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DTM

"Diffe tial Target Multiplexed"
Cord Stimulation

d how does it work?

Eric Grigsby, MD, MBA

Founder and CEO, Neurovations
A Patient Care and Innovation Company

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Director of Research, National Spine and Pain Centers

Research Professor, Psychology Department, Illinois Wesleyan University

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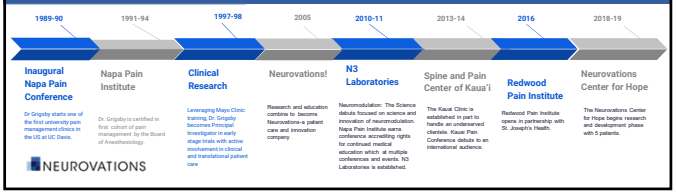

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Clinics which do clinical research

→ An innovation company which also provides medical services

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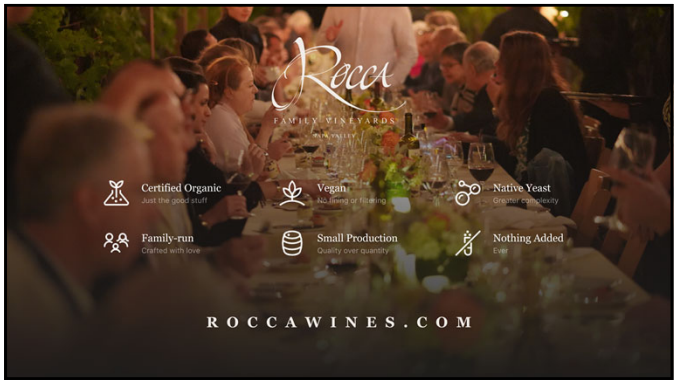


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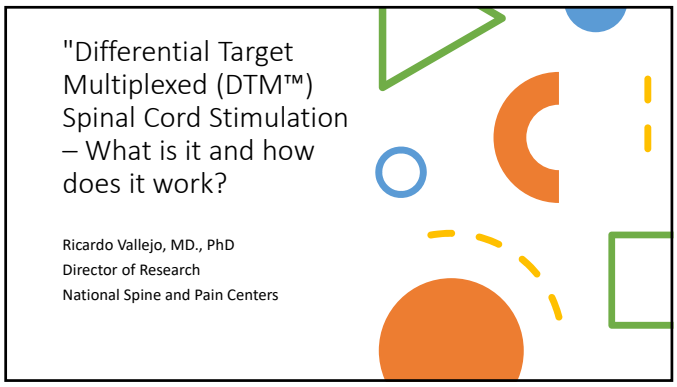

"Differential Target Multiplexed (DTM™) Spinal Cord Stimulation – What is it and how does it work?
Ricardo Vallejo, MD., PhD
Director of Research
National Spine and Pain Centers

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

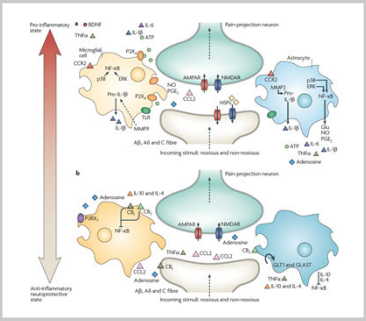
- Drugs = Electrical Signal AKA: Waveform
- Body = Spinal Cord
- Disease = Pain

'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

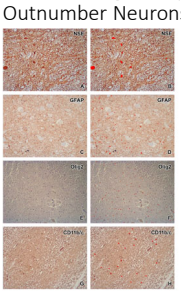


'Doctors put drugs of which they know little into bodies of which they know less for diseases of which they know nothing at all.'

- Voltaire

Glial cells greatly outnumber neurons in the spinal cord

Outnumber Neurons 12:1

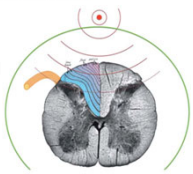


Journal of Anatomy

Glia to neuron ratio in the posterior aspect of the human spinal cord at thoracic segments relevant to spinal cord stimulation

Amparo Ruiz-Sauri,[1] Jorge M. Orduña-Valls,[2,3] Arantxa Blasco-Serra,[4] Carlos Tornero-Tornero,[2,3] David L. Cedeño,[5,6,7] Daniel Bejarano-Quisoboni,[4] Alfonso A. Valverde-Navarro,[4] Ramsin Benyamin[5,6,7] and Ricardo Vallejo[5,6,7]

