I. BIOLOGICAL SUCCESS CRITERIA:

Teams interested in the challenge need to demonstrate reproducibly over 60 days the ability to record, stimulate, and block/silence neural signals that elicit functional changes at the end organ in rat models as specified below:

1) **Recording of neural patterns that correlate with end-organ function upon physiological perturbation:**
    A. Teams should show that they can record a distinct neural signalling pattern from the target nerve upon a physiological perturbation
    B. The derived neural signalling pattern should correlate with the measured end-organ function. The pattern should be distinct from signalling in the same nerve not triggered by the perturbation
2) **Stimulation of nerves to elicit end-organ function without perturbation:**
    A. Teams should stimulate the target nerve with a specific pattern that induces the same end-organ function without the perturbation.
    B. Defined "off target" functions should not be affected by the stimulation with this specific pattern
3) **Reversible blocking to inhibit end-organ function upon perturbation:**
    A. Teams should block/silence the target nerve with a specific pattern that suppresses the end-organ function upon perturbation
    B. Defined "off target" functions should not be affected by the blocking/silencing with this specific pattern
    C. Upon removal of the blocking/silencing, the end-organ function should be restored upon perturbation

The first team to demonstrate **full functionality in 1 model organ** will win the prize.

Table 1. Summary of the four organ model systems and the specific neural input that they receive which must be neuronal points of interface. The perturbations to be used, the organ on- and off-target functions to be studied, and the specific measurements required for each of these are also listed.

Organ	Target nerve	Target function	Physiological perturbation to trigger the target function	Target function measurement	"Off target" functions	"Off target" function measurement	Species
Selective Motor Functions							
Adrenal Medulla	Greater splanchnic nerve branches to the adrenal medulla	Catecholamine secretion	Hypoglycaemic shock induced by insulin injection	Plasma catecholamine levels	Adrenal neuro-peptide secretion	Plasma Chromogranin A levels	Rat or mouse
Urinary Bladder	Pelvic nerve	Detrusor contraction	Bladder filling by catheter	Intra-bladder pressure (cm H_2O)	Lower GI/colon peristalsis	Intra-colon pressure	Rat or mouse
Bronchial Tree	Vagus or its branches	Bronchial tone	Exposure to airway irritants	Airway resistance and conductance	Cardiac function	Heart Rate	Guinea Pig
Selective Sensory Functions							
Carotid Body	Carotid sinus nerve and its branches	Oxygen sensing	Hypoxia	Renal sympathetic nerve activity (RSNA)	Barosensing	Blood pressure	Rat or mouse

Table 1: Summary of the 4 model systems from which 1 should be selected to prove the ability of the wireless neural interface to record, stimulate, and block functionally selective neural signals

In addition to the summary provided in Table 1, a detailed experimental protocol for each model system is given below. Teams must show proof-of-principle with their finalised device in **at least 3 animals** per organ model with at least two-thirds of the animals implanted meeting the full set of success criteria specified below.

II. DETAILED EXPERIMENTAL PROTOCOLS

A) ADRENAL MEDULLA

Implantation of device on the splanchnic nerve:

- The site of device implantation should be on the greater splanchnic nerve branches to the adrenal medulla.
- To determine the efficacy of the blocking protocol described below, the rat's splanchnic nerve should be denervated on the contralateral side with respect to the implanted device, or a device must be implanted on each side.
- Additionally, a chronic cannula should be implanted into the carotid artery for blood collection. The catheter should be back-flushed with heparinised saline with the manifold outlet closed when not in use, and treated with antibiotics following each procedure.
- The rat should recover from surgery for 1 week with no detrimental effects.
- Acclimatization protocol: The rat will be acclimatized to the handling and isoflurane anaesthesia procedure prior to the experimental component of the 6-week protocol. This is accomplished by a sham protocol on 5 successive days whereby the rat is anaesthetised for 60 minutes and allowed to recover.

