RARE DISEASES AND ORPHAN DRUGS

An International Journal of Public Health

October 2015, Volume 2, Number 3, Supplement 3

Print ISSN 2284-2543
Online ISSN 2385-2364

Publisher
Istituto Superiore di Sanità

JOURNAL TITLE: **RARE DISEASES AND ORPHAN DRUGS** ***An International Journal of Public Health***

PUBLISHER:

Istituto Superiore di Sanità, Legal representative (Fabrizio Oleari)
Reg. Stampa Tribunale di Roma, n. 35/14 del 10 marzo 2014
Print ISSN 2284-2543, Online ISSN 2385-2364

CONTACTS:

RARE Journal Secretariat
National Centre for Rare Diseases
Istituto Superiore di Sanità (ISS)
Viale Regina Elena, 299
00161 Roma, Italy

E-MAIL: secretariat@rarejournal.org
URL: http://rarejournal.org/

The Rare Diseases and Orphan Drugs Journal has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n° 305690: RARE-Bestpractices project: www.rarebestpractices.eu. Sole responsibility lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein.

WWW.RAREBESTPRACTICES.EU

RARE DISEASES AND ORPHAN DRUGS

An International Journal of Public Health

October 2015, Volume 2, Number 3, Supplement 3

Index

The Global Rare Disease Week, Mexico, October, 12-16 October, 2015

The RARE-Bestpracticies project is founded by the European Union Seventh Framework Programme. Project Ref.: N 305690. Sole responsibility lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein.

WWW.RAREBESTPRACTICES.EU

PROCEEDINGS FROM THE 10th INTERNATIONAL CONFERENCE ON RARE DISEASES AND ORPHAN DRUGS (ICORD).

Mexico City (Mexico), October 15-16, 2015

A Decade of Discoveries and Current Challenges in the World of Rare Diseases and Orphan Drugs

Introduction from the President

On behalf of ICORD I would like to thank the local organisers (FEMEXER, GEISER and Proyecto Pide Un Deseo México), the excellent speakers and everyone who attended the 10th annual ICORD meeting in Mexico City, Mexico. More than 250 delegates, from all continents and representing many different stakeholders such as patients, patient support groups, health care professionals, researchers, industry, politicians, regulator and health authorities, came to take part of an inspiring programme, to network and to share their experiences in the field of rare diseases and orphan drugs. The ICORD meeting was part of the "Global Rare Diseases Week, Mexico 2015" and back to back with the 4th Latin American meeting of Rare Diseases (ER2015LA) on 12 October and the Discoveries and Innovations in Orphan Drugs Congress (D&IOD), 13-14 October.

The attendees received an update of progress in the rare disease field in Mexico and Latin America from different perspectives; patients, industry, regulatory authorities, researchers and health care workers. International key leaders shared their experience on global strategies, ethics on resource allocation for rare diseases, successful collaborations, access to patient registries and biobanks, the work of patient organisations, orphan drug regulations, prevention, the NIH undiagnosed diseases program and inborn errors of metabolism. In addition, during a poster and a discussion group session the attendees had the possibility to present their perspectives and to network with peers. The abstracts of the speakers, posters as well as the conclusions of the discussion groups are included in this publication. The presentations from a majority of the speakers are available at the ICORD website, www.icord.se.

Unlike other organisations in the rare disease community, ICORD is unique in that it is a society for all rare disease stakeholders from all over the world as it is ICORD's belief that the rare diseases challenges can only be conquered by joint efforts of all parties. Rare diseases and orphan drugs are undoubtedly global matters, which in ICORD find a unique and transparent forum for discussions, presentations of ideas and collaboration.

ICORD is very grateful for the opportunity to join the Rare Disease Week in Mexico City, for the commitment of the local organisers and the dedication of our members in the organisation of the event.

While reflecting on the success of this meeting in Mexico, we now look forward to the year ahead and the next meeting. ICORD was delighted to welcome representatives of the local organising committee of ICORD 2016, the Rare Disease Society of South Africa (RDSSA, www.rarediseases.co.za) to Mexico City, as well as Rare Disease International (RDI, www.rarediseasesinternational.org) who will be part of the organisation as well. The 11th annual ICORD meeting will be held in Cape Town, South Africa, 19-22 October 2016 and will be the first ICORD conference on the African continent. ICORD looks forward to a fruitful meeting, with the overall aim to contribute to increased awareness of rare diseases in South Africa/ Africa and in the long run an improved situation for rare diseases patients in Africa and world-wide. ICORD warmly welcomes you to interesting days in Cape Town!

John Forman,
ICORD President

10th Annual ICORD Meeting – Organisation Committee

ICORD

John Forman (ICORD President, New Zealand)
Steve Groft (National Institutes of Health, USA)
Virginia Llera (GEISER, Argentina)
Ann Nordgren (Karolinska University Hospital, Sweden)
Manuel Posada (Instituto de Salud Carlos III, Spain)
Emilio Roldan (GADOR S.A., Argentina)
Fernando Royo (Fundación Genzyme, Spain)
Domenica Taruscio (Istituto Superiore di Sanità, Italy)
ICORD Secretariat (Désirée Gavhed and Annika Larsson, Karolinska University Hospital, Stockholm, Sweden)

Local organisers

Celia Palacios (Proyecto Pide Un Deseo México, FEMEXER, Mexico)
David Peña Castillo (Proyecto Pide Un Deseo México, FEMEXER, Mexico)

Supporting Institutes and Organisations

FEMEXER (Mexican Federation of Rare Diseases)
GEISER Foundation (Rare Diseases Latin-America)
ICORD
ISSSTE (Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado)
Karolinska University Hospital, Sweden
Proyecto Pide Un Deseo México

Commercial Sponsors

Genzyme (a SANOFI company)
Shire Pharmaceuticals
Bristol-Myers Squibb
Actelion Pharmaceuticals Ltd
BioMarin Pharmaceutical Inc.
CSL Behring
SOBI (Swedish Orphan Biovitrum)
Orphan Europe, Recordati Group
Audentes Therapeutics, Inc.

Abstract Review

Each submitted abstract was blinded and scored by a minimum of two reviewers according to the scientific or institutional merit of the abstract, originality and adherence to instructions. Abstracts of oral presentations have not been reviewed by the publisher or by ICORD. These abstracts are published as received from the authors, plus some editorial adaptions on its structure. The opinions and views expressed are those from the authors who accept the responsibility for the statements made or the accuracy of the data presented.

Abstract Review Panel

Simon Day (Clinical Trials Consulting & Training Limited, UK)
Yukiko Nishimura (University of Tokyo and ASrid, Japan),
Emilio Roldan (GADOR S.A., Argentina)
Rumen Stefanov (Medical University of Plovdiv, Bulgaria)
Maja Stojiljkovic (University of Belgrade, Serbia)

Abstract Review Coordinator

Annika Larsson (ICORD Secretariat, Karolinska University Hospital, Stockholm, Sweden)

About ICORD and the 2016 Annual Meeting in South Africa

ICORD (International Conference on Rare Diseases and Orphan Drugs) is an International Society for all individuals active in rare diseases and/or orphan drugs, including health care, research, academic, industry, patient organizations, regula-

tory authorities, health authorities, and public policy professionals. The mission of ICORD is to improve the welfare of patients with rare diseases and their families world-wide through better knowledge, research, care, information, education and awareness (for more information or becoming a member see www.icord.se or email the ICORD secretariat, icord@karolinska.se).

The next annual ICORD meeting will take place in Cape Town, South Africa, 19-22 October 2016 under the RAREX week and will be organised together with Rare Disease International (RDI) and Rare Disease Society of South Africa (RDSSA). The conference will be the eleventh since the first ICORD took place in Stockholm 2005. The meetings are usually attended by 150-300 participants representing all stakeholders in the rare disease field from all continents. In addition to an excellent scientific program, the annual ICORD meetings are very collegial and provide a great opportunity for interaction, networking and sharing of best practices. Many of the attendees are international and regional key leaders.

Board of ICORD

Conclusions of the discussion groups

The ICORD discussion or working groups offer an opportunity for the conference delegates to meet and discuss matters of importance with other delegates with similar interests. The discussion group session provides a forum where conference attendees can network, learn from each other and bring new ideas back home. The groups are open to everyone and their contents are decided by the participating delegates. Each discussion group has a coordinator who functions as facilitator to drive the discussion.

Discussion Group 1 – Communication: Crowdsourcing and Social Media Role

Coordinator: Janine Lewis, MS, CGC, ICF International, USA

ICORD participants from a range of advocacy organizations, from disease specific to umbrella organizations were active conversationalists in the social media and crowdsourcing discussion group at ICORD 2015. We are grateful to Patricia Lucki, with the National Guatemala Association for Lysosomal disorders (ANGEL) for her translation of the group's discussion from English/Spanish. There was a wealth of experience among members of the group about the various social media platforms. The discussion group gave us an opportunity to learn from each other's experiences, both pros and cons.

Most of the group participants are using Facebook and Instagram as their primary platform to engage with their constituents and provide support. We talked about advantages and challenges with Facebook. Some examples of the advantages discussed using Facebook included: the platform crosses culture and age groups; and the Facebook metrics are valuable for measuring communication successes. The challenges included experiences with "trolling"; the need for moderation of posts, depending on the community; and without clear objectives and a roadmap for communication goals, it can be overwhelming. Finally, members of our group suggested tools like Hootsuite to aggregate all social media efforts in one place.

At the end of our discussion, since we were only able to scratch the surface of this vast topic, many in the group decided to continue our discussion and share our experiences via email. We have communicated since the ICORD meeting a number of times and shared more information about the wide range of social media platforms and some additional resources.

Discussion Group 2 – Research Infrastructures

Coordinator: Yaffa Rubinstein, NIH, USA

Members of the Research Infrastructure Group were a good sample of global representation from seven countries. The group first distinguished between patient registry and natural history. Then, most of the discussion was about the importance of patient registries and the many challenges associated with establishing, sustaining registries and sharing data.

It was apparent, that there was a wide range of differences among the different counties in terms of infrastructure, support, information and tools that is available for patient and their advocacy groups to establish a registry. In addition, differences in national health systems, best practises, regulations and ethical/legal consideration constitute a serious hurdle in linking and sharing data globally.

Common concerns were the involvement of patients in the process of data collected and sharing with others, quality of data, data ownership, and IT support.

Another topic that was covered was biospecimens. Members expressed concerns how to know who collects them and where they are stored, access to the specimens and the added value of biospecimens to registry data collection. Financial challenges in establishing, labelling, storing and distribution of the samples were also mentioned.

Conclusions:

1. Patient Registry is a system that collects patient's data and serves as a tool for different studies.

Natural History is a kind of study that can use data collected in patient registries.

2. Patient registries and its challenges;

- **a.** More collaboration, exchange of ideas, best practise resources, and tools are needed globally, especially providing the help from well to do countries to countries with less resources and expertise t o assist in establishing needed patient registries.
- **b.** Proper patient consent, patient voice and concern must be respected in the process of establishing and maintaining patient registries.
- **c.** When establishing a registry suitability of the registry must be addressed.
- **d.** Much more effort is needed to facilitate implementation despite the different international policies and regulation that will continue to exit.

3 Bio-specimens

- **a.** Specimens are important resource for rare diseases research.
- **b.** Registries should be encouraged to link to biobanks and collect samples.
- **c.** There is a need for biobank locator to identify existing specimens collected that are in need for research.

Discussion Group 3 – Changes in Regulatory Environment

Coordinator: Catarina Edfjäll, CSL Behring, Switzerland

This workshop with participation from Regulators, Academia, Patients and Industry discussed the impact of changes in the regulatory environment in relation to patient's ability to provide their views and input on potentially associated risks.

Globally there are various new regulatory pathways to accelerate patient access to new medicines. Most are not specific to orphan drugs but many are relevant as the criteria are often applicable to rare diseases, e.g. serious or life threatening conditions, unmet medical need. Specifically there are some new pathways available in the US (Breakthrough designation) and in the EU (Adaptive licensing) that could allow innovative treatments to become available to patients earlier but based on a more limited data set which would be completed with information gathered after approval and launch of the product.

These pathways allow faster access for patients to new treatments, however, this needs to be balanced with the potential increased risk to patients (as products are authorized based on less information and data). Therefore, strong patient advocacy group engagement is critical as well as a good understanding of Clinical Trial design issues, e.g. End Point Selection, use of surrogate endpoints etc. To mitigate and allow for successful outcomes, health authorities provide increasing opportunities for dialogue and researchers, patients and companies are encouraged to seek frequent and early dialogue.

In the workshop the following issues and questions were raised and discussed:

- Do patients have tools to assess the 'risk' of being treated with a new medicine which was approved based on less efficacy/safety data?
- How to ensure patient's input on relevant end points for more meaningful and robust clinical trials?
- In the rare disease setting (small, geographically dispersed populations) there continues to be a need to develop different approaches to clinical trial design and utilize novel trial methodologies which need to gain acceptance from Health Authorities globally.
- After Marketing Authorization in the EU there is a national implementation step of Risk Management plans with negotiations with each Member State prior to launching of any new product. This leads to a delay in patient access of up to 2 years. How could this be avoided or better managed?
- Some 'old' (existing) products could be developed for a 'new' rare disease indication:

Who is responsible for developing and making this product available? There is no real incentive for industry as the return on investment is going to be low.