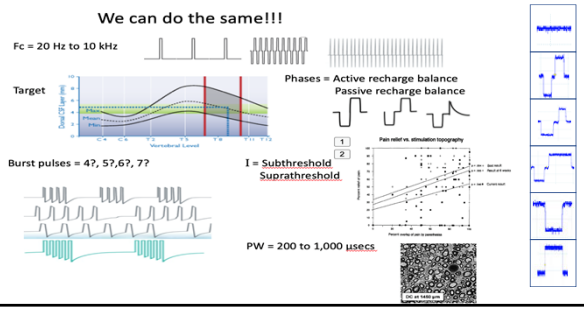
- **SCS electrical pulses reach glial cells in addition to neurons**



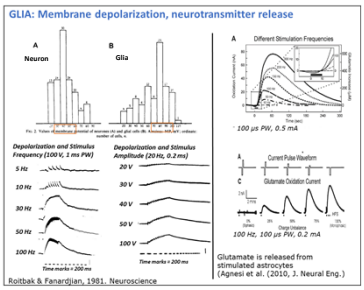
'Doctors put drugs of which they know little into bodies of which they know less for diseases of which they know nothing at all.'

- Voltaire

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



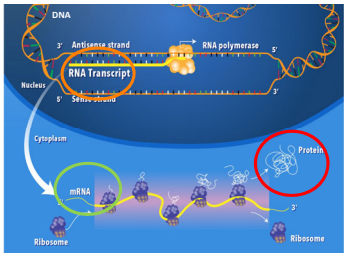
Glial Cells Respond to Electrical Stimuli…



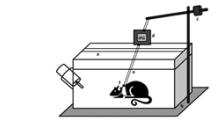
M1

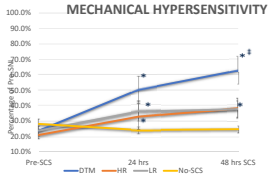
Molecular Mechanisms of SCS for pain: Transcriptomics, Proteomics and Cell Functionality

- 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-Glial Interactions**
- ELECTRICAL FIELD, APPLIED IN THE RIGHT WAY, MAY BE USED TO HELP TO BALANCE IT



From National Human Genome Research Institute (genome.gov)





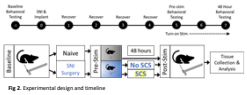
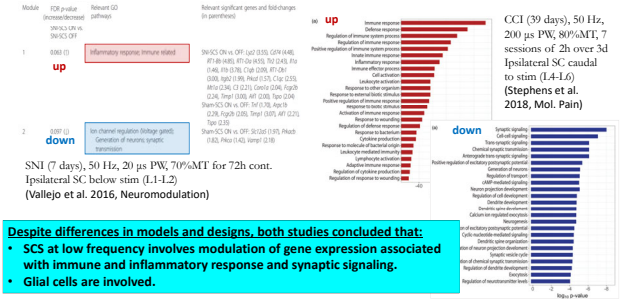


Fig 2. Experimental design and timeline

Fig 3. Scheme of phosphorylated protein purification and analysis

Transcriptomics – Rodent Models in SCS



SNI (7 days), 50 Hz, 20 µs PW, 70%MT for 72h cont. Ipsilateral SC below stim (L1-L2)
(Vallejo et al. 2016, Neuromodulation)

CCI (39 days), 50 Hz, 200 µs PW, 80%MT, 7 sessions of 2h over 3d Ipsilateral SC caudal to stim (L4-L6)
(Stephens et al. 2018, Mol. Pain)

Despite differences in models and designs, both studies concluded that:

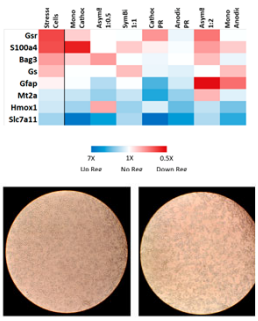
- **SCS at low frequency involves modulation of gene expression associated with immune and inflammatory response and synaptic signaling.**
- **Glial cells are involved.**

Slide 19

M1 Last bullet rephrased slightly
M, 6/25/2019

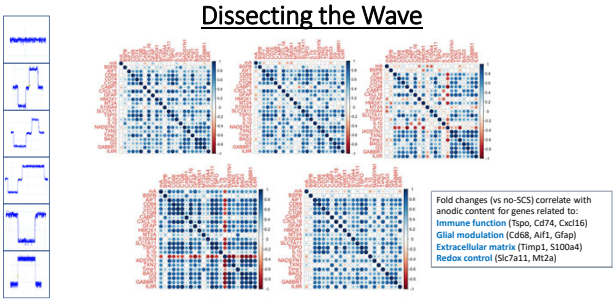
Invitro

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



1: Light microscopy images (40x) of the same cell population before Cathodic PI (right).

