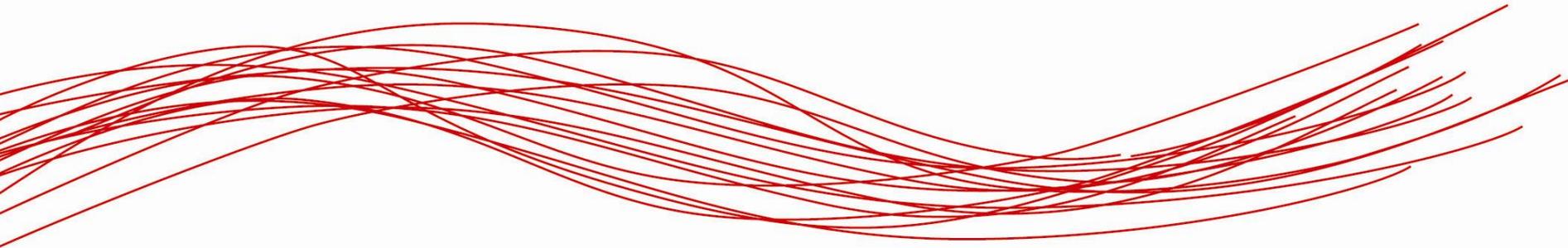


Perspective of the European Commission on the 4th IMI Call*



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*based on the working document

Revision of the IMI Scientific Research Agenda

Reasons for revising the IMI Scientific Research Agenda (SRA)

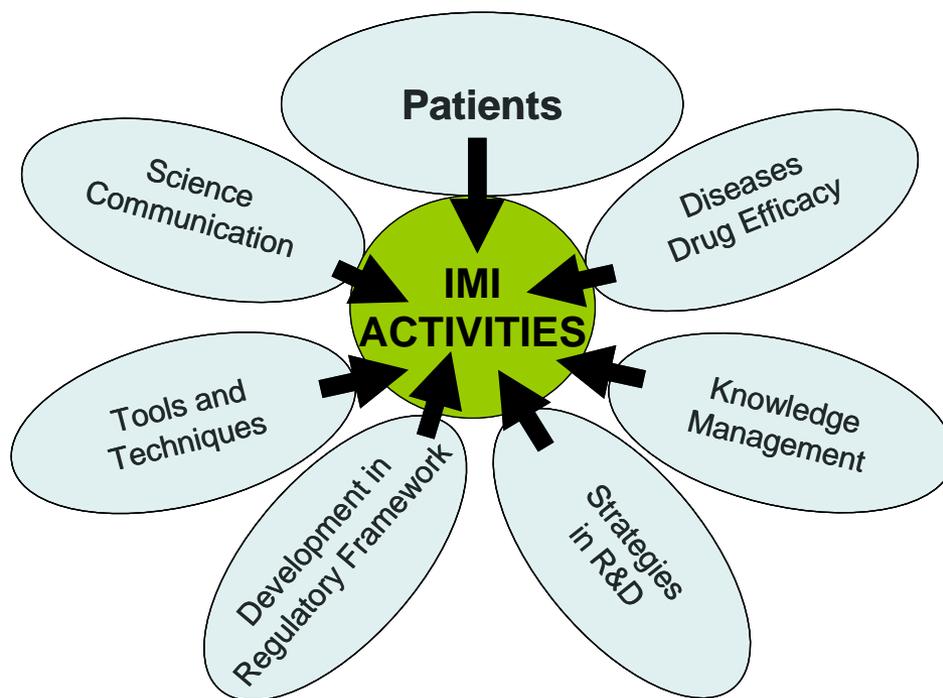
- In the initial 3 calls of IMI, a number of the priorities originally presented have already been addressed
- Science has advanced since the SRA was defined in 2008
- The pharmaceutical industry has changed

Process for revision led by IMI Scientific Committee with input from EFPIA, the States Representative Group and independent experts;

➡ Revised SRA to be adopted shortly

Revision of the IMI Scientific Research Agenda

Revised SRA builds on the 4 pillars of the original SRA:
Knowledge management – Efficacy – Safety – Education and Training



Revision of the IMI Scientific Research Agenda

Eight new research areas are proposed to be addressed:

- Pharmacogenetics and taxonomy of human diseases
- Rare diseases and stratified therapies
- Systems approaches in drug research
- 'Beyond high throughput screening'- pharmacological interactions at the molecular level
- Active pharmaceutical ingredients development (drug compound development)
- Advanced formulations
- Stem cells for drug development and toxicity screening
- Integration of imaging techniques into drug research

4th call topics bridge the previous SRA and the revised SRA



IMI 4th Call: 7 topics in 3 Pillars

EU MEDICAL INFORMATION SYSTEM

1. A European medical information framework (EMIF) of patient-level data to support a wide range of medical research
2. ETRIKS: European translational information and knowledge management services

CHEMISTRY, MANUFACTURING AND CONTROL

3. Delivery and targeting mechanisms for biological macromolecules
4. In vivo predictive bio-pharmaceutics tools for oral drug delivery
5. Sustainable chemistry – Delivering medicines for the 21st Century

TECHNOLOGY AND MOLECULAR DISEASE UNDERSTANDING

6. Human induced pluripotent stem (hiPS) cells for drug discovery and safety assessment
7. Understanding and optimising binding kinetics in drug discovery

Key aspects of the 4th call

- First “Think Big” topics are launched: the Commission welcomes launch of the EMIF (€ 24 million from both EFPIA and the public side) and the hiPS topic (€ 26 million from both EFPIA and public side)
- In addition, new research areas in pharmaceutical chemistry, oral drug delivery, binding kinetics, optimising delivery of biological macromolecules will be addressed
- The topics will continue to bring together data, resources and expertise from the public and private sectors to improve pharmaceutical research

Patient level health information has potential to significantly advance medical and pharmaceutical research; particular need for such information for paediatric populations



Potential so far not used because of hurdles

By submitting a proposal to this topic, researchers can contribute to fulfilling the vision for EMIF to create a lasting and comprehensive framework to use patient level data:

- Broad network for access to existing data
- Governance model for ethics and privacy
- Data management and analysis

Three topics under EMIF

- Information framework / knowledge management service layer
- Metabolic complications of obesity in adults and children
- Protective and precipitating markers for the development of AD and other dementias