It was recommended that these are topics that would merit to be further discussed at future ICORD events.

Discussion Group 4 – Access to Diagnostics and Treatments Interventions

Coordinator: Antoni Matilla Dueñas, Health Sciences Institute Germans Trias i Pujol, Spain

The group included worldwide representatives from industry, patient associations, geneticists, and clinical, basic and translational researchers. Topics discussed were focused on the problems of accessibility to diagnostic tests and treatments interventions in the different countries represented in the discussion: mainly Mexico, Spain, India, Serbia, the European Union, and the United States.

The role and empowerment of patient Associations for Rare Diseases (RDs)

Special emphasis was made regarding the efforts to be heard by the Government representatives and policy makers who decide where public funds are allocated in order to provide patients with the resources needed to implement diagnosis and treatments. There was an overall feeling of frustration because of the difficulties to have access to existing treatments, and the ability of these Associations to make the government officials aware of the priorities and needs of patients.

The importance of lobbying actions and empowering of the patient Associations in each country was highlighted, as often having proved effective in developed countries (EU and USA) leading to the implementation of policies for RDs, but proving useless in the remaining countries such as Mexico. Despite the cultural, economic and development differences among countries, the patient Associations play a very important role in representing patients with the Administration in order to implement policies addressing rare diseases. International cooperation among patient Associations are proving useful and effective.

The role of Industry on R&Ds

The need for Pharma industry to invest more in the research of rare diseases was discussed, often they are not engaged because of less return from orphan drugs. This appears to be changing since now Industry envisages Rare Diseases from a global perspective and a wider market, but it was acknowledged that the efforts made from most of Pharma companies were not enough to advance in developing orphan drugs and treatments for RDs. A few companies were seen as an exception.

The importance of legal regulations implemented in the EU, USA, etc. regarding orphan diseases and orphan drugs were acknowledged, and in this regard industry plays an active role mainly in setting pricing schemes, since these could halt, in some cases, the drug development process. Higher flexibility is needed and total economic burden, when this is the case, should be shared not only by industry, but also by public agencies and optimally between both. Currently, a treatment for a RD could

be excluded from the public health system because of disagreement between industry and governments to set the drug price. Capacity of production of a drug could also be a limitation in order to release the drug to the market. Developing generic or small molecules could be a solution. The need for collaboration between industry and academy research groups for drug development and repurposing was noted.

Research on RDs

The need of developing treatments for RDs was acknowledged and that this could only be possible with more excellent scientific research, supported from both public and private (industry, patient associations, foundations, etc.) funding agencies.

There has been a significant increase in the research dedicated to RDs in the recent years, but this has not been enough since the translation from the laboratory to patients is still slow. The relevance of the established international scientific consortiums such as IRDIRC, Neuromics, Epirare, RARE-Best practices, etc., in the advance and release of guides, research, knowledge, etc. specific for RDs were acknowledged.

Genetic diagnosis

More than 80% of RDs have a genetic origin and the importance of genetic diagnosis for implementing effective treatments were recognized. Up to recent years, genetic diagnosis was limited by the genomic technologies, but with the expansion and affordability of Next-Generation Sequencing (NGS) technologies this is fortunately changing. With the wider use of these technologies, the genetic defects are identified in an increased number of RDs making possible accurate diagnosis, genetic counselling, prevention, and treatments when available. A few drawbacks were identified:

- phenotype-genotype correlations are still weak and poorly known highlighting the importance of the need to make more clinical research studies.
- the importance of prevention measures. These are still not sufficient and available.
- More efforts in education and information are needed.
- Genetic counselling is not widely available, especially in developing countries, and should be provided with each genetic diagnosis.
- An important limitation is that not all genetic laboratories have access to NGS technologies because of the costs albeit these are being progressively decreased, particularly in developing countries.
- NGS technologies are still not included in the public health systems in most countries, because policy makers and administrative officers still consider NGS expensive without realizing the gain in time, cost savings and the diagnostic benefits. Everybody agreed that NGS should be implemented everywhere and that genetic diagnostic tests based on NGS are not expensive when considering these factors.
- Finally, how to handle the incidental findings identified when using NGS technologies in genetics tests was discussed and it was agreed that they should be carefully studied.

Discussion Group 5 – Establishing Research partnerships

Coordinator: Simon Day, Clinical Trials Consulting & Training Limited, UK

It was considered that all stakeholders in research on rare diseases (industry / private foundations, academic researchers, business units stemming from academic departments, government agencies and patient groups) should form part of a joint partnership – there is more strength in collaboration than working alone. Partnerships are likely to be most productive the earlier they begin. Collaborations work best when the respective contributions, roles and responsibilities of the different parties are clearly established and agreed. However, in addition to a willingness to cooperate, appropriate resources and grants are crucial for international research collaboration, in particular for the participation of developing countries in such partnerships.

Open and full communication from a very early stage is vital so that all parties understand the wishes and intentions of all others. This particularly applies to the "delicate" issues of financial agreements and conflicts of interest. It was noted that perceptions of conflicts of interest are at least as important as actual conflicts.

Education in the rare diseases area using an international network is one important way to both establish partnerships and reach a common platform, especially education in developing countries. ERARE (http://www.erare.eu) may bring together researchers both within the programme and those outside who are interested. There are examples on international training programmes in EU, such as Marie Sklodowska-Curie (http://ec.europa.eu/programmes/horizon2020/en/h2020-section/marie-sklodowska-curie-actions), as well as the RDCRN in the US, in which every country may participate (https://www.rarediseasesnetwork.org).

Collaborative conferences are seen as beneficial but it is difficult to have conference material that truly aims at all parties, without it becomes several "sub-conferences." Each party should have full involvement rather each sub-conference merely being co-located. It was suggested that a possibly valuable conference theme would be a certain therapeutic area around which patient organisations, academia, health care professionals and industry could meet.

Discussion Group 6 – The Right to Health

Coordinator: John Forman, ICORD President, New Zealand

The range of options for rare disease patients in need of attention to their health needs, span the extremes from emotional pleading to angry demanding, and many shades in between. In addition there may be legal arguments and human rights

considerations to assist the case for care, and in all circumstances there will be moral arguments that assist the cause.

Remember there is a right to health expressed in the Universal Declaration of Human Rights and in various international conventions. Most governments have signed these and this imports those rights into the legal framework of signatory countries. This strengthens the case.

Many countries have specifically inserted the right to health into constitutions, along with another key matter of great relevance to rare disease – protection from catastrophic costs of health care.

The preferred arguments and approach will be dependent on the political and cultural environment in each country. Different approaches may be more influential or more acceptable in different societies, but it is useful to remember that legal and moral arguments will have some degree of force in every state.

Thus, a range of arguments need to be considered, so that directly influencing lawmakers and officials by direct lobbying at an emotional level, can always be further reinforced by identifying the legal and moral issues they should be considering. For some, these may be even more influential. Remember that lawmakers and officials will most likely have at least an instinctive understanding of the mix of issues and arguments, and may have a deeper academic knowledge of them too.

In a practical sense, moral arguments that may carry force in each health system are in fact the practical application of the right to health, as for other rights, because every society has significant aspects of legal and policy decision-making grounded in the dominant moral philosophies in society.

Patient advocates should seek advice from lawyers and philosophers, in addition to working to understand the health economic and regulatory processes that are applied in the health system they wish to influence.

Remember there are likely to be allies for the rare disease cause in political institutions and among health administrators. Identifying them and seeking their advice and support is an important tactic.

Examine health policy documents that are developed to guide healthcare for the general population. Often they will contain statements that aim to provide fairly for all of the population, to specifically address disadvantage and disparities in health status. Many of these arguments are directly applicable to the dilemmas faced by rare disease populations and could be usefully rephrased for a rare disease context and quoted back to those you aim to influence.

Practical ways of gaining health provision for rare diseases may be through protected budgets, or protection of rights within an overall budget. There is debate about the preferred option but each can achieve the objective of defending equity in health care provision.

Note that there can be wide variation within countries as well as between countries. Examples from one country can be a useful model system for another. At the same time differences within a country can be useful arguments, whether in relation to social deprivation, remote location, or type of disease, that may give much better care to certain sections of the population, and these may serve as model arguments for dealing adequately for the needs of rare diseases.

It is important to emphasise that the right to health for rare diseases is much more than funding of orphan drugs when they become available. Rare disease policy must provide comprehensively for all aspects, from prevention, diagnosis, early intervention, good general health care and social support, through to orphan drug discovery and funding.

At almost any point in time the greatest benefit to all people with rare diseases will come from rapid improvements to diagnosis and early intervention. After all, that is fundamental to any later gains they may get from discovery of orphan drugs. If a broader range of needs is argued, it may add credibility to the overall case for rare disease policy and action plans, compared to a narrow focus on funding of orphan drugs.

It is fundamental to good provision for rare diseases, that universal healthcare is in place. There are good recent examples of significant improvements to healthcare access in a variety of countries. The Affordable Care Act in the US, and recent significant expansion of health insurance coverage in Mexico and the Philippines, have together given a great boost to the chances that millions of people with rare diseases will survive, get diagnosed, and get their general healthcare needs met. This will build a platform on which the needs specific to their rare disease can be addressed.

In building the mix of arguments that you may use to win the right to health in your country, always keep in mind questions such as: what will we settle for? And what will we trade off?

October 2015, Volume 2, Number 3, Supplement 3

Oral Presentations – OP

OP-01 ICORD's vision and the Yukiwariso declaration: making rare disease issues and policies truly international

John Forman
President of ICORD, New Zealand, john@johnforman.nz

More than 30 years of advocacy and policy development has seen significant advances in the diagnosis, clinical care and therapy development for rare diseases. But these positive gains must be evaluated in the context of limited real gains for the rare disease communities outside of the US, Europe, and a limited number of countries in the Asia Pacific and Latin American regions.

A number of "middle" income countries are now making progress with rare disease policies, yet significant challenges remain in respect of vast numbers of the world's rare disease populations in developing nations.

ICORD's mission includes the aim of promoting research, ethics, policies and actions on rare diseases and orphan products in all regions of the world. New organisations like RDI – Rare Diseases International, and APARDO – the Asia Pacific Alliance of Rare Disease Organisations, also aspire to improve the lives of rare disease patients and their families through rare disease policies and action plans.

To succeed in these aims, ICORD and its allies will need a framework that speaks to the ideals yet also deals with the economic realities and health system challenges. Our Yukiwariso Declaration provides a basic rationale and guidance. The declarations of RDI and APARDO set aspirational goals too. IAPO – the International Alliance of Patients' Organisations, sets Universal Health Coverage as one of its major strategic objectives. Collaborative efforts are needed from all allied groups to produce a rare disease framework that will address the aspirations yet also deal with the reality of the present. Such a framework could appeal to international agencies like the World Health Organisation, the UN Development Agency, and the World Bank. Winning their interest will be an important step towards winning the interest of individual governments across the rest of the world. The challenge for all of us as we work to internationalise rare disease policies and action plans, is to find the policy formula that can offer guidance and solutions for the developing world, rather than raise demands that those countries may see as a difficult burden to address.

Fortunately, some useful models and ideas have been discussed and worked on. The challenge is to develop and extend these in a comprehensive way.

OP-02 Accelerate R&D for diagnostic and therapy of RD: initiatives from the International Rare Disease Research Consortium (IRDiRC) and progresses so far

Ségolène Aymé*, Lilian Lau, Sandra Peixoto, Paul Lasko
*IRDiRC Scientific Secretariat, France

Objectives: Despite considerable advances in the scientific field, genetic disease patient needs are far from covered, both in terms of diagnostic measures and in terms of effective therapies. To ensure that data generated by research is optimally used for the benefit of patients, an international consortium was set up as an initiative of the European Commission and the United States' National Institutes of Health.

Methods: The consortium conducted in-depth discussions with all stakeholders on the obstacles to overcome in efforts to accelerate R&D in rare diseases. This brainstorming period resulted in recommendations for funding agencies and researchers to optimize the use of shared data through database and knowledge accessibility and interoperability, and the adoption of an action plan.

Results: Six actions were launched.

The first consists in promoting the use of ontologies to describe phenomes, essential for clinical databases to become interoperable, and to recommend the adoption of a set of core terms to be included in all terminologies intended to describe rare clinical phenomes.

The second is to support the creation of a data exchange platform, enabling recognition of clinically similar cases according to clinical features or genomic data in efforts to identify new clinical entities, jointly with the Global Alliance for Genomics and Health.

The third is to reach an international agreement on acceptable alternatives methods to conduct clinical trials when the study population is very small.

The fourth is to accelerate the development of criteria to measure treatment effects that are relevant to patients, so-called patient-relevant outcome measures, by federating the efforts of the large organisations already involved in the development of patient-relevant outcome measures for common diseases.

