

European Union – USA Bilateral Workshop on Rare Diseases and Orphan Products “Fostering Transatlantic Cooperation on Research into Rare Diseases”

27-28 October 2010, Reykjavik, Iceland

Executive summary

Maximising scarce resources and coordinating research efforts are keys to success in the rare diseases field. Worldwide sharing of information, data and samples to boost research is currently hampered by the absence of an exhaustive rare disease classification, standard terms of reference and common ontologies, as well as harmonised regulatory requirements. Duplication of research efforts must also be avoided, and links between teams working on similar issues must be fostered.

The European Commission, Health Directorate, DG Research and Innovation, and the US National Institutes of Health organised in October 2010, in Reykjavik, Iceland, a workshop to explore international cooperation in rare disease research. Scientists from leading organisations in the field, industry and patient representatives, and regulatory bodies from both Europe and the USA were brought together to take stock of the ongoing activities on either side, to identify areas that would most benefit from trans-Atlantic and international cooperation, and to reflect on potential strategies and contributors for implementation.

Both funding agencies decided to launch an International Rare Disease Research Consortium (IRDiRC). IRDiRC will team up funding agencies and researchers around the world with the goals to deliver, by 2020, **200 new therapies for rare diseases and diagnostic tests for all rare diseases**.

A number of grand challenges will need to be addressed through collaborative actions to reach these 2020 goals:

- establish and provide access to harmonised data and samples,
- perform the molecular and clinical characterisation of rare diseases,
- boost translational, preclinical and clinical research,
- streamline ethical and regulatory procedures.

A second workshop, devoted to the preparation of the IRDiRC policy agenda will take place in Washington on 6-8 April 2011. Top scientists and representatives of funding agencies from all over the world will be invited and will contribute to the drafting of the policy document that will frame this important international initiative.

Report

Wednesday 27/10/2010

The background and the aims of the workshop were introduced by Dr Draghia-Akli, Director of the Health Directorate, Research and Innovation Directorate General of the European Commission. Rare diseases (RD) can serve as models for the development of personalised medicine, requiring personalised and timely diagnosis and treatment for the individual patient. The small number of patients for each RD poses significant challenges for the collection of data and biological samples and for performing conclusive clinical trials. There is a recognised need for greater international cooperation in this field to optimise scarce resources in order to accelerate the development of new diagnostic and therapeutic options. Potential priorities for this cooperation are to establish and provide access to harmonised data and samples, to perform the genetics, molecular and clinical characterisation of RD, and to strengthen translational and clinical research. The aims of the workshop were to identify areas that would most benefit from a trans-Atlantic and international cooperation, and to reflect on potential strategies and contributors for implementation.

Research activities on RDs supported by the US National Institutes of Health (NIH) were highlighted by Dr Steve Groft, director of the Office of Rare Diseases Research, who flagged the tremendous interest for such research, and the vast unmet medical needs of the area. Dr Draghia-Akli presented RD research activities supported by the European Union through the Framework Programmes for Research and Technological Development.

Session 1 - Linking Research Investigators

Scientific issues:

Quality of collected data and material, harmonisation of existing resources, adaptability of existing resources to new orientations, privacy protection, gaining approval from multiple ethics committees, extending existing research sites and protocols.

Speakers:

Dr John **Gallin** (NIH Clinical Research Center Hospital), Prof. Olaf **Hiort** (University of Lübeck), Dr Marshall **Summar** (Rare Disease Clinical Research Network, Children's National Medical Center, Washington, DC), Prof. Stuart **Tanner** (University of Sheffield).

Data collection: challenges and bottlenecks:

- The agenda of various stakeholders (patients, academia, clinicians, industry, policy makers, and treasury) is different, and sometimes difficult to reconcile.
- Multiplicity of databases, with different purposes, frequently “reinventing the wheel”, leading to a waste of resources. More collaboration, data sharing and common databases are essential (informal or formal).
- New registries may not be needed if the patient data collected through the health systems were accurate and with sufficient details, shared and made available for research.
- Ethics issues: consent, methods to preserve protection of patient information, ethical committee approval necessary but very heterogeneous and often not transferable between various ethical bodies, custodianship of the ‘conditional gift’ of the patient.
- Data quality: to date very heterogeneous, but crucial.