Experiment 1. Splanchnic activity measurement:

- Recordings are made in awake animals. After recording, the animal should be anesthetised as described below. For each procedure requiring handling and blood collection the rat will be anaesthetised by isoflurane inhalation through a vapouriser.
- Animal core temperature should be regulated by a heat lamp and monitored using a rectal thermometer during anaesthesia.
- Following the onset of anaesthesia, the animal should be given a hypoglycaemic perturbation via a short acting insulin injection (2 U/kg). This perturbation will induce an increase in splanchnic nerve activity to release catecholamines at the end organ. These signaling patterns must be recorded and correlated to plasma catecholamine and chromogranin A release at 10, 30 and 60 minutes post insulin injection ($P < 0.05$, $R^2 > 0.5$). Hypoglycaemic shock should induce >100 fold change in catecholamine concentration correlated with an increase in splanchnic nerve firing pattern. Plasma levels of Chromogranin A should not increase during hypoglycaemic shock.

Experiment 2. Stimulation:

- Stimulation experiments should take place under anesthesia, post surgical implantation on odd weeks (1, 3, 5, 7 etc).
- A stimulation pattern should be applied that reproduces the level of catecholamine secretion triggered by the hypoglycaemic perturbation +/- 20%
- Off target effects are defined as the co-release of higher molecular weight adrenal-derived peptide transmitters. Thus, stimulation must not increase plasma chromogranin A levels by more than 2 times the baseline level.
- Plasma catecholamine and chromogranin A levels should be determined by blood collected during stimulation at the time points corresponding to the sampling times in Experiment 1 (10, 30 and 60 minutes post insulin injection).
- The required stimulation effect should be reproduced on 4 subsequent days.

Experiment 3. Blocking:

- Blocking experiments should be done post surgical implantation on even weeks (2,4,6,8,… etc).
- After switching on the blocking mode of the device, stress-evoked catecholamine release will be triggered by exposing the anaesthetised rat to hypoglycaemic shock (injection of 2 U/kg short acting insulin).
- Plasma catecholamine and chromogranin A levels should be measured at 10, 30 and 60-minute time points post insulin injection.
- Successful blockade will be considered to be achieved when hypoglycaemic shock fails to elevate plasma catecholamine levels by more than 2 times the baseline level.

At the end of 60 days:

- Chronic nerve functionality and interface stability should be assessed as described in section V below.
-

B) CAROTID BODY

- Unless otherwise stated, all experiments are in awake, conscious rats.
- Implantation of the device should be bilateral on the carotid sinus nerve (CSN) or its chemoreceptor branch
- Implantation of a commercially available RSNA telemetry probe. [1, 2]
- Implantation of a commercially available blood pressure (BP) telemetry probe. Animals should recover for 1 week with no detrimental effects.[1]
- Acute hypoxia (AH) should be defined as 15-minute hypoxia (10% O_2, 90% N_2) followed by 30 minutes of room air, repeated twice on a given day for assessing reproducibility. Specialised cages with airflow monitors should be used. Care should be taken to ensure air switching (room air to 10% O_2 and vice versa) and that its equilibration in the cage happens within 70-90 seconds of switching.
- Exposure to high frequency noise – 80 kHz, 100 dB for 10 seconds (increases sympathetic tone short term) should be carried out once a week to assess the reliability of the RSNA implant.
- Off-target effects are assessed in anesthetised studies fortnightly.

The following three experiments are performed weekly:

Experiment 1

- After allowing the animals to acclimatise in the cage for 1 hour, baseline afferent recordings and RSNA measurement should be performed for a 5 minute duration in awake, freely moving rats.
- AH should be applied to animals, while simultaneously recording the CSN afferent activity, RSNA, and BP. Experiments should be performed at the same time of the day to exclude circadian variation in sympathetic nerve activity.
- A firing pattern from the CSN recording that temporarily correlates with the start of the AH and increased RSNA ($P < 0.05$) should be detected with <5% change in BP should be observed.[3]
- During week 1, and once every fortnight during the odd weeks (weeks 1, 3, 5 etc.) post implant, animals should be lightly anesthetised under isoflurane anaesthesia and laid supine

on a plank. The animal's head and torso should be taped down for head tilt experiments. The head tilt should then be performed and the BP response recorded.

