Unlocking the Solute Carrier Gene-Family for Effective New Therapies (Unlock SLCs)

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Central Challenge: SLCs are heavily understudied and underexploited as drug targets.

The SLC family is the largest class of membrane proteins (~400 members) and plays a vital roles across many cell-types in all tissues.

50% of SLCs are associated with a human disease-related phenotype compared to a rate of only ~20% for the broader human genome; highlighting their importance in disease.

A recent publication analysis suggest SLCs are highly understudied with >200 SLCs having less than **15** publications !

SLCs have given rise to a few important drug classes, such as the SSRIs for depression, and the SGLT2 inhibitors for diabetes. **However, only ~2-3% of current drug targets are SLCs**

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Need for public-private collaboration

- The scale of work required to **unlock** the SLCs is ***beyond*** the reach of any single company or institution
- Advances in a range of scientific disciplines and methods hold great promise to accelerate the field, *particularly if applied in concert*.
  - Techniques for the production, isolation and characterization of integral membrane proteins
  - Metabolomic techniques may be applied for the more rigorous characterization of endogenous SLC substrates
  - Advances in methods for studying protein interactomes should allow the identification of obligate binding partners for SLCs and reveal regulatory mechanisms
  - New physical methods and techniques for the detection of membrane transport
  - Gene-editing capabilities will enable SLC research

Pre-competitive nature.

Bring together a level of funding, focus and stakeholder commitment sufficient to unlock the potential in the SLC family.

Employ a system-wide approach to investigation of the SLC family

Leverage novel techniques and methodologies for understanding and profiling SLCs

Coordinated focus on SLC transporter deorphanization

Deliver new open access research tools, techniques, reagents, and knowledge to the biomedical research community

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Objectives of the full project

- To “unlock” the SLC family to enable drug discovery efforts to be conducted “at will” across the whole family of ~400 proteins by acclerating the detailed study of SLC transporters
  - Generation of cell lines, reagents, small molecule tools and antibodies for the study of SLCs
  - Development of novel methodologies for assessing transporter function
  - Deorphanization or identification of endogenous substrates of SLC transporters
  - Generation of purified SLC proteins for more detailed study
  - Characterization of SLC interactome to identify obligate binding partners

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Expected impact

- This project is expected to deliver new open access research tools, techniques, reagents, and knowledge to the biomedical research community that will rapidly accelerate the pace of research in the field of SLCs. Advances of this magnitude will impact both basic research and drug discovery.

- As SLCs are broadly expressed, their therapeutic potential spans many disease areas, including, oncology, immunology, neurosciences, metabolism and cardiovascular diseases.

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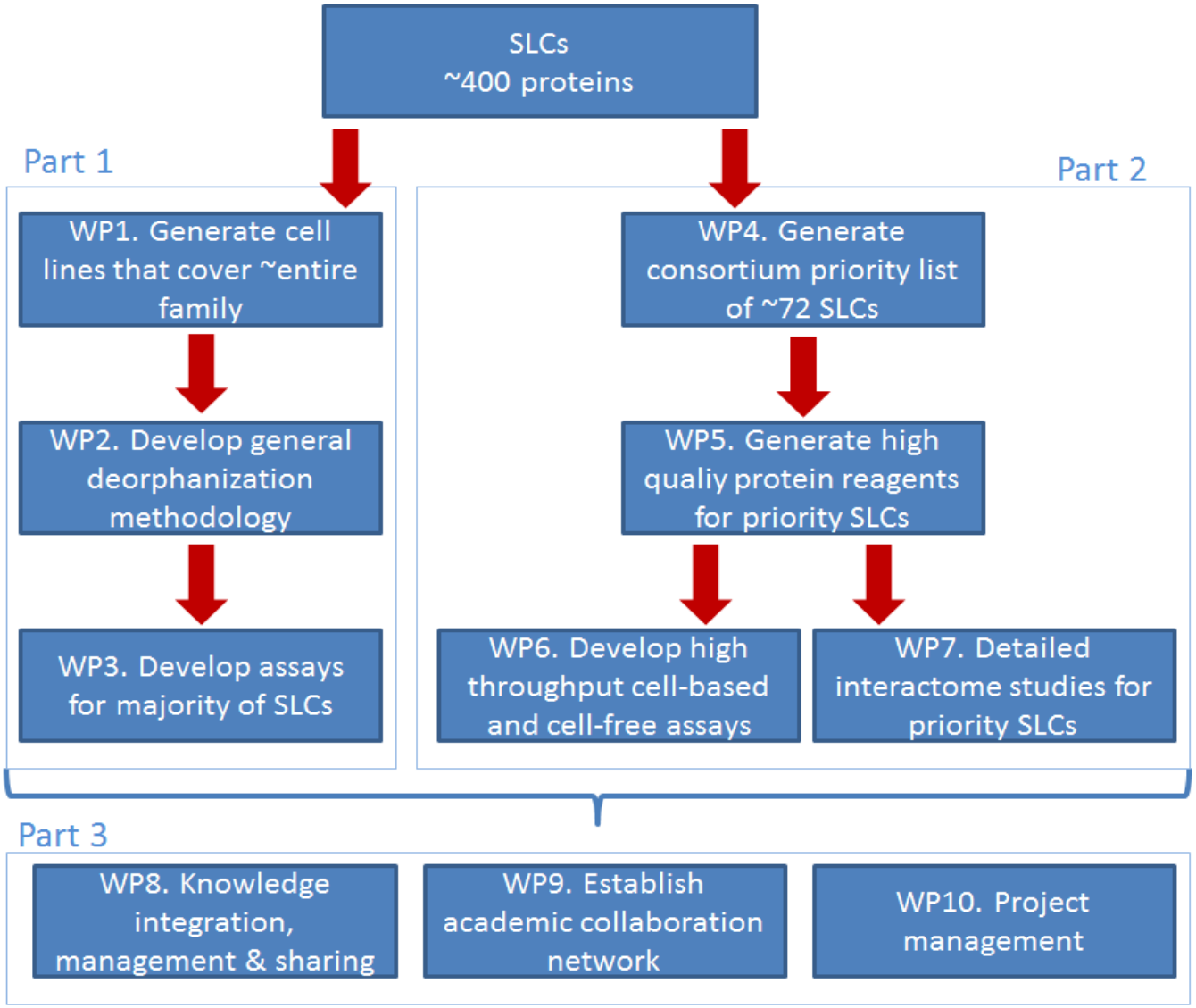
Suggested architecture of the project