- Efforts and costs: not to be underestimated, and no easy mechanism for continued support exists; reflection to be carried out on the necessity to maintain a database/registry (aims might change over time).
- Professional boundaries difficult to cross (e.g. paediatrics/adults, doctor/IT technician, academia/industry, professional/politician).

Bottlenecks for international research cooperation:

- Classification of diseases and nomenclature are suboptimal.
- Difficulty to link research with routinely collected clinical data.
- Methodology: standard operating procedures (SOPs) publicly available are essential.
- Ethical review at different levels: this is much too heavy, and needs to be simplified.
- Registry rules (detailed in lively documents): importance of setting the standard for technical, legal and ethical issues.

Potential solutions:

- Internationally acknowledged and followed nomenclature and classification: ontologies.
- Selection of centres driving quality assured information.
- Strict adherence to SOPs.
- Ethical rules applying to (harmonised) national and international standards.
- Sustainability of databases: through international societies or long-term secured funding (not to rely on projects or individuals).
- Sharing data platforms, IT tools and infrastructures such as virtual research environments, ProtoType (for clinical protocol writing) or BTRIS (Biomedical Translational Research Infrastructure – data warehouse for research and clinical information).

Discussion:

- Importance of collecting comparable (hence compatible) data, so treatment and good practices can be optimised through the comparison of outcome from various treatment regimens and the development of consensus guidelines.
- Do we need a “disease by disease” approach or have a global approach? Take a more systematic approach? Could we have an economy of scale?
- Disadvantage of global approach: we may miss the patient, family involvement, and the enthusiasm to their disease registry; research into specific diseases needs to be supported. Disadvantage of disease by disease approach: duplication of efforts, very expensive and time consuming.
- Importance of standardising the phenotyping: strong need for common classification, nomenclature, ontologies.
- Need to find a way to coordinate at the global scale registries and data sharing. This is not trivial since RDs are highly heterogeneous. Will need a network of expert centres to contribute, so as to make sure that data entry is correct (e.g. concerning the diagnosis).
- For diagnosis: the clinical significance of a detected mutation remains difficult to define: this issue needs to be coordinated at global level and linked to the human variome project.
- How to create new opportunities while keeping moving the excellent ongoing projects? We might need to move from the specifics to the generalities, and integrate all the existing efforts into a more general, large effort.

Session 2 Translational Therapeutics

Scientific issues:

Establishing new approaches to the development of therapies; preclinical and clinical development of orphan products.

Speakers:

Dr Ségolène **Aymé** (Institut National de la Santé et de la Recherche Médicale), Dr Tim **Coté** (Food and Drug Administration, Office of Orphan Products Development, Repurposing of Orphan Products Project), Dr Susan **Old** (Therapeutics for Rare and Neglected Diseases Program, National Human Genome Research Institute), Dr Noel **Southall** (Therapeutics for Rare and Neglected Diseases Program, National Human Genome Research Institute, Repurposing of Approved and Investigational products), Prof. Kerstin **Westermarck** (Swedish Medical Agency).

Points presented:

- Indicators of success for developing a therapy: positive outcome more likely if development of a community of stakeholders (often triggered by patient organisations), infrastructures (patient registry, biobank, expert network), increase in the number of clinical trials.
- Most diseases are covered by one research project only; a few diseases have several.
- No link between prevalence and basic research: even very rare diseases can be covered.
- No totally neglected area, although some clinical areas are over-represented.
- If there is no understanding of the genetic and molecular mechanism underlying a RD, then translational research is unlikely.
- Development of therapies more likely in areas for which there is a history of developing drugs, as well as in areas with a potential for innovative approaches such as gene or/and cell therapies.
- Bottlenecks for therapies development:
 - scarcity of clinical experts and reference centres
 - difficulty to stratify by stage and severity because of clinical heterogeneity within a single RD
 - lack of validated biomarkers and surrogate end-points, for generally small, dispersed patient populations
 - lack of predictive and validated pre-clinical in vitro and animal models
 - registries being often geared towards science, not regulatory requirements: this should be reconciled to serve both aims.