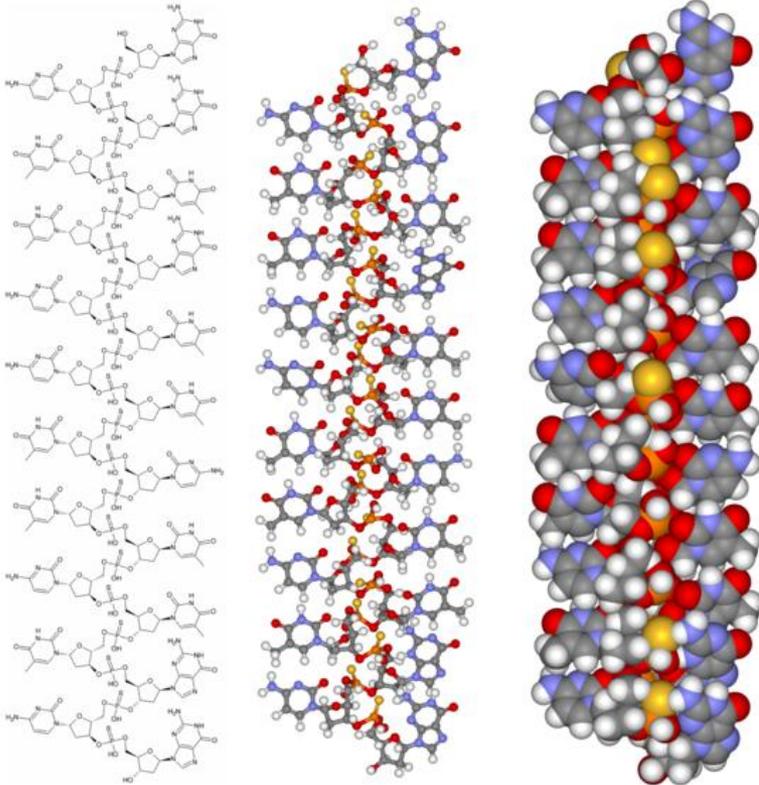


EMIF Will Address Important Unmet Medical Needs

- Patient level data contributes to harnessing the power of the extreme phenotype approach for understanding less extreme variations in the phenotype, which represent a much larger share of the patient population; also important for diagnosis and the development of innovative therapeutics
- Obesity is an important health problem with limited success so far in addressing it through modifying behaviour or pharmacological intervention; only some obese individuals develop complications and it would be important to be able to identify them
- Patient level data in the field of AD will help to deal with the multiple challenges of developing treatments in this area such as absence of predictive biomarkers, efficacy markers and the slow progression of the disease

- Translational research needs management and sharing of lots of data between clinical and pre-clinical activities (e.g. correlation between animal models and human data)
- **Proprietary solutions in companies; J&J ready to move their transSMART to the public domain**
- Major opportunity to capitalise on this through the development of a knowledge management service, open standards etc. and active community research in translational research analysis and methodology
- eTRIKS will make accessible wealth of data from translational research projects (both IMI projects and other) available for the global translational research community
- Long term expectation that eTRIKS will seed a stable, sustainable platform and service to support academic and commercial translational research across Europe

Delivery and Targeting Mechanisms For Biological Macromolecules



Fomivirsen; first approved antisense drug.

Biological macromolecules have high potential as therapeutics because they are very specific and can address targets « non druggable » with chemical small molecule drugs

To realise potential major hurdles in pharmacokinetic properties and drug disposition need to be overcome; e.g. to reach an intracellular target, a biological macromolecule has to escape different excretion mechanisms and must traverse the endothelium wall and finally the cell membrane of the target cell and there avoid intracellular degradation.

Delivery and Targeting Mechanisms For Biological Macromolecules

Chemical stabilisation and delivery of macromolecules = collaboration of different disciplines:

- Drug development
- Molecular and cellular biology of cellular uptake mechanisms
- Protein and nucleic acid chemistry
- Manufacturing and characterisation of biological macromolecules
- Nanotechnologies

Impact on pharmaceutical industry can be huge, because it may open many new avenues for developing treatments in currently intractable areas

In Vivo Predictive Biopharmaceutical Tools for Oral Drug Delivery

Oral administration of drugs preferred in most cases

Developing a drug compound that lends itself to oral delivery and optimising oral drug delivery is still very much an empirical process; illustrated by the almost 15 year old « Lipinski rule of 5 » for properties that a molecule should have to be orally bio-available

Problem is getting worse for the pharmaceutical industry because molecular tools to improve drug binding characteristics often lead to very hydrophobic drugs, which are difficult to formulate for oral delivery