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Key deliverables of the full project

- ***Overall we aim to deliver new research tools, techniques, reagents, and knowledge to the biomedical research community such that on completion of the five year project the pace of research in the field of SLCs will markedly increase, thus leading to accelerated discovery of new drug targets and drugs which target SLCs.***
- Specific key deliverables are listed below:
- **<u>Gene Family Wide Deliverables:</u>**
- Generation of cell systems which express - in functionally competent form - *a large majority (>80%) of the ~400 SLCs*
- Generation of methodology to “deorphanise” (identify endogenous substrates for) the large majority (>80%) of the ~400 SLCs, and application to rigorously assign endogenous substrates for the vast majority of SLCs (e.g. using metabolomics methods)

Key deliverables of the full project

- **<u>Gene Family Wide Deliverables (continued):</u>**
- Development of novel, broadly applicable screening methodologies for SLCs
- Screening methods to be available that would be applicable for >80% of the gene-family
- Develop specific assays that cover >50% of the protein family
- Establish novel assay methodologies for SLCs located in intracellular compartments

Key deliverables of the full project

- **Deliverables for a Focused Set of ~72 SLC Targets**
- Generation of purified SLC protein and/ or cell-free systems to facilitate the detailed study of SLCs
- Generation of high quality biochemical reagents and techniques for studying the focused set of roughly 60 SLC family members
- Highly selective SLC antibodies
- Techniques to define the interactome of SLC members to build knowledge of obligate binding partners and regulatory mechanisms
- Generation of high throughput screening assays for studying a focused set of SLCs

Expected contributions of the applicants

- Advisory role with ability to leverage expert knowledge
- Expertise on experimental design, reagent generation
- Validated reagents: cDNA clones, cell lines, transgenic and KO mouse models, si/shRNA or CRISPRs, antibodies
- Technical expertise: mass spectrometry for metabolomics/proteomics, protein expression for integral membrane proteins, protein characterization, protein and protein-ligand crystallization and X-ray structure determination, screening technologies to monitor SLC transporter function, elucidating protein interactomes
- Proven ability for development of novel biochemical and/or biophysical assays
- Ability to integrate bioinformatically ‘omics platforms
- Infrastructure to support large scale and high throughput experimentation

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Expected (in kind) contributions of industry consortium

- Expertise on experimental design, reagent generation
- Validated reagents: cDNA clones, cell lines, si/shRNA or CRISPRs, antibodies, small molecule ligands, substrates and imaging agents
- Technical expertise: mass spectrometry for metabolomics/proteomics, protein expression for integral membrane proteins, protein characterization, protein and protein-ligand crystallization and X-ray structure determination, screening technologies to monitor SLC transporter function, synthetic and computational chemistry expertise for chemical probes
- Ability to integrate bioinformatically ‘omics platforms
- Advanced high throughput screening methodologies and expertise

What's in it for you?

- Academic researchers
  - Opportunity to discover novel biology and deepen our understanding of SLC transporter structure and function
  - Deliver significant scientific advancement of the field of SLC transporters
  - Play a role in identification of new therapeutic targets
- SMEs
  - Opportunity to develop and validate new technologies on the structure and function of SLC transporters
  - Ability to link molecular and mechanistic insights on clinically important membrane transporters to human disease
- Patients' organisations
  - Potential for novel and effective therapies for a broad spectrum of diseases with unmet medical need

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Pharma partners

- Pfizer (coordinating)
- Bayer
- Boehringer-Ingelheim
- Novartis
- Sanofi
- Vifor Pharmaceuticals

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Questions?

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