Potential solutions:

- Public funding to:
 - go from mechanism of disease to proof of concept and clinical evidence
 - establish and maintain registries, create links between registries
 - run academic (investigator-driven) clinical trials for orphan indications
 - run protocol trials.
- Public-private partnership for registries, and support international patient databases and bio-repositories.
- Bridge the gap between basic research and clinical research: develop databases, information systems, biobanks in general, bridge ontologies.

- Encourage trans-Atlantic cooperation on the human phenome project: develop a standard terminology, ontology of terms to allow the cross-referencing with other ontologies, complete the ontology of diseases to allow the comparison with other ontologies such as mouse and zebrafish, and reveal commonalities between diseases.
- Identify and encourage testing of valuable hypotheses that are not being tested although the reasons for this can be addressed.
- Support the pre-clinical (“valley of death”) and clinical development of designated orphan medicines. Interesting models of NIH’s Therapeutics for Rare and Neglected Diseases program to de-risk projects to be further developed and marketed, and FDA’s Office of Orphan Products Development trial grant program.
- Support the creation of an Orphan Contract Research Organisation for clinical trials of designated orphan medicines; this could benefit from international cooperation.
- Re-purpose existing drugs whenever possible: apply existing drugs to rare diseases.
- Train (and incentivise from a financial and career point of view) new experts, notably in clinical experimental medicine, facilitate the development of expert centres and centres of reference, and stimulate trans-Atlantic links between them.

Discussion:

- Need to identify which research can be done to help regulatory exploitation, for example the definition of appropriate outcome endpoints or surrogate markers in clinical trials.
- Understanding what it takes from a discovery to get a product on the market is a real barrier. The collaboration with regulators is key to find faster and easier solutions for the patients, but without compromising safety and efficacy. Structures, information and advice channels (such as European Medicines Agency’s small and medium-sized enterprises (SME) office, scientific advice procedure) should be put in place and/or better advertised.
- Therapies’ developers should be better trained in the drug development path, and sharing information is a key aspect. Major information, including scientific advice by regulators, is often ignored by the developers. This is a real problem to carry their business within the right regulatory framework, and often leads to failure.
- Harmonisation of procedures between regulatory agencies (FDA/EMA) would help saving resources and time. The ongoing collaboration and harmonisation process should be continued and encouraged.
- A more segmented way of defining diseases is the current trend in big pharmaceutical industries. Rare diseases could serve as a good model for personalised medicine.
- Orphan drug designation is not exclusive for industry but can be used by any type of sponsor. Any project in this area that would be supported by public funds should obtain the orphan drug designation.

Session 3 Obtaining the Diagnosis

Scientific issues:

Procedures for expanding current newborn screening programs; building on information from evaluations and studies of patients with undiagnosed diseases; -omics for better diagnosis of patients.

Speakers:

Dr William **Gahl** (National Human Genome Research Institute, Undiagnosed Diseases Program), Dr Michele A. **Lloyd-Puryear** (Genetic Services Branch and Division of Services for Children with Special Health Needs, Health Resources and Services Administration), Prof. Willem **Ouweland** (University of Cambridge); Prof. Béla **Melegh**, (University of Pécs).