The fifth is to coordinate efforts to develop the use of scientific and clinical data by using dispersed resources, including natural language, for selecting drugs as potential treatment options for rare diseases. Initiatives, both academic and commercial, have bloomed recently, targeted at identifying new therapeutic targets and to repurpose drugs. They leverage on developments in Computational Linguistics and Graph Theory, to build a representation of knowledge which is automatically analysed to discover hidden relations between any drug and any disease, representing possible Modes of Action for any given pharmacological compound. Their efficacy for selecting drugs as treatment options for genetic diseases is already documented.

The sixth action is the creation of "IRDiRC Recommended", a quality indicator, based on a specific set of criteria. Any resource compliant with the criteria set forth is entitled to the label. "IRDiRC Recommended" is a public label which could, and should, be made visible on and by the resource, giving the users a certain guarantee of its quality/appropriateness. IRDiRC encourages the long-term sustainability of the resources and their societal value.

Conclusion: All these initiatives constitute IRDiRC's roadmap which will be presented. The participation from all stakeholders in these on-going efforts is encouraged.

OP-03 Global strategies for rare diseases: the patients' perspective

Paloma Tejada
EURORDIS, Switzerland, paloma.tejada@eurordis.org

The need for an international approach in the field of rare diseases is obvious. Rare Diseases expertise is scarce and scattered. Therefore there is a need to bring together a critical mass of patients and medical experts, scientists and public health authorities.

By bringing everyone together we will be able to map existing expertise; improve diagnosis and access to treatments, organise the provision of multidisciplinary care and delivery of products. Foster cutting edge basic and clinical research, explore unchartered territory, develop new orphan drugs. Encourage public private scientific partnerships, push forward health care and social policies at national regional and international level. This does not go without challenges. There are 6000 -7000 rare diseases with great heterogeneity between them, affecting different organs, presenting different disabilities, present in different age groups. The definition of a rare disease is not exactly the same everywhere. Although there are Orphan Drug Regulations in certain countries, most of the world is desperately lagging behind. The good news is that there are commonalities across all rare diseases. They share many of the same challenges and issues in all parts of the world which allows for common healthcare policies. Now is the right time to do it. In the 21st century, new opportunities are coming into play from translational research, innovative regulatory science, and information technologies to bring more innovative treatments to patients. We are also witnessing a technological revolution that has increased access and flow of information to help overcome "the scarce and scattered problem", encourage partnerships and help create networking opportunities globally.

The Globalisation of Rare Diseases is already underway, as seen by:

- Development of National Plans and Strategies worldwide
- International initiatives in rare disease research (International Rare Disease Research Consortium (IRDiRC), E Rare, ReACT). More investments in rare disease research with increased budgets from the US National Health Institutes and the European Commission
- Increased investments from industry with market exclusivity incentives provided in several legislations (US Orphan Drug Act, EU Regulation (EC) 141/2000 and others
- Pharmaceutical and biotech companies getting organised at the global level
- Increased collaboration amongst international medicines agencies
- Development of international platforms for rare disease registries
- Rare disease patients getting organised across borders

These developments are not happening in a vacuum. Several EURORDIS initiatives have become increasingly international over the past years

- EURORDIS covers 37 countries in Europe and has members in more than 60 countries worldwide
- Over 80 countries participated in the *Rare Disease Day awareness campaign in 2015*
- *The RareConnect* Online Platform has more than 70 international communities
- The European Conference on Rare Diseases & Orphan Products (ECRD) is attracting an increasing number of participants from outside Europe
- EURORDIS has signed agreements with the national patient umbrella organisations in the US, Canada, Japan, Russia

and Australia. Also with the International Federation of Human Genetics Societies (IFHGS)

- Rare Diseases International, the global alliance of patients and families of all nationalities across all rare diseases, launched in May 2015

Our aim is to bring all stakeholders together to build a solid ecosystem at the international level:

- Rare Diseases International
- International Rare Diseases Research Consortium (IRDiRC)
- International Conferences for Rare Diseases and Orphan Drugs (ICORD)

OP-04 Challenges and opportunities for rare diseases and orphan drugs in Latin America – an industry perspective

Alison Joslyn
Shire, Brazil

Rare diseases affect a small number of people but their impact on patients and families is profound. Most people with rare diseases are socially, economically and health-disadvantaged. Lack of awareness among physicians and the general public, missed diagnosis or delays in diagnosis and lack of treatment options and access to treatment are some of the key issues faced by this underserved and often overlooked population.

In Latin America, people with rare diseases face additional challenges with regards to accessing treatments where available. Most countries in the region in general have not created specific, systematic mechanisms for the review of and access to orphan drugs. Once treatments are prescribed, the governments that do finance them do so because of the influence of interest groups or by way of judicial action, with limited criteria and often no prioritization.

Going forward, it is crucial that all stakeholders collaborate to elevate rare diseases as a public health priority at an international, regional and national level. It is imperative that governments, HCPs, patient organisations and industry work together to raise awareness of rare diseases, formulate patient access pathways with appropriate assessment methodologies for orphan drugs, ensure sustainable funding for the diagnosis and treatment of rare diseases and devise policy incentives and frameworks to encourage the development and commercialization of new treatments.

OP-05. Progress on regional laws

Ignacio Burgos
Ex-senator, Coordinator on Rares Deseases in the Assessor Council of the Health Ministry, Spain

In spite of the fact that patients and its associations maintain their needs as a motive and their courage as a method, little will change without the involvement of politicians, either from Parliament or Governmental environments.

Compared with other pathologies, well known and well covered with medications, in the field of rare diseases there is much to know, and consequently much to do. But without Government's intervention it is not possible to favor research with fiscal incentives and sponsorships; to create registers aiming to learn more about the diseases and their phenotypes; to know about their impact and encourage the research of the clinical cases; to state adequate legislation on orphan drugs, which in turn will support research, development and the access with equity; the education of health professionals in all their life stages; to structure health assistance of persons affected by complex diseases, which in occasions are economically catastrophic; to define a social and health model able to respond to the non-strictly health issues being required by these patients and their families; to create and coordinate Reference Centers, at both national and international levels; to define reimbursements mechanisms so as to make them swift and transparent; to establish the mechanisms of integration of scholar, labor and leisure times; to impulse genetic laboratories, as without them diagnostics are not possible even though 80% of cases have genetic origins, to establish protocols regarding Information & communication technologies through which patients could be assisted without requesting displacement, and to inform colleagues and families.

In brief, without a steady political compromise, it will not be possible to achieve all what persons with rare diseases need, even though the country and the continent could provide it. We should not forget that for these diseases the answers should be global. Therefore only with the cooperation of Governments it will be possible to achieve international agreements to foster their development.

The outcome of the Round Table with Latin American political representatives, to be carried out during the 4th Latin American Rare Diseases and Orphan Drugs congress, will be reported at the second session of the Xth ICORD Conference.

OP-06 About the rare diseases (RD) latin american day: building a regional identity

Virginia A. Llera
GEISER Foundation, Argentina, fundgeiser@yahoo.com.ar

The idea of making "RDs a global health issue" is turning rationale and viable at the same time. Notwithstanding, a number of significant factors, such as biological, geographical, socio-cultural, technological, political and economic issues make different the features and priorities of any given RDs. Therefore, how the differences will be managed within a global plan of action?

Certainly, "becoming global" is not an easy task. It should be managed by experts, handled with transparence and care, and with great consideration to the regional priorities. For example, Latin American countries have big concern about accessibility, according to some elementary survey done by us. This critical vulnerability comes from different areas; some of them are the high prices of some imported goods and low local production which challenges the sustainability of the health finances. Under these circumstances the impact in health economy will be more dramatic in the region than in the development countries. In addition, the performance of health assistance systems ranges from excellence to frankly inexistent. This lack of efficiency and structural shortages, challenges the equity of health assistance. The affected citizens and NGOs have few or no support from governments, this increase its vulnerability. Moreover, the lack of a regional cooperation and master plan, plus the imbalanced participation of the different social actors challenge the opportunities.

GEISER foundation first launched in 2002 the concept of uniting different rare diseases and working groups in order to gain visibility and influence in Latin America. Many other organizations emerged in the last 3-4 years. Countries as Brazil, Mexico or Argentina culturally work challenged by distances and some groups may contact more easily to abroad organizations than to the ones in their own place. Also, there are vast populations' remains forbidden in the mountains, forest and plantations, sea-sides, deserts and small towns. Therefore, the messages from the emergent organizations more likely reflect the foreign RDs priorities than locals. A RDs Latin American and Caribbean Day is needed to save the gap. This also will function as a tool to work-out on our own regional problems in the field. Due the oldest official document in the region stating the relevance of groups working for RDs, was dated August 13 2003, it is being selected as the day in which Latin American and Caribbean organizations can fully express their problems, their particularities and achievements. The aim is to enrich the WRDD (February 29) actions by including in it the local works prepared during a previous and specific Day for the region. Also looks after enhancing the concept of being global with originalities, creativity and sense of belonging. The Latin American and Caribbean countries owns huge differences in awareness, opportunities, and feasibilities, financial and socio-cultural aspects with the pioneer countries in the RDs field. Therefore, to achieve a sustainable international cooperation is mandatory to consider all those differences in any action plan. The regional needs and priorities of Latin America can find an expression in the Latin American and Caribbean Day of RD, each August 13, positioning the regional as a peer of others while working for becoming global.

OP-07 Rare diseases – our ethical responsibility

Mariana Kruger
Department of Paediatrics and Child Health, Tygerberg Hospital, Stellenbosch University, South Africa, marianakruger@sun.ac.za

Dealing with rare diseases have many challenges including both lack of effective medicines, as well as therapeutic access. Public health policies usually adopt a utilitarian approach in health care resource allocation, whereby the greatest number of patients shares the greatest good. The key question to ask is whether it is ethical to allow benefit to one patient but no benefit to another based on the prevalence of the disease? To answer the question it is important to investigate the underlying ethical arguments to determine health care resource allocation in general and attempt to determine fair resource allocation for rare diseases. A key concept is distributive justice, which according to Aristotle, is a need for proper distribution of benefits and burdens in society. According to Rawls' theory of justice the greatest benefit should go to those most disadvantaged. To attempt to apply this in health care resource allocation, it is important to determine "accountability for reasonableness" (Daniels 1988). This requires decision makers to reach consensus about the goals of health care delivery. For rare diseases it is necessary to agree that the therapeutic goal is to offer reasonable a normal range of opportunity. A careful cost-effective analysis of the intended therapy will provide information about the both the effectiveness and safety, as well as the possibility of a normal range of opportunity. The proposal is therefore active documentation of effective, safe therapy, as well as research for novel efficacious therapies and to ensure access to these therapies. To improve access such efficacious medicines for rare diseases should be included in the WHO Essential Drug List (EDL), which is a guideline about medicines intended to save lives and improve heath. By inclusion, guidance is given to countries to budget for these medicines for rare diseases with improved access. In conclusion it is our ethical responsibility to actively advocate for rare diseases in the face of existing effective therapy to ensure fair access to all.

OP-08 A short introduction to metabolic disorders

Stephanie Sacharow and Olaf Bodamer
Boston Children's Hospital and Harvard Medical School, Boston, USA, stephanie.sacharow@childrens.harvard.edu

Alkaptonuria was identified as one of the first inborn errors of metabolism (IEM) by Archibald Garrod in 1902 who recognized its autosomal recessive inheritance. Garrod coined the term "chemical individuality" as one of the driving forces for selection and evolution. The advent of novel analytical techniques led to the molecular and biochemical characterization of known IEM and the delineation and recognition of novel clinical phenotypes some of which were presumed not to be due to IEM. The completion of the first draft of the human genome in 2001 and the subsequent "genomics revolution" laid the foundation for the successive identification of many additional IEM through next generation sequencing bringing the total number of catalogued IEM to more than 1500.

IEM occur in all populations, although their incidence and prevalence rates may vary substantially due to differences in carrier rates. Founder mutations in different populations (Ashkenazi Jews, Amish and others) may lead to a relative increase in recessive mutant allele frequency. Knowledge of carrier frequencies is essential for preconception genetic counseling. While IEM are individually rare, their cumulative frequency can be as high as 1:500 or higher in some populations.

IEM are monogenic conditions that follow autosomal recessive or dominant, X-linked recessive or dominant or mitochondrial inheritance pattern. The existence of genetic and/or environmental modifiers contribute to the inter-individual or intrafamilial variability of phenotypic expression, although for most IEM these modifiers remain elusive.

The severity of any given IEM depends on the degree of enzyme deficiency and the complex interaction of the underlying pathogenic mutations, genetic modifiers and environment. Hypomorphic mutations may not lead to overt disease until adulthood whereas severe mutations in the same gene may lead to infantile onset disease associated with significant morbidity and mortality. The underlying pathophysiologic mechanisms may contribute individually or in combination to the disease state. Complete blockage of a catabolic pathway may result in accumulation of toxic substrates, activation of secondary minor pathways and/or a relative shortage of downstream products. As a consequence, different organs may be affected by the same metabolic defect.