In Vivo Predictive Biopharmaceutical Tools for Oral Drug Delivery

Testing still mostly in animal models – resource intensive

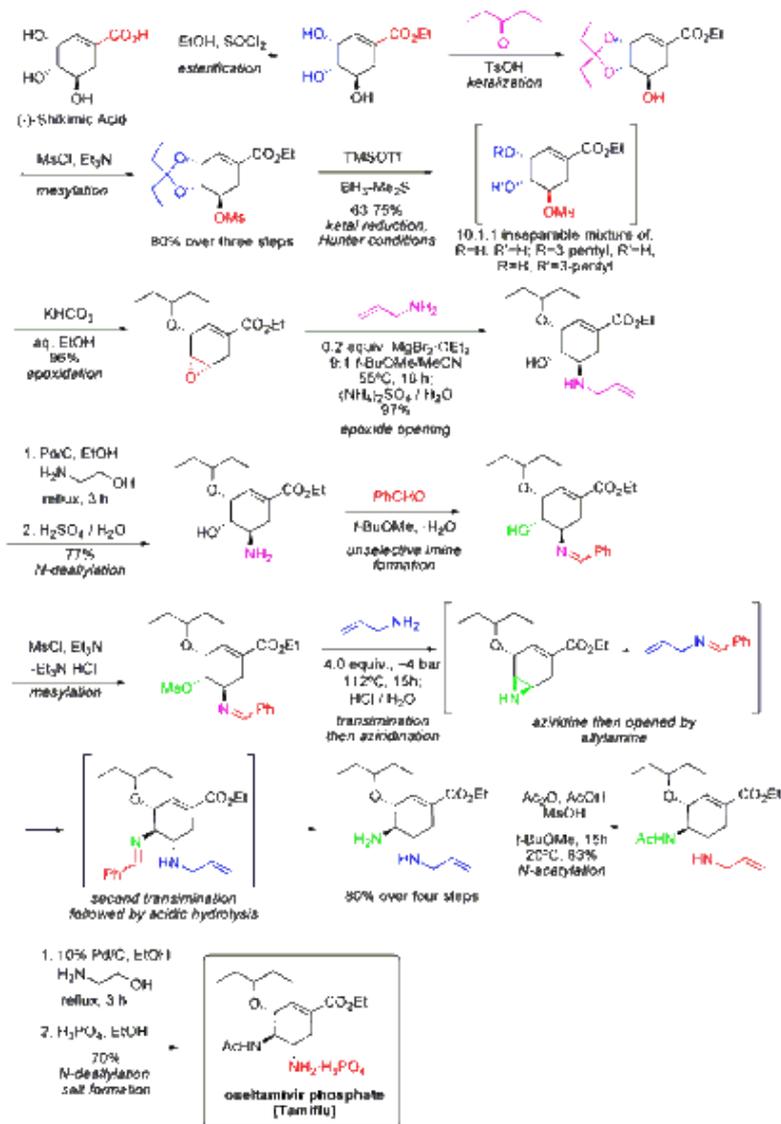
→ Predictive in vitro tools, integrated with *in silico* models are urgently needed

High potential for combining expertise between different pharmaceutical companies and between the pharma and public as well as SME research sector

Producing drug substances can be difficult, time consuming and expensive; sometimes sourcing of raw materials also may be an issue

Examples: bark from the endangered pacific yew tree was used for a time as raw material for paclitaxel (Taxol®); shikimic acid (sourced from Chinese star anise) shortage in the multistep production of oseltamivir (Tamiflu®)

Possible shortage of noble metal catalysts

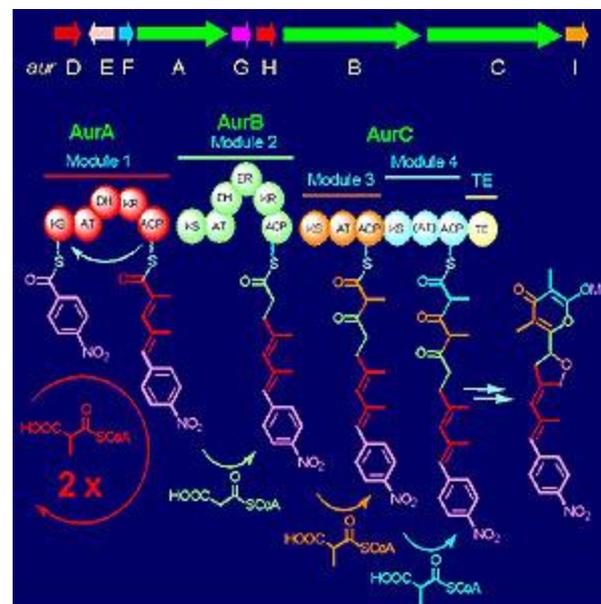


Sharing expertise between researchers in the pharmaceutical industry and academia/SME needed: pharmaceutical industry provides information and expertise about their problematic reactions, public/SME sector provides expertise in many areas of chemistry

Objectives:

- Novel organic and organo-metallic catalysts
- Process intensification / flow chemistry
- Bio-catalysis
- Synthetic biology

Example:
Polyketide
synthesis



Translate sustainable chemistry principles into PhD and post-doctoral training

Human-induced Pluripotent Stem Cells

hiPS cells have opened up many new areas of research, including access to improved in vitro systems for disease modelling, drug discovery and safety assessment