Dissecting the Wave

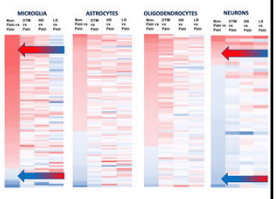


Fold changes (vs no-SCS) correlate with anodic content for genes related to:
Immune function (Tspo, Cd74, Cxcl16)
Glial modulation (Cd68, Aif1, Gfap)
Extracellular matrix (Timp1, S100a4)
Redox control (Slc7a11, Mt2a)

Correlograms illustrating relationships between gene expression, SCS Current (mA), and Behavioral Score as % of Baseline (BSPB).
A: Sham, B: No-SCS (SNI), C: biphasic symmetric SCS, D: monophasic cathodic SCS, E: monophasic anodic SCS, F: asymmetric biphasic SCS 1:2, G: asymmetric biphasic 1:0.5. The blue dots represent a positive correlation and red dots represent a negative correlation. The size and darkness of the dot is proportional to the value of the Pearson correlation coefficient

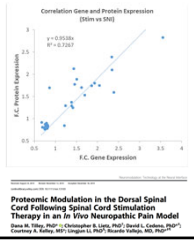
Differential Target Multiplex best modulates **Cell Specific Glial and Neuronal Cell Gene Expression** back towards the non-pain state.

	Microglia	Astrocytes	Oligodendrocytes	Neurons
# of genes in data set	101	188	154	72
Correlation with DTM	**Strong (+)**	**Strong (+)**	**Strong (+)**	**Strong (+)**
Correlation HR	Strong (+)	Weak (+)	Weak (+)	Moderate (+)
Correlation LR	Weak (-)	NS	NS	Weak (-)



Correlated Gene and Protein Expression

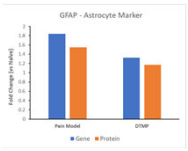
- **Gene expression modulated by SCS correlates proportionately to protein expression changes (Stim *vs.* SNI, R^2 = 0.73)**

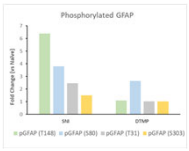


Proteomic Modulation in the Dorsal Spinal Cord Following Spinal Cord Stimulation Therapy in an *In Vivo* Neuropathic Pain Model

Dana M. Tilley, PhD[a,b]; Christopher B. Ligas, PhD[a]; David L. Cedeno, PhD[a,c]; Courtney A. Kelley, MS[a]; Lingjun Li, PhD[d]; Ricardo Vallejo, MD, PhD[a,c]

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

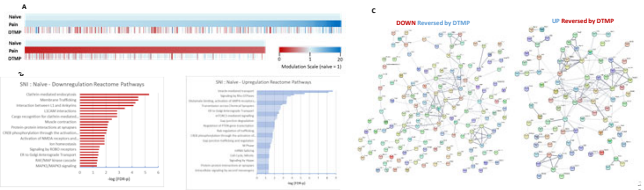


Fig 4. A. Heat maps showing modulation of phosphorylated proteins by DTMP relative to changes by the pain model (SNI) and naïve expression (normalized to 1). **B.** Bar graphs showing significantly enriched pathways (FDR-p < 0.05) containing proteins dephosphorylated and upregulated by the pain model (SNI) relative to naïve. **C.** Protein interaction maps containing proteins that were reversed by DTMP within 25% of the naïve expression.

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THE SCIENCES

Mother Nature's Medicine Cabinet

Scientists scour the earth in search of miracle drugs

By Kate Wong on April 9, 2001

- Aspirin extracted from: Salix Alba, Spirea spp., and Betula
- Quinine (Cincocha colisaya)
- Opiates Papaveracea somniferum)
- Dogoxin (Foxglove plant)
- Paclitaxel (Bark of pacific Yew)
- Vincristine & Vinblastine (Madagascar periwinkle)
- Atropine, scopolamine (Belladonna)

Developments in Neuroscience over the last few decades has 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!

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Eric Grigsby MD, MBA
CEO and Founder of Neurovations

Join the Conversation:
Thursday
September 24, 2020
5:30 PDT/8:30 EDT

Register at
Neurovations.com/webinars/

David Caraway MD, PhD
Chief Medical Officer, Nevro