IEM typically affect multiple organs and in more than 50% of cases the central and/or peripheral nervous systems and/or muscles. One or more organ manifestations may dominate the clinical phenotype, although oligo-symptomatic cases may occur. The clinical phenotype represents a continuous clinical spectrum ranging from the severe end, presenting during infancy, to the mild end of the spectrum, presenting during adolescence and/or adulthood. Recent data from newborn screening programs suggest much higher incidence rates for some inborn errors of metabolism due to the detection of a high rate of mild cases who may never develop disease related signs or symptoms. Some clinical signs are pathognomonic for IEM, while others should raise the suspicion for the presence of an IEM. IEM can be classified based on the underlying pathomechanism, on the nature and/or localization of the protein involved or on the clinical phenotype. The most logical classification is based on the nature and/or localization of the affected protein and pathway.

OP-09 Ongoing trends in inborn errors of metabolism research

Luis Alejandro Barrera
Javeriana University and San Ignacio Hospital, Bogotá, Colombia

The research on inborn errors of metabolism (IEIM) have focused in new alternatives for the diagnosis and treatment, and in advancing of the understanding of the mechanism of the diseases using the new tools of genomics, proteomics and metabolomics. In the diagnosis, significant improvements have been made in the early diagnosis of IEM using the tandem mass technique, that allows the assay of more than 40 different diseases in a drop of blood of a newborns and it may be expanded even further. The possibility of fast sequencing the whole genes or the coding parts of the genome, at affordable prizes, has enabled the discovery of new mutations responsible of IEM and confirmation of the diagnosis of IEM in disease´s variants in which the activity of the enzyme is not conclusive, or in asymptomatic cases of late onset variants. However much has to be learned about natural history of diseases and epigenomic factors in order to be able to use molecular data to accurately predict the relevance of the molecular findings for the outcome of the disease. The possibility of analyzing the enzymes in one drop of dried blood taken in filter paper has increased the diagnostic possibilities and now it is feasible to send samples for screening and diagnostic porpoises from very remote areas to specialized laboratories, with optimization of resources in the health systems. In the therapy the efforts have focused in enzyme replacement therapy (ERT), which in brief is the use of enzymes synthetized via recombinant technology in mammalian cells, bacteria or yeast and more recently in plants in order to produce safe and effective therapeutic proteins for human use at lower costs. The ERT besides being extremely expensive, is temporary and has been developed only for less than ten lysosomal disease. The efforts are directed to produce multimeric proteins which are the vast majority of the ones needed for therapeutic uses. The advances in the use of small molecules such as chaperons and substrate synthesis inhibitors that reach brain and bones are promising approaches to be used in combination with other approaches. In gene therapies the efforts are mainly concentrated to produce vectors of viral or chemical origin that insert in places of the genome

where there are no risks of activating or deactivating other genes. The advances have led to the authorization of three therapies for clinical use, and there are more coming to the market in the near future. The recent news of gene therapy done in germinal cells should arise again an intense debate about the dangers of non-controlled permanent modifications of the genome in human beings. The use of bioinformatics permits partially or completely silencing of enzymes to mimic IEM, and study the effect of a defective enzyme on the related metabolic pathways, energy production, and on the overall function and survival of the cells and the whole organism.

OP-10 Inborn errors of metabolism – a biopharmaceutical industry perspective

Fernando Royo
Fundación Genzyme, Spain

Besides rare cancers, inborn errors of metabolism are the area which has triggered more therapeutic R&D initiatives, and successfully lead to new orphan medicinal products. Moreover, it is also the area where the broadest range of therapeutic approaches has been proposed and successfully developed.

From the simplest -and by now well established - **dietary management** with

- restriction of absorbable offending substrates (specific aminoacids in PKU, maple syrup urine disease, organic acidemias and urea cycle disorders), and/or
- administration of "medical foods" (Phe-exempt products for PKU, lactose & galactose-exempt in galactosemia) and/or
- specific supplements (arginine or citrulline in urea cycle disorders, carnitine in organic acidurias, betaine in homocystinuria, cornstarch in some glycogen storage diseases),

to **pharmaceutical intervention** through

- chelators of absorbable offending substrates (zinc acetate in Wilson's disease, penicillamine in cystinuria),
- metabolic pathways diversion (phenylacetate and benzoate in various urea cycle disorders, mercaptamine in cystinosis),
- substrate synthesis inhibition (nitisinone in type 1 tyrosinemia, miglustat and eliglustat in Gaucher's disease)
- stimulation of residual enzyme activity through
  - activation (carglumic acid in N-acetylglutamate synthase deficiency, sapropterin dihydrochloride [BH_4] in PKU) or
  - stabilization (tafamidis meglumine in familial amyloid polyneuropathy);
- hormone supplementation (somatropin in Prader-Willi syndrome, adrenal hormones in X-ALD) or
- enzyme replacement at various sites, from
  - the intestinal lumen (sacrosidase for congenital sucrase-isomaltase deficiency) to
  - plasma (pegademase [PEG-ADA] in ADA-SCID),
  - all the way down to the lysosomes of specific cell lines (imiglucerase for Gaucher's, agalsidase for Fabry's, and alglucosidase for Pompe's diseases, laronidase, idursulfase and galsulfase in MPS-I, II and VI, respectively)

until the most **advanced therapies**, current frontiers of medicine, such as

- transplantation of allogeneic bone marrow/hematopoietic stem cells (ALD, MPS-I, Krabbe's disease), liver (severe porphyrias and urea cycle disorders) and/or kidney (severe glycogen storage diseases, methylmalonic acidemia, oxalosis) or
- gene therapy (T lymphocyte-directed in ADA-SCID, alipogene tiparvovec [Glybera®] in severe lipoprotein lipase deficiency)

Of course, the patients' accessibility to these treatments is equally diverse, depending not only on strictly medical, but also on societal and economic factors, that often determine the feasibility of a prompt and accurate diagnosis, and subsequent access to specialized and comprehensive management.

With respect to some of the new, most innovative drugs, its high price is a growing concern for healthcare administrators, in emerging as well as in the most developed economies. However, without an adequate return on investment, R&D in rare diseases would probably fall back to its pre-orphan drug legislation(s) dormant state.

Regulatory re-consideration of the targeted disease(s) in molecular biology terms could provide a way to increase the cost-effectiveness of R&D, as some promising IND's tackle pathogenic mechanisms underlying not just one, but many –even hundreds- rare diseases.

Also, given the extreme rarity of many of them, the economical issues are often more linked to local, immediate affordability than to the overall sustainability of healthcare systems, and therefore amenable to joint cooperative approaches and equally innovative pricing and reimbursement schemes.

OP-11 Prevention of birth defects: new opportunities for the 21st century

José F. Cordero
College of Public Health, University of Georgia, USA

Birth defects are a leading cause of infant mortality in most high and middle-income countries of the world. The 20th Century witnessed major developments in biomedical research that led to a better understanding of the pathogenesis, genomics, and environmental factors linked to birth defects. Prevention of birth defects worldwide became a reality with the discovery that preconceptional use of folic acid lowers the risk of anencephaly and spina bifida, both known as neural tube defects. Fortification of cereal grains, as a public health prevention strategy, resulted in increased consumption of folic acid in the population and a marked reduction in the rate of neural tube defects where it was implemented. Some countries, like Costa Rica, fortified other food products, such as milk, rice, and corn flour with similar success. Much remains to be done to ensure the benefits of preconceptional folic acid consumption. In some countries fortification with folic acid has not been implemented because of lack of political will, and in others because limited resources or lack of a common staple or vehicle to deliver folic acid.

A major lesson from the folic acid public health experience is the recognition that the best opportunity to prevent serious birth defects is before pregnancy begins. There are multiple opportunities for preconceptional prevention strategies, as described by the 2006 US Centers for Disease Control and Prevention report on preconceptional care. They include addressing maternal conditions, such as diabetes and other chronic diseases, avoiding environmental and occupational exposures, maternal vaccination against rubella, and other specific strategies. The challenge for implementing preconceptional prevention of birth defects and other adverse pregnancy outcomes worldwide is that nearly half of pregnancies are unintended and there infrastructure for access to health care may be lacking in many middle-income and most low-income countries. That reality calls for strengthening access to health care and reproductive health programs, as well as expanded community education on the benefits of preconceptional care.

OP-12 European recommendations on policies for the primary prevention of congenital anomalies

Domenica Taruscio, Pietro Carbone, Alberto Mantovani
Istituto Superiore di Sanità, Italy, domenica.taruscio@issit

Congenital anomalies (CA) are the paradigm example of rare diseases liable to primary prevention actions due to the multifactorial etiology of many of them, involving a number of environmental factors together with genetic predispositions. Yet despite the preventive potential, lack of attention to an integrated preventive strategy has led to the prevalence of CA remaining relatively stable in recent decades.

CA are a major cause of perinatal mortality, childhood morbidity and chronic disability, with a total prevalence of 2.5% of births. Most CA are Rare Diseases (<5 per 10,000 population). The live birth prevalence of rare CA in 2010 was 96.2 per 10,000 births, extrapolating to approx 4.7M affected persons in the EU, 12-15% of the total estimated persons affected by Rare Diseases.

Primary prevention of CA is feasible because scientific evidence points to several risk factors (e.g., obesity, infectious and toxic agents) and protective factors (e.g., folic acid supplementation and glycemic control in diabetic women). Evidence-based community actions targeting fertile women can be envisaged, such as risk-benefit evaluation protocols on therapies for chronic diseases, vaccination policies, regulations on work place and environmental exposures as well as the empowerment of women in their lifestyle choices. A primary prevention plan can identify priority targets, exploit and integrate ongoing actions and optimize the use of resources, thus reducing the health burden for the new generation.

Two European projects EUROCAT (www.eurocat-network.eu) and EUROPLAN (www.europlanproject.eu) have joined efforts to provide the first science-based and comprehensive set of recommendations for the primary prevention of CA in Europe.

The recommendations exploit interdisciplinary expertise encompassing drugs, diet, lifestyles, maternal health status, and the environment. The recommendations include evidence-based actions aimed at reducing risk factors and at increasing protective factors and behaviors at both individual and population level. Consideration is given both to topics specifically related to CA (e.g. folate status, teratogens) as well as to risk factors of broad public health impact (e.g. obesity, smoking) which call for specific attention to their relevance in the pre- and periconceptional period. The recommendations, reported entirely in this paper, are a comprehensive tool to implement primary prevention into national policies on rare diseases in Europe. Primary prevention of CA can be achieved here and now and should be an integral part of national plans on rare diseases.

References

Taruscio et al. European recommendations for primary prevention of congenital anomalies: a joined effort of EUROCAT

and EUROPLAN projects to facilitate inclusion of this topic in the National Rare Disease Plans. Public Health Genomics. 2014;17(2):115-23.

Taruscio et al. Primary prevention of congenital anomalies: recommendable, feasible and achievable. Public Health Genomics. 2015;18(3):184-91

OP-13 Patients' voices: international cooperation within patient groups. Why, who and how?

Gema Chicano Saura

EURORDIS, Spain, gema.chicano@eurordis.org

International cooperation amongst patient groups should increase the awareness of law and international treaties related to human rights.

International cooperation should respect the physical and mental integrity, human dignity and equality protection under the law, for the good of all people living with rare diseases in the world.

Several conditions should be fulfilled in the area of rare diseases: adequate financial resources (public, private or its own source of funding), political will, and in my opinion, it is necessary to use existing European and national initiatives.

The current economic situation has changed fundraising to a mixed model for the rare diseases. Economic diversification is the key to guarantee the independence of patient associations.

In this context, it is necessary to guarantee transparency, credibility, independence and confidence in fundraising. Therefore, a code of ethics should be established, which develops general goals and specific goals with the companies and the pharmaceutical industry.

As for data protection, in today´s globalized and digital world, informed consent, genetic analysis, data protection, registrations, medical confidentiality and so forth, are very important in the patient´s rights to privacy, freedom from discrimination, right to equality before the law, patient autonomy, justice and responsibilities in health care.

OP-14 The NIH undiagnosed diseases program: Medicine for the 21st century

Cynthia Tifft

National Institutes of Health (NIH), USA

The NIH Undiagnosed Diseases Program (UDP) was launched to fulfill the unmet need of patients with rare or unique symptoms whose diagnostic odyssey had stretched from months to years and sometimes decades. During the first 7 years the program received 7500 inquires, carefully evaluated the 2800 complete medical records it had received, and accepted 780 patients for an extensive, week-long evaluation at the NIH Clinical Center. Clinical acumen, single nucleotide polymorphism analysis and exome sequencing of patients and their family members led to a diagnosis in ~25% of patients. The diagnosis of rare or unique diseases in this population has informed our understanding of more common diseases and has expanded the phenotypic spectrum for a variety of extremely rare disorders. The overwhelming success of the UDP has created enthusiasm for an expanded Undiagnosed Diseases Network funded by the NIH Common Fund to include a Coordinating Center, 6 additional clinical sites, 2 core sequencing centers, a metabolomics core and a model systems core, engaging basic scientists poised to study potential disease-causing genetic variants associated with previously undescribed human conditions. To respond to the desperate need of undiagnosed patients globally, the NIH Undiagnosed Diseases Network has hosted two international conferences on rare and undiagnosed diseases to synchronize clinical evaluations and facilitate data sharing.