- All “blocks” of life are being defined ((epi)genome, transcriptome, proteome, cellulome, metabolome). This will help defining the state of health, and will ultimately provide a definition at genetic and molecular levels for most rare diseases. The genetic and molecular basis of about 3000 RDs has been resolved, but this is not the case for the remaining 3000-5000 RDs.
- Access to the genetic and molecular diagnosis for known RDs is patchy in Europe. It would be important to reflect on which steps could be taken to improve the diagnosis of patients with RD of which the genetic basis has been resolved.
- Omics and particularly next generation sequencing technologies will allow the identification of causative mutations for the majority of the 3000-5000 rare disorders without a known cause. It would hence be important to connect RDs clinical communities with “-omics” centres.
- Promises of induced pluripotent stem cells (iPSC): based on the scientific progress, not only DNA should be banked, but also viable cells. iPSC approaches to investigate mechanisms of disease and to screen for orphan drugs should be developed. Pan-European effort in biobanking, which could be internationally expanded: Biobanking and Biomolecular Resources Infrastructure (BBMRI).
- Better diagnosis requires the setting up of efficient service infrastructures, to provide tools for organising and sharing the knowledge (e.g. virtual repository for biobanks). Such an infrastructure can also support research (e.g. US newborn screening translational research network).
- Targeted genotyping will increasingly be replaced by the sequencing of large fractions of the genome (the parallel screening of genes for multiple RDs with sample multiplexing will bring cost down) or the entire genome. The “tipping point” for the introduction of the sequencing of the entire genome is expected to happen *before 2015* and sequencing of the “exome” (*entire coding fraction of the genome*) is already affordable for research purposes.
- In order to identify sequence variants that modify rare disease severity (“modifier genes”) at least 2000 cases per disease are required and a similar sized replication cohort is necessary: importance of international collaboration and of new statistical methodologies.
- The situation for newborn screening is heterogeneous, both in EU and in US. A number of RD could be selected to develop the systems for a roll out of routine screening.
- Both top quality basic and translational research are imperative if we want to drive forward innovation in the diagnosis and treatment of RDs: importance of understanding the genetic basis and molecular mechanisms of RDs, and deciphering the clinical heterogeneity for each RD in order to maximise the chances of developing an effective intervention.

- Clinical research: implement as fast as possible into practice to establish the clinical utility.
- It is up to the society to determine what is reasonable to screen in newborns.
- NIH Undiagnosed diseases program (UDP): to help patients with unknown disorders reach a correct diagnosis. This program should also help in discovering new diseases, and provide insight into human physiology.
- Many cases from UDP are complex paediatric genetic disorders: this is a model for personal genomics (important role of SNP arrays, high density comparative genomic hybridization (CGH) arrays, exome sequencing and eventually sequencing of the entire genome).
- This programme links with basic researchers, and could be extended to international collaboration (including other medical centres and researchers).

Discussion:

- Newborn screening is a matter of policy. Ethical issue relating to genetic screening were discussed. In this respect, there is a notable difference between US and EU. In Europe, no screening in children will generally be implemented in the absence of treatment; nevertheless, a diagnosis is important for genetic counselling of the parents. An EU mapping exercise on newborn screening is currently ongoing. The results of this exercise might open new perspectives for collaboration with US, but genetic screening should probably not be part of an international effort, but a matter of national policy.
- In EU, there is generally a good healthcare system, taking patients in charge even if this is costly, so that if a patient remains undiagnosed, it is mainly because of a lack of local expertise: what is diagnosable is generally being diagnosed if the patient is referred to a reference centre (expert network). In this context, working together on a specific disease or group of diseases (establishing expert reference networks) would be more beneficial than a general approach trying to tackle everything.
- Access to EU large scale DNA sequencing facilities needs to be improved and results need to be linked via centralised databases for genome and phenome information.
- Strong support is needed to train a new generation of bio-informaticians, physicists, mathematicians and statisticians, to work with the pentabytes of stored data. More funding should be allocated to the development of methods to interpret data.
- The training of clinicians on the diagnosis and genetic analysis of RD cases is also very important.
- US-EU should invest in the human variome project, aiming at the complete capture and sharing of information on all genetic variations of human disease.
- The discovery of the causative mutations of RDs could benefit from a close EU/US collaboration. Projects with principal investigators (PI) from both sides would be useful. This could be implemented through programme-level cooperation: each country funds its own researchers, but the PI should meet once or twice per year, put their data together, and make them available to others.
- Combined funding programmes for common biobanks/registry platforms would be useful; getting to know the experts from both sides and increasing coordination is essential for the progress of RDs research (e.g. common rules on DNA sample ownership).
- USA started the phenotyping of diseases with standardised phenotyping procedures/tools and nomenclature. Human phenome project should be done at the international level.

