptic transmission → Slc7a11 & Glul
- Neuroprotection → S100a4
- Oxidative stress processes → Mt2a, Gsr, Hmox1
- Cell adaptive responses to stressful stimulation → Bag3.

**Dissecting the Wave**

Fold changes (vs no-SCS) correlate with results obtained for gene-related to
glial modulation (Table 1), microglia (Table 2), and neuronal cell (Table 3).

**Differential Target Multiplex best modulates Cell Specific Glial and Neuronal Cell Gene Expression** back towards the non-pain state.
Correlated Gene and Protein Expression

Example: GFAP gene and protein expression increased by pain model and modulated toward naïve levels by DTMP programming. Phosphorylated GFAP proteins are also increased by pain and modulated downward by DTMP programming.

The pain model upregulated 1,252 and down-regulated 896 phosphoproteins by at least 2.5-fold relative to naïve levels.

**Upregulated**
- Proteins involved in transport, signaling, glutamate binding mediated activation, and ECM regulation

**Downregulated**
- Involved in endocytosis, membrane trafficking, protein interaction at synapses, signaling, and activation of NMDA receptors

DTMP reversed expression of 52% of these by at least 2.5-fold in the direction of naïve expression

40% of these had expression values within 25% of the naïve levels.

Mother Nature's Medicine Cabinet

Scientists scrounge the earth in search of miracle drugs

- Aspirin extracted from: Salix Alba, Spirea spp., and Betula
- Quinine (Cinchona speciosa)
- Dihydropseudoephedrine (eucalyptus)
- Dihydropseudoephedrine (eucalyptus)
- Nicotine & Yokohama (Najoule perrieri)
- Atropine, eschscholzia (Belladonna)
Developments in Neuroscience over the last few decades have shown us that neuroinflammation and glial cells are pivotal in the development and maintenance of neuropathic pain.

Different components within the waveform have differential effects in pain-related biological processes.

Cell-specific modulation may be obtained by multiplexed signals.

Modulation of neuron-glial interactions can be achieved.

Molecular technology may help us unravel the effects of the different components of the waveform on neural tissues.

Differential Target Multiplex is supported by strong preclinical data.
Questions?
Thank you for attending!