OP-15 Updates on recent changes in incentives for rare disease drug development in the United States

James H. Reese
Office of Orphan Products Development, FDA, USA

The Orphan Drug Act has provided incentives to drug developers in the United States since 1983. A brief overview of the incentives will be provided followed by a more thorough discussion of recent changes and additions to the incentives program. These changes include changes to the Orphan Grant Program, the Pediatric Rare Disease Designation program, the Pediatric Device Consortia Program, changes in device incentives, and others.

OP-16 Rare diseases in Mexico: Regulatory environment

Fernando Fon
AMIIF Rare Diseases Working Group, AMIIF, Mexico, ffon@amiif.org.mx

Rare diseases as a single pathology are far from being understood in general by the society, but as a group of more than 7,000 different illnesses that could affect more than 350 million people worldwide1 it is impossible to deny its importance. In Mexico, the General Law of Health added a statement in 2012 to include the definition for orphan drugs and at the same time a definition of rare disease in terms of its prevalence.

Some countries have made the decision to promote a better knowledge of rare diseases; but they have also designed strategies to protect and to reward the research and development of treatments for these diseases. In the USA, the Orphan Drug Act (ODA) enacted in 1983, has permitted the approval of 486 orphan products to treat 289 diseases. On the other hand, in Mexico, as in many other countries, it is not clear enough how the burden of rare diseases are affecting the society and we have no certainty on their real impact into the national productivity.

Recently, the regulatory agency Cofepris (*Comisión Federal para la Protección Contra Riesgos Sanitarios*), implemented several strategies focused on giving early access of innovative and generic medicines to the Mexican market. It is now possible to become the first country worldwide for a new product registry. Cofepris has been recognized as a Reference Sanitary Agency by the Pan American Health Organization (PAHO) for medicines and vaccines and by the World Health Organization (WHO) for vaccines.

In Mexico, the history of regulation for orphan drugs started on the first decade of this century. We have 55 products recognized as orphan drugs by Cofepris since 2009. On the other hand, only 18 (32.7%) of these medicines have been included into the National Health Formulary and some of them are available into the health public institutions (e.g. IMSS has 9 (16.3%) products)

From the perspective of AMIIF (*Asociación Mexicana de Industrias de Investigación Farmacética A.C.*), the Innovation Pharmaceutical Industry Association in Mexico that represents 43 companies in the sector, this is the right time to work not only with Health authorities and other officials, but also with all sectors, public and private, including patient advocacy organizations, healthcare professionals, care givers and others, in order to assure access for the treatments for rare diseases. We should always remember: we all are patients.

OP-17 The NIH/NCATS GRDR® Program – Global Rare Diseases Patient Registry Data Repository: Linking patient registries data to bio-specimens data

Yaffa R. Rubinstein
National Institutes of Health (NIH), USA

The NIH/NCATS/GRDR® Program goal is to establish a large global Web database of de-identified rare diseases patient data. The data would be integrated in a standardized manner to facilitate interoperability with other databases as well as data exchange and sharing. The ultimate goal is to accelerate the development, dissemination and of new knowledge to improve the health and quality of life for millions of people.

The GRDR program is divided into two main arms:

1. Development, Engagement, Demonstration and **Dissemination** of tools and resources. Develop tools and resources such as: Common Data Elements (CDEs), informed consent template, GUID, patient registry template, Institutional Review Board

(IRB) services, and recommendations.

Engage with all stakeholders such as patients and their families, patient advocacy groups, academia, and the private sector including pharmaceutical companies to create a network for collaboration and linking to other databases.

Disseminate resources, tools, data, information, recommendations and acquired knowledge through collaboration and communications including publications, the media, conferences and meetings.

2. GRDR® Data Repository. The GRDR data repository will include developing a global Web database of de-identified rare and common disease patient information and integrating the data from patient registries, Electronic Health Records (EHR) and other data sources. The aim is to provide a resource for a range of biomedical studies including clinical trials. The GRDR program will facilitate linking patient data to bio-specimens data through the use of Global Unique identifier-GUID.

OP-18 Medical ontologies and registering activities. What are their added values?

Posada M., Alonso V., López E.

Institute of Rare Diseases Research (IIER-ISCIII), Spain, mposada@isciii.es

In computer science, the word "ontology" is used to describe a structured, automated representation of the knowledge within a certain domain in fields such as science, government, industry, and healthcare. Therefore, ontologies describe concepts in the world or some domain, some of their properties and how the concepts relate to each other. Thus, ontology can be used to define a standard, controlled vocabulary for a scientific field; for example, ontologies can assist in the standardization of data stored in patient registries.

Patient registries are resources which store, preserve and update patient information on personal data, type of disease, clinical features, phenotypes, genotypes, treatments and follow up, among some other information, that is used for scientific, clinical or policy purposes. Usually, this information is stored in databases that contain diverse fields, attributes or elements. The standardization of signs, symptoms, and clinical phenotypes stored in fields of patient registries can be achieved through international medical classifications or languages, such as UMLS, SNOMED-CT, among some other terminologies. More recently, the use of phenotype ontologies is becoming one of the most promising tools for phenotype standardization.

The Orphanet Ontology (ORDO) and the Human Phenotype Ontology (HPO) are the most widely used phenotypic ontologies in the field of rare diseases. While ORDO is used to designate complex phenotypes (diseases), HPO is used to describe the clinical phenotype observed in patients (signs and symptoms). Both ontologies have established mappings among their terms and also with other databases, classifications or terminologies, such as LDDB, PhenoDB, MedDRA, MeSH, SNOMED-CT, ICD and UMLS. The establishment of these mappings to other phenotype vocabularies allows integration of existing datasets and interoperability with multiple biomedical resources.

Therefore, phenotype ontologies might be useful for describing the disease by providing standardized phenotypic terms to the registry and also for interoperating with other information systems and/or registries (including electronic medical records). In all of these scenarios, mappings between clinical items, phenotype items and standardized terms should be carefully addressed, especially when we are facing on historical information. In this regard, it is necessary to understand how clinical signs and symptoms are fed into registry's common data elements and how common data elements need to be defined in order to allow for interoperability with other registries. In addition, it would be important to consider how phenotypes are defined or constructed and how ontologies help to standardize them. For undiagnosed cases, phenotype ontologies also could be used for assisting in differential diagnosis by means of HPO-based tools such as Phenomizer, Phenotips or Phenome Central.

Because patient registry fields are related not only to phenotypic traits, it may be necessary to consider other registry elements as well. The other fields could provide relevant information for researchers, which could be critical for the diagnostic process. This additional information could be standardized through the utilization of other biomedical ontologies, such as ontologies related to pharmaceutical issues, anatomy ontologies, etc.

OP-19 The Rare Diseases Clinical Research (Rdcrn) Program: A model for international collaboration to facilitate multi-site clinical research

Rashmi Gopal-Srivastava
Office of Rare Diseases Research, National Institutes of Health (NIH), USA, gopalr@mail.nih.gov

Any disease which has a prevalence of less than 200,000 in US is defined as a rare disease. To facilitate multi-site natural history studies and clinical trials for rare diseases, the Office of Rare Diseases Research (ORDR), at the NCATS, established the Rare Diseases Clinical Research Network (RDCRN) program. The RDCRN is an innovative and successful international clinical studies network of 22 distinct clinical research consortia and a central Data Management and Coordinating Center (DMCC). The goal of RDCRN is to contribute to the clinical research and treatment of rare diseases in a collaborative manner to identify biomarkers for disease risk, disease severity and activity, and clinical outcome, while encouraging the development of new approaches to diagnosis, prevention, and treatment. Collectively, the RDCRN is studying 282 rare diseases in natural history and clinical trials at 253 clinical sites located in the US and in 17 countries with more than 130 patient advocacy groups (PAGs) as research partners. There are 2,937 collaborative consortium members. Collaboration with international sites has helped in reaching the goals of the network. RDCRN productivity is testament to the efficacy of this model having enrolled 32,019 patients with rare disorders in more than 90 active protocols and trained 208 investigators.

Each consortium is required to conduct two multi-site clinical studies on a minimum of three related rare diseases, develop a training program for new investigators, involve PAGs as research partners and provide Website information about rare diseases to healthcare professionals, investigators, patients and general public. The RDCRN-DMCC supports consortia by providing technologies, tools to collect standardized clinical research data and support for study design and data analysis. It coordinates site visits for auditing individual consortia sites and monitors network protocol adherence, data collection and data submission. It also oversees and maintains RDCRN Patient Contact Registry. RDCRN has generated new diagnostic methods, facilitated gene identification and new therapies. By creating collaborative multi-site research consortia consisting of PAGs, academic researchers from domestic and international sites and project scientists from NIH as collaborators, the RDCRN has demonstrated that collaborative effort can accelerate research initiatives and expand access to research for affected individuals. Through these collaborative research consortia, the RDCRN has proven to be an effective and working model to maximize investigator participation including international sites, initiate clinical trials, facilitate patient recruitment, accelerate young investigator training and engage patient support, enabling pharmaceutical industry and government sponsored clinical studies to proceed with a supportive infrastructure to complete the clinical studies in a timely fashion.

OP-20 Example of a successful R&D collaboration: The RIBERMOV Latin-American collaboration on movement disorders in the genomics era

Antoni Matilla Dueñas
Universitat Autònoma de Barcelona, Spain, amatilla@igtp.cat

RIBERMOV is the acronym for a thematic network funded by the Iberoamerican Program of Science and Technology for Development (CYTED) during the period 2010-2013 within the Health Area. RIBERMOV aimed to establish an Iberoamerican multi-disciplinary collaboration to increase the etiological knowledge in two inherited movement disorders such as Parkinson's Disease and the Spinocerebellar Ataxias among the eight participating countries: Argentina, Brazil, Chile, Cuba, Ecuador, Spain, Peru and Portugal. The acquired knowledge was applied for implementing new molecular diagnostic tools and developing therapeutic strategies. Among the main objectives and results of RIBERMOV included:

1. Clinical Research was promoted in the thematic network. Methodologies were standardized in order to implement clinical, epidemiological and interventional studies. Information systems were implemented to include the Hospital records of clinical information with natural histories and epidemiological data. DNA samples for each registered individual were collected and a BioBank network for biological samples was created for the study of these pathologies.
2. The epidemiological impact, prevalences, and risk factors for these diseases in each participating country were studied.
3. Diagnosis and genetic counseling were implemented as preventive measures. Family studies were carried out using linkage, disequilibrium and wide-association genetic studies to identify new disease genes and causal deficits. Modifier genes were identified. Genotype-phenotype correlations were performed to identify causal molecular defects and potential neurophysiological biomarkers. Collaboration with industry was implemented to develop diagnostic tools.

4. Clinical studies were complemented with basic research aimed to increase our knowledge of the underlying physiopathological molecular mechanisms. New risk factors including modifier genes were identified to explain the clinical variability with subsequent applications for the prognosis.
5. New molecular pathways and biomarkers were identified and characterized using molecular tools, structural biology, proteomics and transcriptomics studies to increase our knowledge of the underlying mechanisms to assist in diagnosis, prevention, and the design and establishment of therapeutic strategies.
6. Collaborative pre-clinical and clinical assays were implemented for the studied pathologies.
7. Training and exchange of research specialists were implemented along with the transfer of knowledge and technologies among the participating countries in the various disciplines of Clinical, Epidemiology, Genetics, and Basic Research. European standards were implemented in the Latin-American participating groups for genetic and clinical protocols as well as in the regulations on consent and confidentiality in data processing, and for the use and shipment of biological samples.
8. An interactive platform was generated for the exchange and dissemination of knowledge, results, ideas, and for discussing projects or needs of each group and that of other groups in Latin-American countries.

Conclusion: RIBERMOV is a clear example of a successful R&D collaboration among Latin-American countries. Albeit the network was funded by CYTED for the period 2010-2013, the successful and fruitful scientific still ongoing collaboration among the Latin-American partners demonstrate that supporting collaborative research networks, particularly dedicated to rare diseases, can result in increased R&D funding as well as invaluable return and translatable output to benefit patients.

OP-21 The Genetic and Rare Diseases Information Center (GARD): Twelve years of improving access to hard-to-find genetic or rare diseases information and resources

Janine Lewis
National Center for Advancing Translational Sciences, USA, janine.lewis@icfi.com

The Genetic and Rare Diseases Information Center (GARD) provides the public with access to current, reliable, and often hard-to-find information about rare or genetic diseases in English or Spanish. GARD is funded by two components of the National Institutes of Health (NIH), the National Center for Advancing Translational Sciences' Office of Rare Diseases Research (NCATS-ORDR), and the National Human Genome Research Institute (NHGRI).