Thursday 28/10/2010

Session 4 was skipped, as points to be tackled within this session were already covered in previous sessions, and more time was allocated to discussion and free exchanges. This allowed break-out sessions to take place (on diagnosis, therapies, and information sharing). Summaries of these break-out sessions are appended in annex.

Session 5 Fostering academia/industry partnerships

Scientific issues:

Interactions with industry, chemical libraries, compounds with little commercial interest.

Speakers:

Dr Tim **Coté** (FDA Office of Orphan Products Development), Dr Ed **Mascioli** (Pfizer), Dr Eric **Olson** (Vertex Pharmaceuticals), Ms Samantha **Parker** (Orphan Europe), Dr Anne **Zajicek** (National Institute of Child Health and Human Development).

Points presented:

- Data on long-term clinical outcome need to be collected; however, research projects are typically funded over relatively short periods that do not allow for long-term follow up of patients.
- Academia-industry US/EU partnerships make sense, as this would help avoiding duplication and would allow economy of scale.
- Post-marketing surveillance can be beyond the resources of small and medium-size enterprises: need to partner with academia.
- Important for an industry to build on strong data and knowledge in order to take a product to the market: academia can contribute to de-risking the projects.
- Creation of public-private partnerships on patient registries and bio-repositories to reduce duplication of efforts.
- Benefits of international cooperation: studies of natural history and genetic basis of diseases, identification and validation of biomarkers and surrogate endpoints, global patient registries, disease-specific assays, with an increased involvement of US and EU government officials in the process.
- Paediatric population presents additional challenges, such as need for adapted formulation, different pharmacology and adverse reactions; this is particularly important in the context of rare diseases.
- International cooperation would help to prioritise the needs, and leverage existing infrastructures: develop an international paediatric trials network would allow collecting data from increased number of sites, which would facilitate the evaluation of proposed biomarkers and outcome measures.
- A number of FDA-approved products show promising results in treating RD patients: importance of “repurposing” them, as their toxicity is already known.
- Public funding support should be given in priority to repurposing drugs approved for common diseases, and designated for RDs, as the private development for these is not viable.

Discussion:

- A number of compounds are lying on pharmaceutical industry shelves, which are not developed (because no institutional value anymore) but have a potential as orphan drugs. A procedure should be developed in order to transfer these compounds to the public domain for possible further development.
- A similar programme was running in France (ERDITI, European Rare Disease Therapeutic Initiative): academics who would have ideas on pathophysiology of a disease would ask companies if they have potential compounds. Proposals for collaboration were examined by a mixed panel. However, this initiative did not work very well, potentially because of lack of advertisement. Whether to resuscitate this initiative should be considered.
- Industry is currently reflecting along the same lines: put knowledge about target-specific compounds to be developed in a common ‘cookie jar’, from which you cannot take a cookie (i.e. a compound to be developed) if you do not add a cookie. At the moment, industries are trying to find agreements on the concept; a next step will be to invite academia to collaborate.
- The paediatric legislations in EU and USA provide basis to develop paediatric drugs, but the business model is still not optimal to cover the needs of the paediatric populations, notably when it comes to formulation and biomarkers. There is a need for smart public funding support, not only of existing drugs but for new or re-purposed compounds.

Session 6 How to best implement international level cooperation?

Issues:

What scientific topics would need to be coordinated at international level? How could this be achieved? Structure, governance aspects.

Speakers:

Dr Sophie **Koutouzov** (GIS Institut des Maladies Rares), Dr Jacques **Remacle** (European Commission)

The ERA-Net “E-Rare”: The European Research Area Network on rare diseases

- Aims = coordinate and develop synergies between national research programmes on RDs.
- Develop common research policy on RDs.
- Support basic and translational research, and broaden the scope towards more clinical projects.
- Implement transnational research funding activities, notably through joint calls (variable geometry approach: not all ERA-Net partners are obliged to take part in a call).
- Success rate of applications around 10%, showing the important interest in such activities.
- The ERA-Net is also important for countries that have no programme on RDs research, as it can offer a model.