Experiment 2

- This experiment should be performed in awake, conscious animals.
- Apply the stimulation pattern (20 min) to recapitulate the hypoxic response. This should reproduce the increase in RSNA as seen during AH +/- 20% without alterations in BP (<5% change). The stimulation effect must be reproduced twice on a given day with a period of no stimulation until all parameters have returned to baseline values.
- In anesthetised studies during odd weeks (weeks 1, 3, 5 etc.), perform stimulation and ensure BP is unaffected (<5% change from baseline).
- To assess off target effects, animals should be lightly anesthetised under isoflurane anaesthesia once every fortnight, laid supine on a plank with head and torso be taped down for head tilt experiments. Perform head tilt and ensure BP response can be demonstrated during stimulation.

Experiment 3

- Blocking experiments during week 1 and odd weeks (weeks 3, 5, 7 etc.) should be done in anesthetised animals anaesthetised by isoflurane inhalation through a vapouriser.
- Even week experiments should be performed in awake, conscious animals.
- After a period of baseline recording CSN, RSNA and BP, expose the animals to AH and perform blocking on the CSN for the first 10 minutes of hypoxic exposure. Blockade must be on for 1 minute prior to AH and for 10 minutes into the hypoxic period. The remainder of the 10-minute hypoxic period will ensure measurements of reversibility of blockade.
- AH during blocking should produce no net change in RSNA and blood pressure (< 5% change in blood pressure).
- Perform head tilt in anesthetised animals during blocking to reproduce the blood pressure change (+/-20%) seen in the AH experiment.

At the end of 60 days:

- Chronic nerve functionality and interface stability should be assessed as described in section V below.

C) URINARY BLADDER

- Implantation of the device should be bilateral on the pelvic nerves of female rats.
- No denervation of any other nerve should occur during surgical implantation.
- Animal should recover for 1 week post implantation.
- On days 7, 21, 35, 49, and 60, the animal is lightly anesthetised under isoflurane anaesthesia and firstly recorded from and then stimulated. The bladder is catheterised via the urethra with a pressure monitor attached. A pressure monitor/balloon should also be inserted into the colon to measure off-target effects.

The following three experiments should be performed:

Experiment 1. Physiological perturbation for pelvic nerve recording:

- The bladder should be filled at a physiological rate while the neural signaling patterns in the pelvic nerves are recorded and correlated to bladder pressure.

- These signals will be afferent during filling and efferent during micturition, and the device should be able to differentiate between these two states.
- The device should be able to detect neural signaling patterns from the afferent nerve fibers to the detrusor which correlate significantly ($P < 0.05$, $R^2 > 0.5$) with the slow change in bladder pressure during passive filling.
- The device should be able to detect neural signaling patterns from the efferent nerve fibers to the detrusor which correlate significantly ($P < 0.05$, $R^2 > 0.5$) with the rapid change in bladder pressure associated with detrusor contraction during micturition.
- Colonic pressure should be recorded simultaneously to create an "off-target" baseline.
- The fill, neural recording, pressure recordings, and correlation steps should be repeated three times during the procedure with reproducible correlations.

Experiment 2. Stimulation to induce bladder pressure change

- The bladder should be filled to a sub-threshold level that would not initiate natural detrusor contraction.
- The device interfaced to the pelvic nerve should then apply a selective stimulation pattern that activates the detrusor muscle, triggering changes in bladder pressure which are detectable. The pressure generated by the natural contraction in Experiment 1 should be accurately reproduced by this artificial stimulation within an 80-120% pressure and time window.
- Colonic pressure should not change more than +/- 20% from the baseline level detected in Experiment 1.
- The neural stimulation and pressure recordings should be repeated three times with reproducible effects.