Over the last 12 years, the GARD Information Center has responded to more than 52,000 requests for rare or genetic disease information. Patients and their family members or friends make up two-thirds of the people who contact the Information Center. Another 10% are health care providers. GARD currently receives approximately 400-500 inquiries per month from inquirers throughout the globe. Questions are answered by experienced Information Specialists that include genetic counselors and a medical geneticist. Medical advisors with extensive experience in rare or genetic diseases are also available. GARD Information Specialists provide each user with a custom response via toll-free hotline and/or personalized written responses to inquiries including plain language disease summaries, NIH and other federal resources, high quality vetted Web resources, advocacy organizations, clinical trials, genetic services, and more.

The GARD Information Center's Website also provides access to an extensive database of information and resources at http://rarediseases.info.nih.gov. More than 6,600 diseases has its own Web page where GARD Information Specialists post answers to de-identified questions from the public and a variety of resources including disease management guidelines, CLIA-certified genetic testing laboratories, FDA approved medical products, Human Phenotype Ontology signs and symptoms, patient advocacy groups and more. An interactive GARD Information Navigator tool is also available for diseases about which GARD has received many questions to help people find and learn more about the resources available on the site. This tool can be accessed by clicking the "Need Help" button at the top of the disease page. The GARD Website received approximately 200,000 visitors per month.

The GARD Information Center's experienced Information Specialists and growing online collection of resources are useful for patients, health care providers, and others to quickly find high quality information, resources and services to support individuals living with a rare or genetic condition.

Poster Presentations – PP

PP-01 Research on rare disease medical security system

Ni Huping
Zhejiang Provincial Administration of Human Resources and Social Security, Hangzhou, China, nihuping@163.com

Rare diseases refer to diseases with extremely low incidence. The social security system for rare disease shall have unique features to meet the requirement of rare disease patients. In this abstract, we propose a system for rare disease patients in China. We have concluded the system as having; 1) Responsible party, 2) Priorities, 3) Mechanisms and 4) Layers. The details of each feature are described as follows:

1. Responsible party. In the proposed system, the government should be the responsible party for providing or overseeing the social security products to rare disease patients. The social and medical security services for rare disease are public goods, so its supply could not be relied on the private sector, individuals or charity groups. Government intervention is needed to ensure the services and resources provided to rare disease patients are fair and balanced.
2. Priorities. The system should focus on solving two problems. The first priority is to secure the drug supplies to rare diseases that are diagnosable and treatable. The second priority is to make a list of rare diseases where the treatment cost will be covered by the responsible party. The enrolment into the list is based on public perception of the disease, the affordability of public funding, as well as the severity of diseases.
3. Mechanisms. First, we propose a fund raising mechanism for rare diseases. Funds could be drawn from the existing medical insurance fund and public financial fund. Funds from charity groups can be utilized as supplements. Second we propose a reimbursement mechanism, in which the out of pocket payment of patients should be kept to minimal to avoid catastrophic health expenditure as a result of high-priced orphan drugs and life-long treatment. At last, we propose an evaluation mechanism in which not only health economics data but also disease severity and public perception of disease will be considered for reimbursement decisions.
4. Layers. We propose to combine different existing insurance schemes, using them as layers to achieve complete or near complete reimbursement for rare disease cost. The first layer is the National Basic Medical Scheme which should reimburse the cost for basic diagnostic and treatment procedures or drugs that are already reimbursable within the scheme. The second layer is the National Insurance for Critical Illness. The scheme should partially reimburse the cost for orphan drugs or other high-priced drugs that proved to be effective. The third layer is the National Health Aid. Depending on the sustainability of government funding, this fund could cover the remaining expenditure of rare disease patients after the reimbursement from the first two layers. At last, if there still are large costs remaining for the patients, the fourth layer, which is the charity fund or government financial fund should review individual cases and provide adequate aids.

PP-02 Differential tau processing and aggregation distinguishing among progressive supranuclear palsy and Alzheimer's disease.

Alejandra Martínez-Maldonado[1], Flor Villalobos-Escobedo[1], Vannessa Ibarra-Bracamontes[1], Isidre Ferrer[2], Margarita Carmona[2], María Eugenia Mendoza-Garrido[1], José Luna-Muñoz[3], Raúl Mena-López[1], Benjamín Florán-Garduño[1].
[1]Departamento de Fisiología Biofísica y Neurociencias, CINVESTAV, Mexico City, Mexico;
[2]Instituto de Neuropatología del Hospital Universitario de Bellvitge, Barcelona, España;
[3]Banco de Cerebros LaNSE, CINVESTAV, Mexico City, Mexico, bflorán@fisio.cinvestav.mx

Progressive supranuclear palsy (PSP) is a rare neurodegenerative disease with late onset of supranuclear gaze palsy, postural instability, rigidity and progressive mild dementia symptoms. Nonmendelian genetic risk factors exist, but PSP is almost entirely sporadic, with a prevalence from five to six persons per 100000, a mean onset age of 63, and a median survival of 7 years. PSP is neuropathologically characterized by neuronal loss, astrocytic gliosis with accumulation of plaque and immunoreactive tau tangles within specific brain areas. These accumulations have been well studied in Alzheimer's disease (AD), where tau accumulates in the neuronal soma and they are generated by a series of post-translational modifications: hyperphosphorylations and endogenous proteolysis involved in the genesis of paired helical filaments (PHF) that constitute neurofibrillary tangles (NFTs).

Objective: To analyze posttranslational modifications (truncation and phosphorylation) of the tau protein in Progressive Supranuclear Palsy and compare them with those described in AD to determine their involvement in the formation of the NFTs.

Methods: Human brain tissue sections of hippocampus (10 microns thick) from three cases of PSP patients and three

cases of AD patients were analyzed by confocal microscopy. Double and triple immunostaining with antibodies as well as the use of thiazine red (TR) dye (related to filaments with beta-sheet conformation and used to monitor the state of polymerization of tau) allowed recognizing specific epitopes of phosphorylation and truncation.

Results: We observed that tangles represent the higher aggregation of pathological tau in AD. We also detected a population of NFTs mostly with a balloon-like morphology in PSP cases unlike in AD cases which are characterized by flame shaped NFTs. This population of balloon-like NFTs is characterized by a high expression of N and C-terminal phospho-tau. It showed a great affinity towards TR which corresponds to the initial stages of processing of tau in AD. In AD fibrils are formed by peptides truncated in Glu391 and Asp421 and these fibrils form the PHF. However, in the PSP cases the fibrils did not contain these truncations.

Conclusions: The meaning of the balloon-like morphology of NFTs in PSP requires more study, but changes in neural shape before the higher level of tau aggregation can probably occur since immunoreactivation of these tangles is the same as in AD. Our results suggest that PSP and AD have common processes in the metabolism of tau protein with respect to neuronal fibrillar degeneration.

PP-03 Are rare diseases registries worth it – administrators' point of view

Miteva-Katrandzhieva Tsonka[1], Manuel Posada[2], Stefanov Rumen[1]

[1]Institute for rare diseases, Plovdiv, Bulgaria, miteva@raredis.org

[2]Instituto de Salud Carlos III, Madrid, Spain,

Introduction: The use of observational data methods, including prospective patient registries, is a critical tool in building a comprehensive knowledge base for rare diseases. Nevertheless the registries require combined efforts of all stakeholders plus considerable human, material and financial resources. Logically arose the question "Is it worth spending these resources on assuring the sustainable development of the existing registries?"

Objectives: The survey aim was to answer the question by representing registry administrators' opinion.

Methods: The used questionnaire was included three groups of questions: 1) respondents' socio-demographic characteristics; 2) personal opinion of the respondent regarding issues related to the usefulness of epidemiological rare diseases registries and 3) issues related to the creation, purpose and activities of the registry managed by the administrators.

Results: The questionnaire was fulfilled by 79 administrators. 71 (89.9%) registries were administered within the EU and 8 (10.1%) operated outside the EU. A well-designed registry provides an infrastructure that can support different needs and eliminates barriers to scientific progress. For the majority of registries (60 registries, 75.9%) respondents answered positively to the question whether the registry objectives had been achieved. It was stated that the objectives were not yet achieved for 19 (24.1%) of the registries.

A statistically significant association was found between increasing the number of cases registered in the records and the respondents' positive opinion regarding the achievement of registry objectives ($P < 0.05$). The presence of a larger number of registered patients allowed representative analyzing and proper use of the available information leading to increased stakeholders' satisfaction.

Registry administrators were asked whether the registries needed a management or administrating change. A positive response was indicated by 47 (59.5%) administrators, while 32 (40.5%) stated that the registry was functioning well and there was no need of improvement. The shortcomings in registry planning could be assumed as a probable cause leading to difficulties in achieving specific register targets. Another important issue is the fact that after register launching there are external influencing factors such as law changes, commitment refusal by a stakeholder having a key role in registry maintaining etc.

Conclusions: The increased amount of available information requires more efforts for the database administration and the collaboration with other stakeholders. The results of the study showed that it was necessary to analyze possible risks prior the establishment of rare diseases epidemiological registries and to plan appropriate measures for solving potential problems. Nevertheless epidemiological registries are vigorous and useful tool for studying each rare disease and it is worth assuring their sustainable development.

References:

1. Rubinstein YR et all: Creating a global rare disease patient registry linked to a rare diseases biorepository database: Rare Disease-HUB (RD-HUB). Contemp Clin Trials 2010, 31(5):394-404.
2. Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. AHRQ Publication No.10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 2010.

PP-04 Alveolar proteinosis, experience in National Institute during 10 years.

Ortiz Lobato Laura, Buendía Roldan Ivette, Mejía Ávila Mayra E and Gaxiola Miguel
National Institute of Respiratory Diseases, México City, Federal District, ivettebu@yahoo.com.mx

Introduction: The Pulmonary Alveolar proteinosis (PAP) is an unusual diffuse interstitial disease caused by the accumulation of surfactant phospholipids in the lung alveoli and result in impaired gas exchange. It has been described most often in young people with a history of heavy smoking and the most common form is idiopathic.

Aim: To determine the frequency and clinical characteristics of patients diagnosed with pulmonary alveolar proteinosis at the National Institute of Respiratory Diseases (INER). Methods: A descriptive, observational, retrospective study was conducted in the INER. Through the service of biostatistics cases diagnosed with Pulmonary Alveolar Proteinosis were identified over a period of ten years. Records were reviewed to identify demographic variables, the thorax High Resolution Computed Tomography (HTRC), lung function tests, bronchoalveolar lavage (BAL) characteristics and biopsy, result for diagnostic confirmation of incidence cases.

Results: 17 patients were identified with pulmonary alveolar proteinosis, the average age of onset was 36 years, being more common in women (60%, 10/17 cases). The most common lung exposure observed was ornamental birds (60%), wood smoke (20%) and silicon fertilizers by occupational exposure (20%). Smoking history was 33% but the tobacco index was not significant as pulmonary risk. The predominant clinical presentation was dyspnea (93%) and cough in all patients. In 33% of the PAP patients respiratory infection coexisted at the time of presentation. The microorganisms isolated were Micobaterium tuberculosis, Pseudomonas aeruginosa and Staphylococcus aureus. Incidentally antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA) and rheumatoid factor were elevated in two patients and one had a blood disorder. In HRCT chest "crazy paving pattern" was observed. The diagnosis of PAP was confirmed only with BAL in 60% and the rest required to be biopsied, one case was associated with silicosis. In respiratory function tests predominance restrictive pattern was observed. Almost all patients (94%, n = 16) was treated with lung lavage. At 12 and 24 months of follow-up improvement in respiratory function tests was found in all patients who underwent whole lung lavage. TLC and DLCO tests had fluctuation during the two-year follow-up. Half of the patients (53%) required 1 to 3 lung lavages in the first year and 20% of the patients with history exhibitions required more than three lung washes during the first year of diagnosis. We had limitations in mortality.

Conclusion: In conclusion pulmonary alveolar proteinosis is a disease of low frequency. The fluctuation in the TLC and DLCO are signs of a chronic and insidious evolution. We believe it would be helpful to search for antibodies against GM-CSF for differential diagnosis of different forms of PAP. We would consider the use of GM-CSF inhaled or subcutaneous or Rituximab, as it has shown to improve prognosis of post lung lavage. Because PAP symptoms are similar to other interstitial lung diseases it should be taken into account in differential diagnosis.

PP-05 Japanese latest situation and challenge: Contribution of patient groups to establish "NANBYO" law

Yukiko Nishimura
ASrid / Japan Patients Association (JPA), Tokyo, Japan, yucko@asrid.org

In this abstract the author shows the contribution of patient groups/association for the establishment of the "NANBYO" law, the first law in this field in Japan, and discusses future challenges.

Japan has a long history of measures for NANBYO (rare and intractable/incurable diseases). The outline of measures for "Intractable Diseases" (NANBYO policy) was formulated by Japanese government in 1972, which was the first established national policy in the world related to this field. Based on the above outline, there were several NANBYO research programs (for adult and pediatric) for research promotion, improvement of the medical care system, support of medical costs, and so on.

In Japan there is the Child Welfare Act and the program for pediatric patients are under this law, and also the definition of Orphan Drug at Pharmaceutical Affairs Law. However, there was NO law related to NANBYO in Japan, which means that there was NO definition of NANBYO. In the NANBYO research program, there were only 56 diseases that were able to get the financial assistance from National government, but there are 500-600 disease groups (not individual diseases) in Japan. We needed to set up a comprehensive NANBYO policy based on the law for all disease groups, and also revise the Child Welfare Act.