Potential international consortium on rare disease research: governance

- Examples of the ongoing international consortia on cancer genomics and on human epigenome were presented. Goals of such consortia are to set up common policies to facilitate research.
- Importance to have clear and quantifiable goals and a strong governance structure. Open-ended programmes are not very interesting for funding agencies.

- A governance structure based on the International Cancer Genome Consortium (ICGC) governance structure was presented.
- The concept of an international consortium was strongly supported by the whole assistance. An interim steering committee will be established to develop the policy document that will frame this international effort on RD.

CONCLUSIONS

- The concept of an **International Rare Disease Research Consortium (IRDiRC)** is receiving strong support.
- Two major goals were already identified for 2020:
 - Ø **Find 200 new therapies for rare diseases**
 - Ø **Having diagnostic tests available for all rare diseases**
- Grand challenges to be addressed to reach the 2020 goals:
 - Ø **Establish and provide access to harmonised data/samples**
 - patient registries
 - bio-banks
 - Ø **Molecular and clinical characterisation of RD**
 - classification and standard terminology
 - natural history, genetic basis (including modifier genes), patho-physiology
 - common ontology and cross-referencing to animal diseases ontology
 - Ø **Translational/preclinical research**
 - predictive, validated *in vitro* models and *in vivo* animal models
 - Ø **Clinical research**
 - validated biomarkers and surrogate end-points
 - new diagnostics and therapies
 - “repurposing” existing drugs
 - optimised outcome through the comparison of various treatment regimens and the development of consensus clinical guidelines
 - Ø **Cross-cutting aspects**
 - streamline ethical and regulatory issues
 - encourage stakeholders to cross boundaries (e.g. paediatrics/adults, academia/industry).
- Through collaboration, the cost of R&D for developing new treatments decreases. Rare diseases also offer models to give insight into more common ones, and in particular for targeted, personalised medicine. It is important to use these facts to deploy and increase the efforts put on collaborative research on rare diseases.

NEXT STEPS

- **Next workshop:** 6-8 April 2011 (Washington) to:
 - discuss and finalise a first draft of the IRDiRC policy document
 - officially launch the IRDiRC
 - establish IRDiRC governance structure
 - propose working groups on important policy goals.
- **Interim steering committee** (research leaders + funders representatives) set up to prepare a draft policy document describing research objectives, developing policies, establishing a governance.

Annexes: summary reports of break-out sessions

Summary Report of Workgroup “The Diagnosis” Rapporteur: Prof. Willem H. Ouwehand

PHENOTYPE

- “Deep” (detailed) clinical phenotyping is essential and unified coding needs to be agreed, not dissimilar to gene ontology.
- Phenotyping to be performed by “centres with relevant expertises” and adequate case throughput – set standards for phenotyping centre.
- Reimburse health care system for “deep phenotyping” as per NIH funding models; the old European approach of the health insurer “may pay if we don’t tell” will not work anymore and will surely jeopardise enrolment.
- Funding for phenotyping centres to be linked to meeting enrolment targets (no upfront payment but payment per result).
- Complement clinical phenotyping by patient-driven self-reporting supported by modern IT technologies, e.g. structured wiki pages, Facebook principles (data owner decides on privacy settings levels).
- Consent at enrolment needs to take into account genomics platform revolution. A plethora of DNA samples already banked do meet quality standards to be suitable for the new platforms and the consent is often limited to a single or set of candidate genes.

LONG TERM FOLLOW-UP

- Is costly but required to obtain reliable information about outcomes and the effect of new interventions on outcome.
- Question was raised who is responsible for cohort follow-up and what can the funding model be (combination of big pharmaceutical industry, health insurers, national charities and EU using its funding power as leverage).