Experiment 3. Blocking to reversibly arrest contraction:

- The bladder should be filled to a sub-threshold level that would not initiate natural detrusor contraction
- The device should apply a blocking pattern to the pelvic nerve which suppresses detrusor contraction. Contraction should not be triggered at the onset of the blocking.
- The bladder should then be filled beyond the pressure trigger point seen in Experiment 1, and blocking must inhibit the pressure increase associated with micturition as seen in Experiment 1.
- Colonic pressure should not change more than +/- 20% from the baseline level detected in Experiment 1.
- Upon cessation of the block, the natural voiding mechanism should return without further bladder filling, resulting in detrusor contraction and pressure increase.
- The neural blocking and pressure recordings should be repeated three times with reproducible effects.

After the experiment

The catheter should be removed and the animal allowed to recover.

At the end of 60 days:

Chronic nerve functionality and interface stability should be assessed as described in section V below.

D) BRONCHIAL TREE SYSTEM

Implantation of device on the vagus and/or on its branches:

- All studies mentioned below should be performed in guinea-pigs; as they are a suitable rodent species for studies on bronchial tree.
- Animals must be implanted with neural interface under surgical anesthesia and allowed to recover for a week. Effectiveness of recording, stimulation and/or block can be tested acutely during surgery.
- At the time of the neural recording, an ECG recording electrode needs to placed subcutaneously to record wireless via telemetry. This will be used to assess off-target effects during stimulation and blocking experiments below.

Experiment 1 –Recording of activity in vagal nerve branch:

- On the day of the recordings, animals are placed in double chamber plethysmograph (E.g. Buxco) and baseline respiratory measurements (respiratory volumes, flows during inspiration and expiration, specific airway conductance and resistance) are performed.
- Neural recordings are made in awake animals at the same time as baseline recordings.
- Following baseline recordings, aerosolized histamine (0.1 - 10 µg/kg) or bradykinin (0.03 – 30 µg/kg) must be administered and changes in neural activity, ventilation, airway resistance & conductance are monitored. Increasing doses of aerosolized bronchoconstrictors (minimum of three dosages) must be tested to provide a dose- response (changes in resistance, conductance and neural activity) curves. Each bronchoconstrictor exposure should last for at least five minutes prior to switching to increasing dose.
- The expected result is that bronchoconstriction results in reduction in airway conductance and an increase in airway resistance. There will be a transient change in heart rate with histamine/bradykinin, but this will stabilize within 2-3 minutes with return to baseline values.

Experiment 2 – Stimulation

- Stimulation experiments should take place in awake guinea pigs placed in double chambered plethysmograph on odd weeks (1, 3, 5, 7 etc).
- Baseline neural, respiratory volume, airway resistance, conductance measurements are performed. The nerve should be stimulated to produce changes in airway resistance, similar to the histamine/bradykinin response. The observed change in airway resistance and conductance must lie within +/- 20% of the bradykinin/histamine response.
- Stimulation must not change the heart rate beyond 10%, when compared to bradykinin/histamine induced changes in heart rate.

Experiment 3 – Inhibition of vagal nerve mediated bronchoconstriction:

- Blocking experiments must take place on even weeks (2, 4, 6, 8 etc).
- Similar to stimulation experiments above, baseline recordings must be performed.
- Following this, exposure to inhaled bronchoconstrictors (increasing dose as mentioned above) must be performed as mentioned in the recording experiments.
- The nerve block must be turned on immediately before the aerosol exposure.
- The expected result is that nerve block prevents the changes in airway resistance and conductance response induced by histamine or bradykinin.
- Change in heart rate during neural block must produce no more than 10% change from baseline.