Under the present NANBYO situation, Japanese stakeholders including patient groups/associations, government, and professionals have been discussing NANBYO policy and related measures to make a fundamental law. Japanese government has established the NANBYO national committee, and presidents of NANBYO patient associations became members of Na-

tional Committee of NANBYO in 2009. It was the first time patients' representatives became official members of a committee built by the central government and they recommended many plans, ideas and strategies, based on NANBYO patients' voices and perspectives from whole of Japan.

Based on those voices, several laws have been enacted since 2013; a "Comprehensive Supports for Persons with Disabilities Act" (2013, for disability people), a revised Child Welfare Act (2014, for pediatric and chronic diseases patients), and a NANBYO law (2014). The financial sources of the latter two laws have changed to the mandatory expense using sales tax. The target NANBYO diseases of Disabilities Act have been expanded from 130 to 151. That of Child Welfare Act has also expanded to 704. The NANBYO law clearly describes the necessities of social support for NANBYO patients, development of the basic measures for comprehensive NANBYO policies, and establishment of equal/stabile medical cost subsidy. The number of the target NANBYO diseases covered by the NANBYO law was also expanded to 306 in the summer of 2015.

The author confidently concludes that Japan has achieved some positive results by patients' contribution. However, several points still remain to be resolved.

Acknowledgements: Secretariat / board of JPA and ASrid, Pediatric network in Japan, and MHLW.

PP-06 Useful approach to drug development for mitochondrial diseases – case study from Japan

Yukiko Nishimura[1,2,3], Taro Inaba[1], KOINOBORI project team1 and Masashi Suganuma[1]

[1] KOINOBORI Associate Inc.

[2] NPO ASrid

[3] Japan Patients Association (JPA), Tokyo, Japan, Corresponding author: yucko@asrid.org

In this abstract we would like to introduce our Drug Development Support Program (DDSP) for Mitochondrial diseases.

KOINOBORI is a nonprofit organization, which brings accumulated knowledge and experience together for the development of new therapies to arrest progressions and pursue the recovery of lost functions in rare diseases. Established by medical doctors, venture investors, academic researchers, patient's families, and scientists in 2009, it was registered in 2013.

The activities of DDSP include; 1) Investigation of the latest global research and development efforts, 2) Support of collaborative research and clinical studies, and 3) Encouraging investors and pharmaceutical companies to invest in development programs to foster commercialization of therapies. KOINOBORI has been focusing on mitochondrial disease. The focus came from the fact that one of our members has a relative developed MELAS.

As a part of our activity, we evaluated various programs being developed in the mitochondrial space and decided to focus on EPI-743, discovered and developed by Edison Pharmaceuticals, as our first target compound to support in Japan. Currently, EPI-743 is in a Phase 2B clinical trial for Leigh syndrome, a Phase 2A for Friedreich's ataxia in the US and a Phase 2A for Rett syndrome in Europe according to publicly available information.

In 2013, KOINOBORI led an initiative involving Edison Pharmaceuticals, the National Center of Neurology and Psychiatry in Japan (NCNP), key opinion leaders, physicians and researchers to construct a partnership among them to initiate and conduct an early exploratory clinical research of EPI-743 for MELAS in Japan. KOINOBORI has also financially supported the clinical research providing a fund for Edison Pharmaceuticals. Edison Pharmaceuticals has entered into a strategic alliance with a Japanese established pharmaceutical company and it is conducting a Phase 2B/3 study for Leigh Syndrome in Japan.

Aside from the above project, KOINOBORI has started the Patient Network-Forming Program since 2014. KOINOBORI has coordinated the Aim at Concrete Treatment of Mitochondrial Diseases (ACTION) meeting, the latest information exchange meeting for patients and families. KOINOBORI has also set up two websites about KOINOBORI itself and the reference portal for information on all MITO diseases and orphan drugs, for all stakeholders. The aim of the latter website is to help improve the diagnosis, care and treatment of patients with mitochondrial diseases.

KOINOBORI website: http://koinobori-mito.jp/en

Mito-disease website: http://mito-disease.info/en

PP-07 Medical societies and researchers collaborating with Spanish National Rare Diseases Registry and Spain-RDR network: incorporation of patient registries

Verónica Alonso, Ignacio Abaitua, Ángela Almansa, Ana Villaverde, Manuel Hens and Manuel Posada de la Paz
Institute of Rare Diseases Research, Instituto de Salud Carlos III. Madrid, Spain, valonso@isciii.es

Patient registries are epidemiological tools based on observational methods, which collect data about onset and development of diseases. Their aim is to promote etiological and clinical research and, at the same time, to contribute health services planning for the patients care and their families support. It is essential to establish procedures and requirements to include patient registries, devoted to one rare disease or a group of them, in the National Rare Diseases Registry that belongs to the Institute of Rare Diseases Research (IIER), Instituto de Salud Carlos III (ISCIII).

Spanish National Rare Diseases Registry and SpainRDR network facilitates the required criteria and rules to clinicians, researchers or networks interested in this collaboration. ISCIII establishes institutional agreements with each collaborating medical society or research group. Besides, ethical norms as well as personal and group commitments for all participants are stated in the consortium agreement. This collaboration respects patient registry identity and management autonomy. Patient registries being part of National Rare Diseases Registry should take into account the minimum dataset which is already part of this platform data model. Apart from common data elements for all included patient registries, it is possible to add any disease-specific variable in each patient registry. Likewise the information to be collected should be agreed and standardized, so that every member of the group registers the data in the same way. National Rare Diseases Registry has available an informed consent already approved by IIER ethical committee. This document should be the reference for all patient registries joining the National Registry. If necessary additional considerations could be added to this informed consent, depending on disease characteristics or professional's working institution. National Rare Diseases Registry is stated in the Spanish Data Protection Agency therefore patient registries included in National Registry do not require additional statement.

Following this procedure, the patient registries collaborating with National Rare Diseases Registry to date are: Pediatric interstitial lung diseases, Lymphangiomatosis, Alveolar proteinosis, Alpha-1 antitrypsin deficiency, Traqueal stenosis, Sarcoidosis, Pulmonary histiocytosis, Epidermolysis bullosa, Disorders of sexual development, Congenital renal hyperplasia, Bradikinin mediated angioedema, Wolfram syndrome, Cystinosis, Congenital anemias, Duchenne disease, Hereditary ataxias and Hereditary spastic paraplegia.

More information at:
https://spainrdr.isciii.es/
https://registroraras.isciii.es/

PP-08 A law that benefits patients with rare diseases in Chile

Silvia Castillo Taucher[1,2] and Teresa Aravena[1,3,4]
[1]Sección Genética, Hospital Clínico Universidad de Chile
[2]Sección Citogenética, Laboratorio, Clínica Alemana de Santiago
[3]Sección Genética, Hospital Sótero del Río
[4]Clínica Indisa, Santiago, Chile, scastillotaucher@gmail.com

On June 1, President Michelle Bachelet enacted the Law Financial Protection System for the Diagnosis and Treatment of High Cost. This law becomes part of the general system of health guarantees. The law seeks a health care system that provides appropriate and timely care, and seeks to achieve universal health coverage, understanding health as a right. The law incorporates periods of care and access to diagnosis and treatment. It is a civil law, a feat of society organizations and patient associations. It considers treatments based on medicines, medical devices and foods of high cost with proven effectiveness. The effectiveness of the treatments will be assessed in scientific, economic and social terms. Only those that are effective and safe for patients will join the fund.

Currently the treatment of approximately 2,000 people suffering from rare diseases of high cost are funded. With this new fund regime, it is expected to cover the treatment to about 20,000 people. Those whose treatments will be covered by this law shall be notified of the benefit by the treating physician. The treatments will be delivered through a network of health care providers approved by the Ministry of Health according to their technical quality. The drugs, devices and foods of high cost will be evaluated technically and scientifically, considering medical, economic, social and security aspects. Treatments that are not covered by social security systems in health today and that meet the above requirements will be evaluated.

The recommendation for inclusion of a new treatment system will be made through a committee, with the participation of representatives of patient organizations. The law provides for several instances of social participation and transparency.

The system will be monitored and supervised by a Citizens Committee, ensuring transparency and fairness in the award of treatments. The documents of evaluation of the treatments will be public and recommendations may be challenged by the community.

The Ministry of Health will review all cases informed as requiring costly treatments and deliver a public response about it. The fund is financed with direct fiscal contribution. The benefit is for all.

PP-09 E-Rare efforts towards patients' involvement in rare diseases research and funding activities

In the name of E-Rare-3 Consortium:

Daria Julkowska[1], Marilyn Desrosiers[2], Stephanie Robertson[2], Sonja van Weely[3] and [4]Mathieu Boudes

[1]French National Research Agency, Paris, France

[2]Canadian Institutes of Health Research, Ottawa, Canada

[3]The Netherlands Organisation for Health Research and Development, Amsterdam, The Netherlands

[4]EURORDIS, Paris, France, Daria.julkowska@agencerecherche.fr

Rare diseases (RD) are diseases that affect not more than 5 per 10 000 persons (according to the EU definition). 7000 distinct rare diseases exist, affecting between 6% and 8% of the population (about 30 million EU citizens). The lack of specific health policies for rare diseases and the scarcity of the expertise, translate into delayed diagnosis, few medicinal products and difficult access to care. That is why rare diseases are a prime example of a research area that strongly profits from coordination on a European scale. At present only few European countries fund research on rare diseases through specific dedicated programmes. Therefore, the funding of transnational collaborative research is the most effective joint activity to enhance the cooperation between scientists working on rare diseases in Europe and beyond. **The E-Rare, ERA-Net for Research Programmes on Rare Diseases** was built to link responsible funding bodies that combine the scarce resources and fund rare disease research via Joint Transnational Calls (JTCs). The current E-Rare-3 consortium comprises **25 institutions from 17 European, Associated (Israel, Turkey) and non-European countries** (Canada). Its international dimension is directly translated into close collaboration with IRDiRC and other relevant European and international initiatives.

E-Rare-3 focuses particularly on close collaboration with Patients' Organizations (POs) from Europe, represented by EURORDIS, and beyond. One of the unifying elements among rare disease POs and national funding agencies is the desire to drive research and its translation for better prevention, diagnosis and treatment - and ultimately a cure. Rare disease patient organizations show a high interest in and a strong commitment to research and a strong willingness to collaborate with researchers, including logistical and financial support. In March 2014, EURORDIS launched a survey in which 60 patient organizations expressed their interest to participate in E-Rare-3 (out of those 60, 44 patient organizations have funding capabilities).

Some E-Rare funding organizations have or are gaining experience in collaborating with patient organizations/associations or charities in co-funding (rare disease) research. Building upon this experience, **E-Rare together with EURORDIS will work to develop a funding model for collaboration with patient organizations** that is expanded and adapted to the European context to be used for E-Rare JTCs. EURORDIS will play a key role in brokering conversations with POs and seeking their input to define a funding model. Interested patient organizations will form a pilot group to fund in the Joint Transnational Call JTC 2016 or 2017, dependent on the progress of development of the funding model.

Based on the experience and lessons learned the consortium will establish a working model that will be open to other patient organizations to join in the subsequent joint calls.

Most importantly, EURORDIS will act as a resource that would **enable/facilitate connections between researchers who want to involve patient groups in their research effort** as well as integrating patient organizations into E-Rare-3 strategic activities/workshops. Overall, E-Rare-3 will be ensuring that patient organizations are fully engaged in the development of an innovative research funding model and related E-Rare-3 activities. This task endorses the policies and guidelines of IRDiRC concerning participation by patients and/or their representatives in research.

PP-10 Molecular genetic testing of inborn metabolic diseases in Serbia

Maja Stojiljkovic, Kristel Klaassen, Anita Skakic, Milena Ugrin, Sonja Pavlovic
Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Belgrade, Serbia, maja.stojiljkovic@imgge.bg.ac.rs

We have been developing molecular genetic tests for several rare inborn metabolic diseases to support healthcare and research in Serbia. The aim of our work was to analyze molecular genetic base and to asses correlation between genotype and phenotype of Serbian rare disease patients. More specifically, we aimed to set the base for molecular genetic diagnosis and genetic counseling for a number of rare metabolic diseases in Serbia.

For more than ten years our methodology included PCR based techniques, Sanger DNA sequencing and MLPA analysis for a specific disease-causing gene (e.g., *PAH*, *CYP21A2*). In year 2014 we introduced a high throughput targeted re-sequencing methodology based on a simultaneous analysis of 4813 clinically relevant genes. Combining Sanger DNA sequencing with clinical exome sequencing we reached >90% mutation detection rate. This strategy will enable timely and accurate diagnosis and implementation of the right treatment in our country.

