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Proposal title:
Securing the Safety of Cell Therapies to Realise their Potential.
Identify and Optimize Novel Technology to Evaluate Cell Therapy Safety, Mode of Action and Efficacy.

Key words: *(minimum of two)*
Human, stem cell, mesenchymal, pluripotent,multipotent, inducible, imaging, clinical trial, immunotherapy, T Cell. SPECT, PET, MRI, CT, ultrasound

Describe the problem to be addressed. Why is the issue important? To whom is this issue important?

Problem: Cellular therapies show great therapeutic promise; however stem cell therapies in particular, are taking a very long time to be realised in clinic. One challenge is to generate a comprehensive package of safety data to support progression of cell therapies through clinical trials and the licensing process. Another concern is a lack of detailed understanding of their mode of action (MoA), how they are integrated into the body after administration to deliver their therapeutic benefits. Currently, there are no established tools that can be applied to cellular therapies to enable this data and understanding to be generated.

Importance – Why?:
We believe a clear understanding of the fate, movement, final location and efficacy of transplanted cells is essential for:

1) Confident decision making on safety.
2) Greater understanding of Mode of Action.
3) Improved successful outcome of stem cell clinical trials.

There is much *in-vitro* and pre-clinical evidence to support the potential of cellular therapies for a number of clinical targets, basic research into all aspects of stem cell biology is being conducted in many globally renowned academic institutions and there are numerous phase 1/2 clinical trials using stem cells recorded on the clinical trials databases. We also know that many stem cell therapies are being offered to patients in countries where there is little or no regulation. However, despite all this activity the field does not appear to be progressing quickly towards phase 3 & 4 trials and thus an approved therapy that can be offered to patients.

It is possible this is due to the lack of appropriate or accepted models/tests which can be applied consistently by clinical researchers. Current models/tests may not be sensitive enough for adequate patient stratification and/or detection of clinical improvement. Another important consideration is the fact that traditional DMPK/ADME approaches are not always applicable to cell therapies. In a recent draft guidance issued by Health Canada[(1)], preclinical data on bio-distribution and engraftment are required to

address potential safety concerns. The draft guidance also emphasized that "Traditional pharmacokinetic studies to assess bio-distribution in humans may be challenging for cell therapy products and may require the development of appropriate cell tracking technologies. The presence of cells in non-target sites should be further investigated and the risks fully evaluated whenever feasible. Health Canada may insist on pharmacokinetic assessment for cell therapy products associated with higher risks of tumourigenicity or ectopic tissue formation prior to the initiation of trials in a large number of patients."

Importance – Who?:
Development of such models or tests would be of benefit to the stem cell therapy developers, and ultimately to **public and patient** groups. The diseases being targeted by stem cell researchers and clinical scientists are currently areas of significant un-met need, an appropriate, applicable and approved test should accelerate the development of these therapies.
Regulatory authorities would have reliable models/tests which could be requested as part of new clinical trial applications.
Academic and clinical researchers would gain valuable insights into the Mode of Action of stem cell therapies, enabling expansion and into new therapeutic areas.
The **Biotech and Pharma** companies developing the therapeutic products will be able to more quickly reach decision points on the likely success of a putative therapy.
Suppliers to the cell therapy industry will gain greater understanding of the tools and technology required to enable safe, successful manufacture and supply of therapeutic doses of cells. Recently released data from a Phase 2 study appears to confirm the need for more sensitive and appropriate models/tests[(2)].

(1) Draft Guidance Document: Guidance for Sponsors: Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans (2014): Canadian Minister of Health.
(2) Discussion on results from Preserve AMI Clinical Trial.

Describe the basic project steps or stages to the best of your ability, including an expected timeline, milestones, and deliverables for the first two years.

Milestone 1 (6 - 12 months):

Set up and conduct a symposium with the industry, regulators and academic communities with aim to:

1) Identify and engage with like-minded organizations and working groups.
2) Establish what 'success criteria' are and gain consensus on where greater consistency could be achieved.

OUTPUT: White Paper

Milestone 2 (12-36 months):

Identify any potential technologies (appropriate to target disease) that could deliver aligned to agreed success criteria.

Design and complete preliminary validation of the proposed technology for suitability to stem cell preclinical and potentially clinical investigations.

Engage regulators to establish acceptance criteria for such tools to support stem cell development as therapeutic agents.

What is the potential or anticipated impact of successfully achieving the milestones described above? *(Describe scientific, regulatory, policy, public health, and/or other impacts.)*

Scientific: Greater understanding of cell therapy safety, MoA and efficacy. Access to new tools to advance the development of novel therapeutic targets. Enabling quicker decisions on potential of

Regulatory: Clear expectations of the level of understanding and evidence required to enable therapy registration. Improved confidence in the safety of cell therapies during clinical trials, licensing and use. More rapid assessment of cell therapy safety and efficacy.
Policy: Credible and defensible data to enable clear communication of the benefits of cell therapy to health authorities, reimbursement decision makers and patients. Build a clear understanding of the health economic case for cellular therapies.
Public Health: Benefits to enable a healthier aging population – new licensed therapies for currently in-curable diseases, increased quality of life, reduced stress on care systems.

Describe the interdisciplinary, collaborative nature of the proposed project, and identify potential partners: *(identify institutions, organizations, companies, and or consortia)*

Stem Cell Biology. University of Cardiff
Imaging diagnostics GE Healthcare, and other technology companies
Clinical trials Stemedica/Karolinska/Rotterdam
Patient care Karolinska
Regulatory: UKMHRA, US FDA/CBER/OCTGT, /UKRMP, Japan PMDA, Health Canada, EU EMA/CAT
Payers/reimbursement NHS England/Patient Body in the US
Equipment manufactures GE Healthcare/Catapult/CCRM
Academics Cardiff, Liverpool, Manchester
Clinicians: see clinical trials.
Pharmaceutical companies: GSK, Novartis.
Industry alliance groups, such Alliance for Regenerative Medicine (ARM), International Society for Stem Cell Research (ISSCR).

GE Healthcare has active collaborative projects ongoing with some of the institutions listed above. For some we are actively seeking to partner with, and for all we have had discussions with in connection to cell therapy and/or regenerative medicine.