- On even weeks and on days when blocking experiments are not performed, airway response to bradykinin/histamine dose response must be measured with and without atropine (5 mg/kg). For detailed methods, refer Drazen & Austen J. Appl Physiol., 38(5): 834-838, 1975).
- The efficacy of block (change in airway conductance) will be determined by comparison to atropine response and must be within 20% of airway conductance values seen with atropine.

III. ADDITIONAL ANATOMICAL INFORMATION ABOUT TARGET NERVES

Table 2 provides additional information on nerve fascicular organisation, diameter, myelination and other properties.

Nerve for interfacing	Species *	Fascicles/ diameter	Sens/P/M/ Spre/Spost	Unmyelinated / Myelinated, %	Refs
Greater splanchnic nerve branches to the adrenal medulla	Rat	2 / 0.15mm	Spre/Spost (40/60%)	75/25%	[4-7]
Carotid sinus nerve branches	Rat	2 / 0.06mm	Sens/Spre/ Spost	86/14% (538/87)	[8, 9]
Pelvic nerve branches	Rat	5-7 / 0.2mm	Sens/P/Spost (34/49/17%)	80/20% (4K/1K)	[10, 11]

Table 2: Summary of anatomical properties of nerves of interest. **Abbreviations: Sens = Sensory; P = Parasympathetic preganglionic; M = Motor somatic; Spre = Sympathetic preganglionic; Spost = Sympathetic postganglionic**

*** We are seeking to collect the equivalent information for mice**

IV. DEVICE SPECIFICATIONS:

The aim of the Challenge is to create a research tool (device) to be used for experiments that will facilitate the discovery of neural circuits, visceral intervention points and treatment patterns for future bioelectronic medicines. This implies that the device must be flexible and configurable. The Innovation Challenge criteria for the device are **modality agnostic,** hence it is up to the team of solvers to chose the technical path to solve the Challenge, including the neural interface approach (*e.g.*, electrical, optical, ultrasonic, electromagnetic, neurotransmitter signals, intra or extra fascicular, low or high channel count), the powering approach (*e.g.*, RF, induction, or energy harvesting), and the wireless information transfer approach.

The solution can use different interface modules for recording, stimulation and blocking, including different fundamental approaches and their combinations (*e.g.*, electrical *vs.* optogenetic). The solution can also comprise different interface modules in each of the two model organs where functionality is proven. The interface modules should share a common module for control; signal processing, data transfer and power. These modules together need to meet the following implantation requirements:

1. The device should be fully implantable in a rat model. Percutaneous wires or tethered apparatus are not allowed, and no device components (*e.g.,* backpacks) are to be carried outside the body of the rat. The data should be wirelessly transferred.
2. The device should wirelessly transfer recorded data for the time periods listed for each organ (see detailed experimental protocols above). The device should be able to switch wirelessly between recording, stimulation and blocking/silencing.

3. To ensure flexibility for post-processing algorithms and applicability to a broad set of recording interfaces, the device should be able to transmit raw, full bandwidth signals (12 kHz signal bandwidth) from the neural interface as a minimum.
4. The device should be functional in a standard electrophysiology suite in awake behaving animals throughout 60+ days of implantation.
5. There should be no physiological effects of the implant aside from the effect of neuromodulation, including near-implant temperature increase no greater than 1°C.
6. The implanted device should have inbuilt qualities for detecting device-related failures including electrode impedance measurements, over voltage events, package leak indicators, and package temperature input/output short indicators or over current via the wireless link.
7. The implanted device should be controlled via a base station(s). The implanted modules should wirelessly communicate with the base station(s) built in with programmable and flexible architecture.
8. The implantable device should be remotely configurable but not necessarily real-time.
9. Data to/from modules should be synchronised to a common global clock. Data samples recorded from two different modules or different channels on a single module should be relative and referenced to a common clock.