GENOTYPE/SEQUENCE

- See above statement about consent.
- Technologies for the discovery of causative mutations will evolve rapidly over the next 5 years with rapid improvements in the quality of the reference genomes. The ultimate catalogue of sequence variation will be established by 2015 with 25,000 entire genomes to be sequenced by 2012 and possibly up to 100,000 by 2015.
- A possibly large fraction of the unresolved rare genetic disorders will be of coding nature or caused by “copy number variation”. These mutations can currently be identified by affordable exome-sequencing and high resolution comparative genomic hybridization (CGH) arrays.
- Whole genome sequencing will become affordable by 2012 and will increasingly replace the above two platforms.
- Strengthen/establish national hub and spoke models by linking rare disease networks with a limited number of genome centres.
- Agree on data release rules of sequence information (pre-competitive). If you want to participate then you buy conceptually and contractually in to a set of rules about:
 - o DNA quality and type of consent
 - o Free release of sequencing data
 - o Knowledge sharing
- Discovery of mutations of regulatory nature will be challenging and the International Human Epigenome Consortium will support exploring the territory of non-coding

DNA (98% of the entire genome), which will include the sequencing of coding and non-coding RNAs from the affected tissue (IHEC is supported by a 2010 FP7 call for high impact research initiatives (HIP), <http://ihec-epigenomes.org/>).

- Get agreement on the rules to define “causative mutations”, to be agreed as well with the leading scientific journals.

CLINICAL BIOINFORMATICS, data repositories and cross-platform integration

- If we want to capitalise on genomics for the benefit of the care of patients with rare genetic disorders then we must invest in clinical bioinformatics.
- Tools must be developed which will allow the non-initiated clinician-scientist, genetics scientist or genetic counsellor to navigate the richness of genome-phenome association data (e.g. it should be intuitive and purpose focussed).
- We must integrate data about causative mutations (which are maintained in a central European-US database) with other global computational platforms about signalling pathways (e.g. reactome; <http://www.reactome.org/>), about syndromic mutations (e.g. DECIPHER; <http://decipher.sanger.ac.uk/>), about rare diseases (ORPHANET; <http://www.orpha.net/>) and others.

INDUCED PLURIPOTENT STEM CELLS (iPSCs)

- iPSCs can now be routinely generated from a simple blood sample.
- iPSCs are already one of the key model systems to study the mechanisms by which rare mutations cause disease.
- Therefore iPSCs technology must be made available to the rare diseases community and at time of DNA banking also viable blood cells of the correct type must be banked.
- They will also become one of the preferred screening platforms for novel compounds shortening the time from gene discovery to orphan drug application in the clinic and their use may reduce erroneous rejection of compounds because they have been tested in a non-human model system.
- iPSCs can be differentiated into end-stage cells for the purpose of the above outlined use.
- For some rare disorders iPSCs can be used to generate stem cells that have been “genetically cured”, e.g. in case of rare disorders of haematopoiesis.

BIOMARKERS/MODIFIERS OF SEVERITY

- Discovery of markers for phenotypic variability in disease severity are important for a substantial number of rare conditions.
- The initial prototype discovery programmes should be in rare disorders with a well resolved genetic basis.
- For discovery and validation programmes a large number of cases of the same rare disease and accurate longitudinal follow-up clinical information will be required. Possible examples for prototype studies are:
 - o familial hypercholesterolemia
 - o cystic fibrosis
 - o sickle cell disease
 - o hereditary haemochromatosis
- Link discovery programme for biomarkers/disease modifiers in rare disorders with other initiatives for common disorders.

Summary Report of Workgroup “Drug development”
Rapporteur: Prof. G.-J. van Ommen

- Registries (natural history – full or representative ascertainment?)
 - Stability, maintainability issue.
 - Post approval follow-up.
 - Goal? Background of therapy, longitudinal, natural history. So different from research-based repository.
 - Define the right information. How to make a more formal group to guide the establishment of therapy-oriented registries?
 - NB: to establish registries for e.g. natural history you are earlier in the process than one would be when filing an investigational new drug (IND) application. Networks and consortia generate candidates and mechanistic insights and do not so much know about the regulatory aspects.
 - Quality issue (regulatory approval): acceptability of primary data (coordination EU/US) so investigators and patients would not have to repeat. Industry is more interested if regulatory quality. NB: logistical problems (investigator-driven vs industrial clinical trials)
 - Contract research organisations are helping in two locations?
 - PreIND meetings are key, and are easier if they take place in parallel than coordinated.
 - Grant requirement to first go through FDA/EMA advice and specifications?

