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

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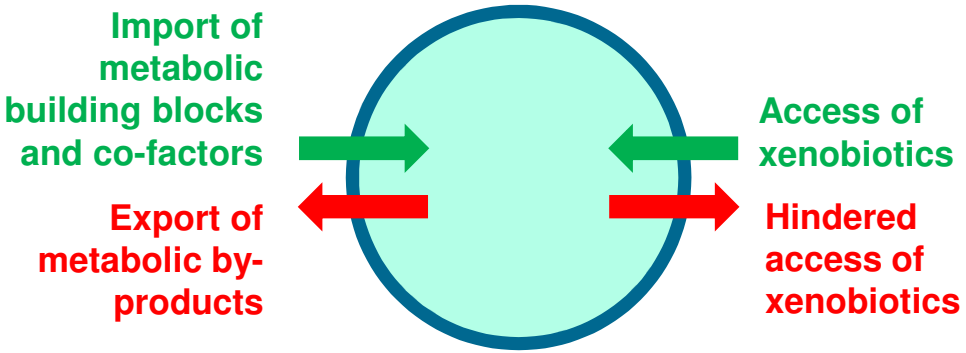
SLCs: Importance but Understudied

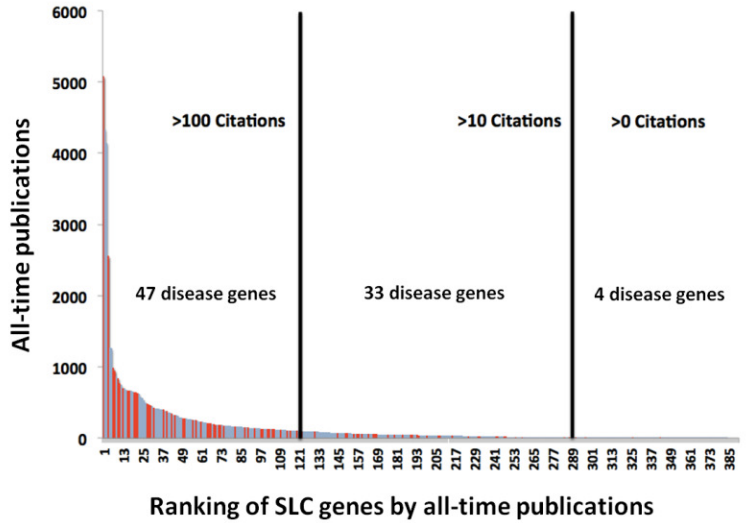
~10% human genome encodes transporters and related proteins



Drugs as Modulators
- Efficacy
- Toxicology
- DDIs

Drugs as Substrates
- ADME
- Pharmacodynamics
- Toxicology

Only few approved drugs



Publications heavily skewed to a few very highly studies SLCs

A. Cesar-Razquin, B. Snijder, T. Frappier-Brinton, R. Isserlin, G. Gyimesi, X. Bai, R. A. Reithmeier, D. Hepworth, M. A. Hediger, A. M. Edwards and G. Superti-Furga, A Call for Systematic Research on Solute Carriers, *Cell,* ***2015, 162(3), 478-87***

SLCs Diversity is a Challenge

Substrate Diversity

- Inorganic anions and cations
- Amino acids
- Carboxylates
- Steroids
- Nucleosides
- Neurotransmitters
- Carbohydrates
- Metabolites
- Vitamins and nutrients

Cellular Location

- Cell membrane
- Mitochondrial membrane
- (endo)lysomes, vesicles and other organelles

