# SPARC Strategic Planning Workshop: Biology and Technology

## Opportunities for the SPARC Program

**Dr. William C. de Groat and Dr. Kevin Kilgore**

Building detailed, integrated functional and anatomical peripheral neural circuit maps in multiple organs in humans

- What information do we need in order to build maps that guide specificity and efficacy of neuromodulation approaches?
    - What parameters of the nervous system would be integral to the maps: consider anatomy, fiber sizes, fiber conduction properties, neurotransmitters, other?
    - What parameters of organs need to be understood, and what assays developed, in order to assess nerve function, and eventually, therapeutic efficacy?
    - How can animal and human data be leveraged to generate useful human maps?

# SPARC Strategic Planning Workshop: Biology and Technology

## Overviews

**Session Chair: Dr. Terry Powley**

1) Need better characterizations and definitions of what electrodes are actually doing, with which fibers in mixed nerves

2) Need some discussion of the disjunctive results that often surface when open trial results (in Europe) versus Randomized Control Trials (more common in U.S.)

3) Need to find paths to get from phenomenology to mechanism

# SPARC Strategic Planning Workshop: Biology and Technology

## Session 1: Neural Circuits in Organs and Diseases – Opportunities for Neuromodulation in the Lower Urinary Tract

**Session Chair: Dr. Helen Raybould**

1) The bladder has two major functions - storage and elimination. This is "binary" and maybe different from other visceral organs where function is graded.

2) Many of the pathways for reflex function of the bladder are quite well described, although changes in the circuits that occur in pathophysiological such as overactive bladder are not fully known and may involve altered activity in one or all of the components of the system.

3) Sacral neuromodulation is being used and can promote both storage and elimination. How can this occur? What neural structures are being stimulated? Is the site of action peripheral or central; what neurotransmitter or neurotransmitter receptors are involved?

# SPARC Strategic Planning Workshop: Biology and Technology

## Session 3: Neural Circuits in Organs and Diseases – Opportunities for Neuromodulation in Complex Systems

**Session Chair: Dr. Ranu Jung**

1) How do cardiac sympathetic afferents impact sympatho-excitation in cardiovascular diseases such as heart failure and hypertension?

   Strategies that need to be undertaken are:

   1. selective ablation (RTX?) of cardiac sympathetic afferents
   2. cardiac affects of afferent neuropeptide release
   3. selective ablation in patients (maybe data from patients treated for chronic pain)

2) How do you take technology developed for mapping in animal studies to that for mapping in human subjects?
3) What approach could one take to select parameters for stimulation?
4) How important is it going to be understand CNS function along with PNS function?
5) The vagus nerve innervates multiple organs; how important will it be for us to understand organ-organ interaction.

# SPARC Strategic Planning Workshop: Biology and Technology

## Session 4: Mechanisms of Nerve/Organ Interaction

**Session Chair: Dr. Yvette Taché**

1) Need for dissecting local reflex circuits within or inter organs at the structural biochemical and functional levels for targeted interventions.

2) Define the time course of vagal stimulation response at different parameters if stimulation.

# SPARC Strategic Planning Workshop: Biology and Technology

## Opportunities for the SPARC Program

**Dr. William C. de Groat and Dr. Kevin Kilgore**

Building detailed, integrated functional and anatomical peripheral neural circuit maps in multiple organs in humans

- **What existing technologies need to be brought to bear, and what technologies need to be developed to discover detailed mechanisms of neural control of organs?**

- **What types of data might be expected from these studies and how could those data be usefully assembled for the community?**

# *SPARC – Technology Summary*

- Technologies for Activation
- Technologies for Block/Modulation
- Sensor Technologies
- System Technologies
- Signal Processing
- Computational Modeling

# *SPARC Technologies – Priority Areas*

- **Translation of animal models to human application** – needs to be addressed
  - Do the technologies scale in size?
  - Does the animal physiology match the human?
- **Selectivity** – technologies and methods that target the specific fibers in terms of fiber location, fiber size, afferent/efferent, transmitters, etc. – minimizes side effects; find the optimum stimulation points; how many fibers do you need to stimulate?
- **Sensing and Sensors** of biomarkers that are closely related to the expected direct neural effect (i.e. not just a depression scale measure or total weight loss); Interpreting neural codes

# *SPARC Technologies – Priority Areas*

- **Understand the effect and importance of all parameters –** e.g. stimulation amplitude, frequency, duty cycle, prolonged effects, etc.
- **“New” modalities**
- **Device-Drug Combinations**
- Understand how to **customize** and tune the technology for each subject; adaptive systems
- **Characterize the technology** to the same extent that you characterize the physiology – inc. long term studies of interventions that can address plasticity effects – therefore devices for chronic implantation are important

# *SPARC Technologies – Priority Areas - 3*

- **Access to technology** – what technologies are out there for activation and block?
- **Enabling tools to understand the physiology**
  - Tissue clearing, optogenetics (cuffs, light delivery), viral vectors (see Vivian's list)
  - Not all need to be targeted to human application – are there some conditions where a device approach doesn't make sense (e.g. use of RTX, denervation…)
- **Proper common nomenclature**
- **Opportunity for cross-fertilization** between physiologists and engineers – i.e training sessions, workshops…
- *If you're going to propose stimulating the vagus, then you better explain how you are going to measure every possible side-effect of your intervention!*

# SPARC Strategic Planning Workshop: Biology and Technology

**Session 2: Data Coordination Panel – Case Studies and Ontologies**

**Session Chair: Dr. Vinay Pai**

1) Development of an electronic lab notebook for capturing not just the data but also the “thoughts” and observations of the submitter.

2) How can we combine data from multiple clinical sources which may/may not have the same standards and are from different clinical trials/studies.

3) How do we get general access to data that is now in a central location? How will this be publicized to audience other than a focused crowd.

4) How do we plan to address issues of IP and / or early stage experiments?

# SPARC Strategic Planning Workshop: Biology and Technology

**Session 2: Data Coordination Panel – Case Studies and Ontologies**
**Session Chair: Dr. Vinay Pai**

1) Development of an electronic lab notebook for capturing not just the data but also the “thoughts” and observations of the submitter.

2) How can we combine data from multiple clinical sources which may/may not have the same standards and are from different clinical trials/studies.

3) How do we get general access to data that is now in a central location? How will this be publicized to audience other than a focused crowd.

4) How do we plan to address issues of IP and / or early stage experiments?

# SPARC Strategic Planning Workshop: Biology and Technology

**Session 2: Data Coordination Panel – Case Studies and Ontologies**
**Session Chair: Dr. Vinay Pai**

**Questions from Chair:**

a. Just because SPARC is a central program for PNS, does this mean that data from studies of the research into vagus nerve mapping/stimulation in different organ systems/diseases have to be centralized? Can it be centralized?

b. b. Are we better off with one central data integration/curation/provenance/reproducibility effort or multiple storage centers with one coordinating center integrating effort? (sort of relates to question a).

c. c. How do we plan to combine mapping data (sketches?), electrical signal data, MRI images, optogenetic data, etc?

# *SPARC Technologies – For Discussion*

- *What would it take for a device approach to become something better than the option of last resort?*

- *Should we consider enhancing implanted systems with biomarker sensors that may not be required for the intervention, but provide us with critical data regarding the response of humans to the intervention?*