Focus of topic is patient-derived iPS cells to be used in

- Neurodegenerative/neuro-dysfunctional diseases
- Diabetes
- Safety assessment

Need for public/private collaborative research to

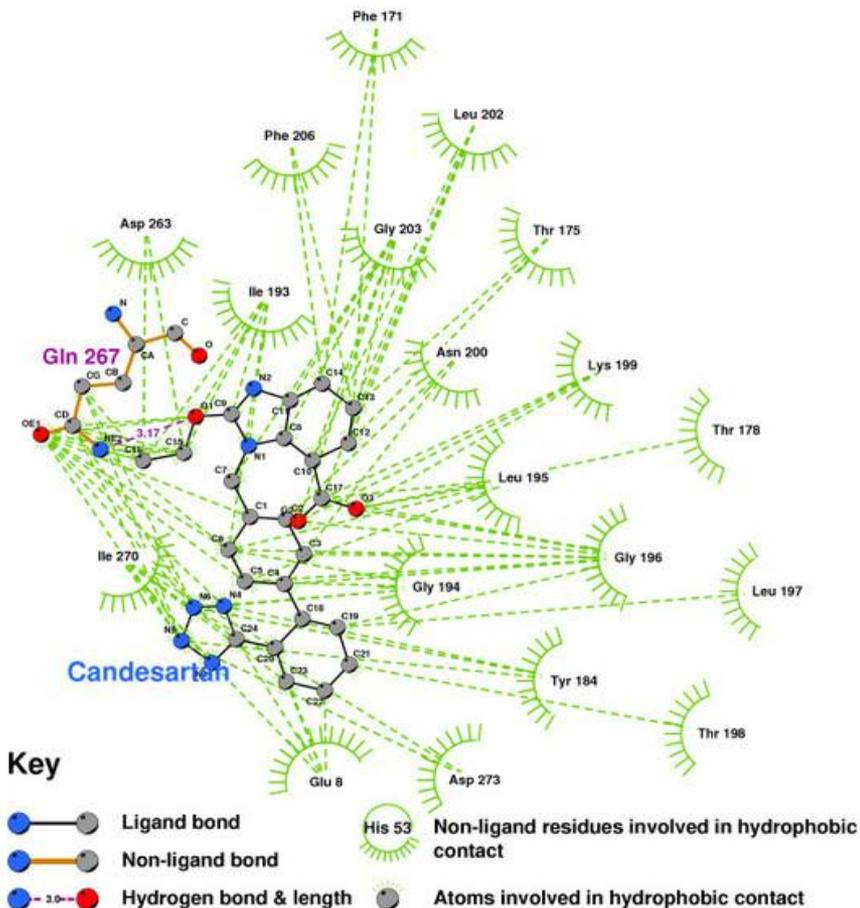
- Establish biobank
- Making accessible iPS cell lines from different ethnicities and patients with defined phenotypes/genotypes
- Establish standardised biological assays
- Strong communicative and collaborative links with other consortia



Understanding and Optimising Binding Kinetics in Drug Discovery

Improved understanding of interactions of small molecules with protein targets:

Drugs with slow off rates such as candesartan more likely to succeed in development



Candesartan docked into the putative AT2R1 binding pocket

Understanding and Optimising Binding Kinetics in Drug Discovery

Topic focused on binding kinetics but may be expanded in future to a « Think Big » topic to understand the critical factors that drive molecular interactions and how they correlate to processes involved in drug action

Need for broad ranging public/private partnership encompassing structural, biophysical, pharmacological (in vitro/ in vivo) and chemical fields

Pharma to provide tool compounds, assay reagents and in vivo models across many different drug targets (both soluble proteins and membrane bound proteins), including from projects that have not been pursued

→ First time that information generated in these projects will become available for use in research!



Outlook for Future IMI Calls

- Future IMI calls will lead to committing significant funding
- More “Think Big” topics: Pharmacogenetics and taxonomy of disease as well as rare diseases and stratified therapies are highly promising areas
- Additional modules for expanding EMIF to be launched

Complementarity to Funding Through FP7

- Most topics in the call about to be launched address research areas that **are not addressed** in Health Theme or other areas of FP7
- Topic on hiPS cells needs to take account of the significant investment already made in projects at EU and national level
- For the areas going forward, pharmaco-genetics and taxonomy of human disease complementary to public efforts on genomic medicine (including large international consortia)

Complementarity to Funding Through FP7

- Rare diseases and stratified therapies to take account of the international rare disease research consortium iRDiRC