Tissue location/ environment

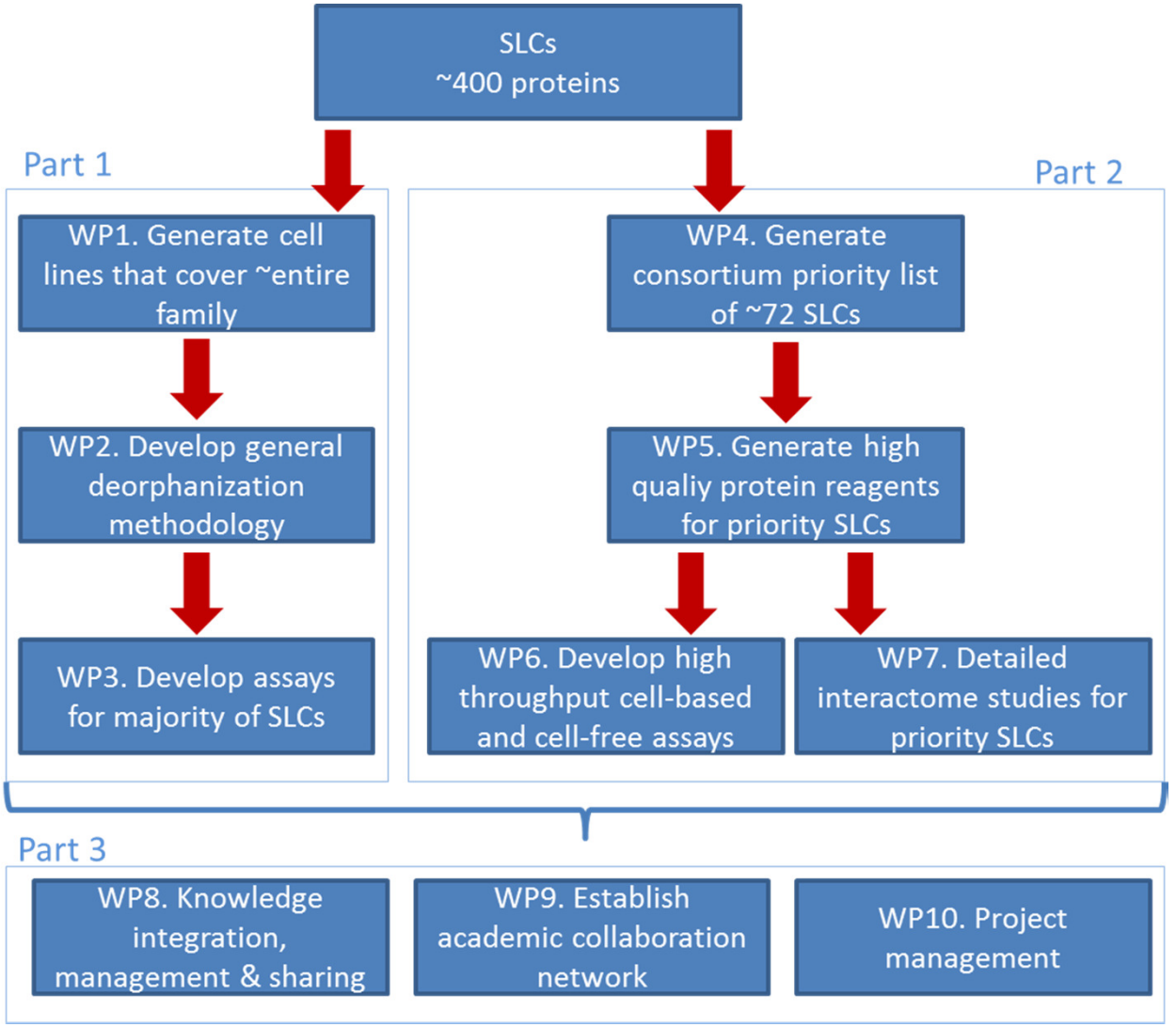
- Intestines
- Kidneys
- Liver
- Central

Function

- Uniporters
- Symporters
- Antiporters
- Electrogenic/ Non-electrogenic

Many SLCs are Orphans

Overview of Proposed IMI Work Plan



Expected Key Deliverables

Gene Family Wide Deliverables:

- Cell systems which express functionally competent SLCs (80% of family)
- Methodology to “deorphanise” the large majority (>80%) of the ~400 SLCs
- Novel, broadly applicable screening methodologies for SLCs (e.g. recombinant proteins in cell-free vesicle systems)
- Screening methods that would be applicable for >80% of the gene-family
- Specific assays that cover >50% of the protein family
- Novel assay methodologies for SLCs located in intracellular compartments

Deliverables for Focused Set of ~72 SLCs

- Generation of purified SLC protein and/or cell-free systems for detailed studies
- High quality biochemical reagents and techniques
- Highly selective SLC antibodies e.g. to study SLC localization at tissue and/ or subcellular levels
- 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

This IMI 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. These advances are expected to impact both basic research and drug discovery alike.

Expectations for Applicant Consortium

Expertise, leadership and a proven track record in technologies needed to achieve the key deliverables

(including human genetic screens, next-generation sequencing for high-throughput RNA and/or DNA sequencing, mass spectrometry to understand systems-wide cellular changes in proteins and metabolites, production of human membrane proteins, i*n vitro* and in-cell target engagement assays,..)

Excellence and a Track Record in Collaborations

(including established a global network of recognized thought leaders in all relevant sectors, with a track record of success, as evidenced by collaborative publications, history of collaboration with clinical researchers (ethics approval), ability and history of leveraging additional funds with a variety of organizations, history of making research output widely available (**open access**), sustainable mechanism to disseminate chemical and biological research material)

Successfully collaborating in a network with industry

(including demonstrated impact on launching or adding value to internal drug discovery projects in the pharmaceutical sector, success in collaborations among networks of academics and SMEs – as evidenced through shared projects and co-authored publications, demonstrated success in governing and managing large projects, including finance, intellectual property etc., ability to consistently set and achieve milestones on time and within budget

Unlocking the Solute Carrier Gene-Family

Key Data	
Indicative duration	5 years
Efpia Partner	Pfizer (coordinating) Novartis Boehringer Ingelheim Vifor Pharmaceuticals Sanofi Bayer
Efpia Budget	12 mioEUR Focus will be in kind: in vitro biology, expertise and reagents for WPs 1 and 4-7 plus contributions to other WPs
IMI2 contribution	Maximum of 12mioEUR

Summary of SLC Opportunity and Challenges

Disease relevant, druggable, untapped potential

Protein diversity, complexity presents challenges

New technologies at inflection point

- IMP structural biology & biophysics
- Metabolomics
- Proteomics
- Gene-editing

With a system-wide attack we believe the SLCs will yield new drugs and drug targets

Precompetitive consortium could rapidly accelerate field

Science For A Better Life

Thank you!