V. ASSESSMENT OF CHRONIC NERVE FUNCTIONALITY AND INTERFACE STABILITY

Viability of the targeted nerves and stability of the neural interface should be assessed by evaluating the changes in recorded neural signals from Section II, Experiment 1, over the 60-day post-implantation period. From these records (high-pass filtered if necessary), the following metrics should be calculated:

- The standard deviation of the whole recording event (voltage change with time curve)
- Average amplitude of detected action potentials (the bipolar detection threshold is set at 3 times the metric above)
- The standard deviation of noise (noise is defined as the record after subtracting the 10-ms epochs containing the detected action potentials)
- Average firing rate for detected action potentials.

Within the same animal, measurements for each parameter (stdev, avg amp, $stdev_{noise,}$ and avg firing rate) should not vary by more than 35%

Further, the stability of stimulation and blocking in Section II, Experiments 2 and 3 should be assessed by comparing the parameters of current, frequency, and pulse width over the 60-day period. These parameters should not require reconfiguration by more than +/- 20% between days.

VI. SUBMISSION PACKAGE:

Teams proposing a final solution to the Innovation Challenge should submit a detailed package including the following items in order.

- List of all authors, collaborators, key personnel and their institutions
- Abstract including the summary of key results and outcomes
- Detailed written approach to solve the challenge with images of the experimental set-up
- Diagrams of neural interfacing technique(s) with micrographs of the interface outside and implanted inside the tissue
- Results and discussion section describing detailed experimental protocols and outcomes
    - Relevant data must be presented separately for each nerve organ model using the protocols in Section II and V to show how each and every criteria therein have been met
    - Detailed performance metrics of the wireless device including capabilities beyond the requirements for the challenge
- A listing of all intellectual property utilized for the Innovation Challenge work, including any new patents that have been filed. Additionally include a list of patents that the submitter intends to apply for a result of this work
- Additional legal agreements may be required, including an acceptance of the Innovation Challenge rules and warrant of availability of relevant Intellectual Property for commercial license

The final submission package should contain high-resolution images, graphs and tables of peer-review journal publication quality. Note that once this solution package is submitted, the Innovation Challenge review panel may request an on-site demonstration of the device to modulate the nerves and verify the authenticity of the submitted data. Alternatively, the review panel may also request that an independent external laboratory repeats the experiments with the submitted device solution. GSK and its review panel reserve the rights to adjudicate the final winner of the Innovation Challenge.

VII. INNOVATION CHALLENGE COMMITTEE AND REVIEW PANEL

The Innovation Challenge Committee comprises experts in disease biology and neuromodulation devices in academia and industry. The committee members are: Ken Yoshida (Indiana, USA), Mike Faltys (California, USA), Daryl Kipke (Michigan, USA), Paul Cederna (Michigan, USA), Rafael Yuste (New York, USA), Victor Pikov (California, USA), Rob Gaunt (Pittsburgh, USA), Nick Donaldson (London, UK), Brendan Canning (Maryland, USA), David Van Wagoner (Cleveland, USA), and Corey Smith (Cleveland, USA). The Committee has advised the GSK Bioelectronics team on determination of these success criteria.

A sub-set of the Challenge Committee will form the review panel that adjudicate whether a submitted solution meets the success criteria above and is eligible to win the $1m Innovation Challenge. At the time when Bioelectronics R&D receives a full submission, members of the Challenge Committee will be requested to declare whether they have a conflict of interest, which precludes them from actively participating in the Challenge from that point onwards. Committee members without a conflict of interest will form the review panel and conduct the diligence process. The review panel will only be finalised upon receipt of a submission.

VIII. INTELLECTUAL PROPERTY, TERMS AND CONDITIONS, ACCESS

The team of solvers and their funders, not this Innovation Challenge, determines ownership and control to intellectual property (IP) for the solution. Receipt of the $1m prize is conditional on the winning team making the device broadly available for research use (which can be on a for-profit basis), and on the availability of all relevant IP for commercial license for GSK. The complete list of Innovation Challenge rules and terms will be published on this website in the coming weeks and investigators who have expressed an interest in the Challenge via the website will be notified about their publication to the site via email.

IX. REFERENCES

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