Gather stakeholders around networks, and sort out issues.

Subjects for actual research:

- In rare diseases: accelerated approval, to arrive quicker from small phase II to pivotal study. Using biomarkers, so skip the de-risking process to some extent.
 - Clinical outcome measures or accelerated, field-accepted biomarker surrogate readout (e.g. TREAT-NMD network, which defines patient-centred endpoints (e.g. what is the relevance of a 6-min walk test when a patient considers more important to be able to use his laptop?).
 - Goals of registries, alignment, access and inter-operability improvement.
 - Gene therapy. Produce vectors, variability, vector safety. (From FDA: *what is coming up in FDA is quite spectacular – we need the same in EU*).
 - Same for cell-based therapies.
 - Set up something ambitious between EU and US to get the companies to work in a combined pharma-portal.
 - o Cookie jar: industry has de-prioritized stuff shelved; this is proposed to be shared. Idea might be to take those and screen them for utility in rare diseases.
 - o Trend: NIH high-throughput screening programme. Hits are cleaned, the optimized hits, so called ‘probes’ end up in public database (PubChem).
- NB: difference between big pharma and small biotech: SME have less to gain and more to lose (at least in their perception); in consortia: risk sharing programmes.
- Under-exposed issue: failure.
 - Why and how do SMEs fail? Too risky, funding gap? Too narrow-focused, too narrow intellectual property portfolio and failure in further licensing? Or too broad approach for the span of control? Disinterested in repurposing?

- Research in animal models? More refined and accurate disease models are increasingly needed, and the cost is so high that international coordination to reduce cost is needed. Also consider long term drug safety studies: drug composition variability!
- Joint funding of US and EC in one programme would be more than the sum of the parts. It would generate focus and convergence, and dramatically increase awareness of what is going on elsewhere.
- International clinical trials programme. Then you internationalize the size of patient registries. Joint proposals that “cross the pond”.

Two wisdoms of Tim Coté:

1. Do not fall in love with a drug: it'll break your heart!
2. A good drug will show itself: no jiggling the noise to find a tiny effect!

Summary Report of Workgroup “Information Sharing”
Rapporteur: Sharon Terry

- Information from the non profits – have a strategy to share that information
 - List major groups – email effort
 - Inventory the resources – email effort
 - Convene these groups – call in one month
 - Assign various elements, find funding for places that need acceleration
- Harmonize Orphanet and National Center for Biotechnology Information (NCBI) nomenclature – goal is to harmonize *in 6 months*, meet via phone to begin in next month.
- Define precompetitive resources – map them across the community via email – shared document.
- Human phenome – harmonize Orphanet, PhenX
 - PhenX
 - Assessment
 - Modify to become the standard for rare diseases
 - Declare as standard
- Organize phenotyping – library of biomarkers and clinical endpoints – assess where we are
- Share the maps of genetic services from Orphanet and National Coordinating Center for the Genetic and Newborn Screening Service Collaboratives (NCC)
- Registries – policy paper
 - International
 - Open source (not moving the data)
 - Shared
 - Compatible
 - Standards based
- Orphan drug approvals – how they are made, variability in review within division – National Organization for Rare Disorders (NORD) published in the next 6 months or so. Standardize the process and make it more predictable.
- Leiden Open (source) Variation Database (LOVD) and NCBI – harmonized and we will continue to use them
- NIH research grants and clinical trials – track their rare disease focus
- Failed clinical trials – Prescription Drug User Fee Act (PDUFA) requires that adverse events and results of the trial be published
- Regulatory freedom for cancer trials – do we want the same for rare diseases?

- Real ontology – web 3.0 to interface this ontology with the mouse ontology – within two years – needs a plan
- Consider work coming out of the reactome
- Term “ultra-orphan” is not acceptable
- Produce recommendations for clinical guidelines for genetic testing – consider various sources for value of tests in different cultures.