We analyzed 75 unrelated patients with hyperphenylalaninemia, 61 with congenital adrenal hyperplasia, 30 with glycogen storage disease, 9 with branched-chain organic aciduria etc. Our research provided the first molecular genetic data for hyperphenylalaninemia and congenital adrenal hyperplasia in Serbia. Interestingly, due to low number of patients with metabolic rare diseases and difficulties for their diagnosis, studies in other Slavic populations or populations residing in South-Eastern Europe that were historically and geographically connected with Serbian population are scarce. To the best of our knowledge, our study provided the first molecular genetic data for glycogen storage diseases, methylmalonic acidura, propionic academia, maple syrup urine disease and mitochondriopathias for South-Eastern Europe. As a consequence, we have detected significant number of novel mutations. Thus, our data contributed to the better understanding of genetic landscape of these diseases in Europe.

For all genetic variants that were first detected in Serbian population, we performed in silico analysis and/or expressional *in vitro* analysis in order to assess their pathogenic effect. Thus, our data will contribute to unambiguous diagnostic interpretation of these genetic variants worldwide. Furthermore, given that patients with particular genotypes are rare, our observations about mutations' effect on patients' phenotypes contributed to the general knowledge of these monogenic diseases.

In our opinion, in small countries like Serbia, high throughput targeted re-sequencing will soon become method of choice in order to precipitate genetic testing, set definite diagnosis and enable rapid implementation of optimal therapy for patients with rare diseases. In recent years, there have been many examples of development of molecular therapeutics specific for missense, splice site and in-frame stop mutations. Due to these novel therapeutic strategies, identification of gene mutation became increasingly important for implementation of individualized treatment. The first data for Serbia showed that majority of mutations are eligible for molecular therapeutics (e.g. Kuvan for missense PAH gene mutations), which in future could become important approach for enhancing quality of life and improving life-time of affected individuals.

Acknowledgements

This work has been funded by the Ministry of Education, Science and Technological Development, Republic of Serbia (grant no. III 41004) and by European Commission, EU-FP7-REGPOT-316088, 2013-2016.

PP-11 Methodology collaborations in the European Union

Simon Day[1], Ralf-Dieter Hilgers[2], Kit Roes[3] and Nigel Stallard[4]
[1]Clinical Trials Consulting & Training, North Marston, UK
[2]Aachen University, Germany
[3]UMC Utrecht, The Netherlands
[4]University of Warwick, UK, simon.day@CTCT-Ltd.co.uk

Three related projects have been funded under the European Union's Seventh Framework Programme for Research, Technological Development and Demonstration (FP-7) call for "New methodologies for clinical trials in small population groups." Each of these is an independent collaboration amongst several academic and industry-based methodologists. Furthermore, all three projects are sharing experiences and regularly interact with each other.

The IDeAl project ("Integrated Design and Analysis of small population group trials" http://www.ideal.rwth-aachen.de/) aims to utilize and connect all possible sources of information in order to optimize the complete process of a clinical trial. Topics for research include assessment of randomization, the extrapolation of dose-response information, the study of adaptive trial designs, the development of optimal experimental designs in mixed models, as well as pharmacokinetic and individualized designs, simulation of clinical studies, the involvement and identification of genetic factors, decision-theoretic considerations, and the evaluation of biomarkers.

The Asterix project ("Advances in Small Trials dEsign for Regulatory Innovation and eXcellence" http://www.asterix-fp7.eu/) includes how to consider (quantitative) methods to include patient level information and patient perspectives in design and decision making throughout the clinical trial process; statistical design innovations for rare diseases in individual trials and in series of trials; reconsideration of the scientific basis for levels of evidence to support decision making at the regulatory level; developing a framework for rare diseases that allows rational trial design choices; and validation of new methods using real life examples to see how they may aid regulatory decisions making.

The InSPiRe project ("Innovative Methodology for Small Populations Research" http://www.warwick.ac.uk/inspire/) is looking at early stage dose-finding trials and dose-finding trials particularly in paediatrics; decision-theoretic designs; design of confirmatory trials and personalized medicines; and evidence synthesis in the planning of clinical trials in small populations.

Each of the separate projects has an external Independent Scientific Advisory Committee and the Principal Investigators from each project sit on each of the other Advisory Committees.

Several papers have already been published stemming from these projects, others are under review and still more in preparation. This talk will summarise the key methodological contributions that are being made.

The authors gratefully acknowledge the EU's Seventh Framework Programme for research, technological development and demonstration grants FP HEALTH 2013– 602552, FP HEALTH 2013–603160 and FP HEALTH 2013–602144.

PP-12 Centres for rare diseases – for improved care of patients with rare diseases in Sweden

Annika Larsson[1], Désirée Gavhed[1], Katja Ekholm[1], Eva Ekblom[1], Rula Zain-Luqman[1], Kristina Gustafsson-Bonnier[1], Alva Ekblom[1], Britt-Marie Anderlid[1], Patrik Georgii-Hemming[1], Veronica Wingstedt de Flon[2], Jan-Inge Henter[1], Magnus Nordenskjöld[1] and Ann Nordgren[1]

[1] Karolinska University Hospital, Stockholm, Sweden

[2] Swedish National Agency for Rare Diseases (NFSD), Gothenburg, Sweden

Patients with rare diseases may have complex disease pictures with different organs involved. To obtain necessary support many rare disease patients therefore need multiple visits and contacts with different health care and social services. Furthermore, for many diagnoses there are no experts in the region and some patients remain undiagnosed.

In 2012 the Stockholm County Council supported the formation of the Karolinska Centre for Rare Diseases (KCRD) at the Karolinska University Hospital. KCRD serves as a coordinating and information office of rare diseases and currently has ten part-time employees. The overall objective of the centre is to improve the living conditions for children, adolescents and adults with rare diseases. This will be achieved through better coordination, increased cooperation between experts (regionally, nationally and internationally) as well as improved education and research efforts. KCRD´s work comprises different areas. These are: Guidance (to patients and health care workers); Collaboration between health care and patients (to ensure that KCRD's activities are patient centered); National and international cooperation (the ICORD secretariat is co-located with KCRD); Expert teams for rare diseases (to support existing teams and to assist in the development of teams for diagnoses that do not yet have well defined teams of experts); Databases and Quality registers; Treatment guidelines; Research and Education; Syndrome diagnostics (patients with an undiagnosed syndrome can turn to KCRD to obtain a diagnosis).

Centres for Rare Diseases are now being developed at other University Hospitals in Sweden. Although their structures are different, their overall aim is the same. The different centres are in close communication and their development is coherent to the objectives of the Swedish National Agency for Rare Diseases (NFSD). NFSD was established in 2012 under the National Board of Health and Welfare. The NFSD activities not only promote coordination of health care resources but also of employment and social services, school and other actors. NFSD also contributes to the dissemination of information on rare diseases and to the exchange of good practice between the hospitals in Sweden.

The regional and national activities on rare diseases in Sweden over the last years are starting to have a positive impact on patients with rare diseases. We hope the support for these activities will be sustained and extended.

PP-13 Identification of genes associated to amyotrophic lateral sclerosis by systematic abstract organization and cataloguing

Roberto-Andrés Medina-Molina, José-Alfonso Meza-Medina, Jorge-Eugenio Moreno-Cuevas and Victor Treviño
Tecnológico de Monterrey, Monterrey, México, vtrevino@itesm.mx, betomedina32@gmail.com

Introduction: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease affecting brain and spinal cord whose progression is fatal. Mutations found in many genes have been associated to ALS in the literature. However, commercial gene tests include only a handful of these genes. To properly diagnose ALS, a broader gene panel is needed.

Objective: Determine the genes associated to ALS reported in the literature.

Methods: We systematically analyzed and catalogued the abstracts of research papers deposited in PubMed using a query containing the words "ALS", "gene", "polymorphism", "mutation", "genes", "polymorphisms", and "mutations". We used PubTerm, a web tool developed in our research group that organizes abstracts by terms such as Genes, and Diseases. The term annotations were obtained by NCBI PubTator service. Only the 1,000 most recent abstracts were considered. Abstracts were manually reviewed to classify and annotate genes in 7 categories depending on the type of evidence found. Only human genes were reviewed.

Results: We analyzed the 1,000 most recent abstracts from the 2,380 abstracts found associated to ALS gene mutations. The abstracts mentioned 595 different genes where 301 referred human genes. After reviewing abstracts per gene, most of the genes were not associated to ALS. We classified 177 genes as "unrelated", 22 as "false", and 46 as "biologically related but no evidence of mutation". In genes that show some evidence of association, we found 33 genes with "experimental evidence of mutations", 9 with "computational evidence", 2 with "bibliographic evidence", and 12 with "controversial evidence". Interestingly, from the genes with mutational evidence, only 13 were mentioned by 10 or more abstracts suggesting that most of the genes have been recently discovered or have received little attention from the scientific community.

Discussion and Conclusion: We found at least 33 genes with evidence of mutations. Many of these genes are not included in common tests for ALS, which could fail to diagnose many ALS patients with familial evidence or carrying de novo mutations. The process of abstract cataloguing and annotation is laborious, tedious, and prone to errors. Thus tools such as PubTerm that organizes and facilitates this process are highly appreciated. Given the high occurrences of genes not associated after cataloguing and the increasing number of scientific publications, precise tools are needed to annotate abstracts or to recognize truly mutated genes directly from the available text. The generated gene list will be useful for ALS genetic screenings.

PP-14 The global GIST patient registry and tissue bank

Michelle Durborow and Sara Rothschild
The Life Raft Group, Wayne, NJ, USA, mdurborow@liferaftgroup.org

Introduction: Alianza GIST (AG) formed in 2009 with the goal to improve the survival of people living with a rare cancer called GIST (Gastrointestinal Stromal Tumor) in Latin America, through scientific research, information, education and advocacy. The group is comprised of patient advocates from 16 countries aiming to help close the gap between scientific knowledge and the clinical treatment of GIST, identify and educate more patients and key medical professionals, empower patients to take charge of their own care, and improve access to safe and effective treatments. AG works in collaboration with The Life Raft Group, an international GIST advocacy organization, in which the LRG helps to provide the scientific knowledge, technology, and other resources to help AG accomplish their goals in the region. The LRG runs a patient registry, in which data collected produces patient-centered outcomes research about the GIST patient population and demonstrates rapid hypothesis generation that could lead to more stringent analysis among this rare disease community. The tissue bank brings together GIST researchers and GIST patients in a unique partnership. For patients, it's an opportunity to reach the world's leading GIST research scientists with tissue donation, maximizing both tissue and precious research time. For researchers, it's an opportunity to access tissue linked to GIST clinical histories from the patient registry and to share valuable tissue and critical data.

Objective: The purpose of the patient registry and tissue bank is to address the need to better utilize "BIG Data" to improve patient outcomes. These programs not only aid in research but serve as a patient-empowerment tool to guide patients to make informed decisions in their treatment.

Methods: The Registry was introduced in Latin America and serves as a surveillance tool to collect statistics of how many GIST cases are prevalent in Latin American countries, as this information is not readily available through LA national cancer institutes. AG representatives collect medical updates from patients in the community and enter it into the database. The tissue bank allows AG to collect tissue and do molecular testing that they cannot readily obtain in the LA region.

Results: Through our data collection, we have seen that 20% of tissues that are evaluated show they are misdiagnosed in LA. A Physician Education CME course was implemented in collaboration with Monterrey TEC, as well as a Tumor Board

convened at ASCO with the goal for physicians across LA to improve their knowledge of treating and managing GIST. Since the implementation of the Monterrey TEC program, GIST cases have been reported more frequently, thus reflecting the success of the program.

Conclusion: The tools that the LRG has provided AG have strengthened their capacity to help patients survive. The information has helped the AG strengthen their educational and advocacy efforts among the patient and physician community.

PP-15 The life raft group establishes virtual gist tumor board in partnership with NIH

Sara Rothschild, Mildred Menos, Norman J. Scherzer and Michelle Durborow

The Life Raft Group, Wayne, NJ, USA, srothschild@liferaftgroup.org

Introduction: In 2008, the National Institutes of Health (NIH) launched an in-person clinic for the Pediatric and Wild-type GIST community allowing clinicians and researchers from across the world to collaborate with each other and meet patients and their families firsthand. This led to several important breakthroughs, including investigating germline mutations in the succinate dehydrogenase complex (SDH), which helps physicians understand how wild-type GISTs are formed, and that Pediatric GIST can be diagnosed after age 18 and should thus be titled "SDH-deficient GIST." Yet, decreases in government funding have reduced the number of in-person meetings to one per year. To supplement this loss of an in-person clinic, The Life Raft Group partnered with the NIH to launch the Virtual GIST Tumor Board.

Objective: The purpose of the Pediatric GIST Virtual Tumor Board is to bring together leading experts to discuss pediatric/wild-type (SDH-deficient) GIST cases, and be an educational resource for physicians.

Methods: The process is an augmentation of how virtual tumor review boards work. If selected, doctors of GIST patients log on and review their de-identified patient case with a panel of experts using the internet, secure servers, and state-of-the-art video conferencing software. The LRG uses cutting-edge technology to connect the local treating physicians and their team with key opinion leaders in the field of Pediatric (SDH-deficient) GIST. Participants virtually access radiology films such as CT scans and other necessary medical reports to help review particular cases and provide advice.

Results: The Virtual GIST Tumor Board has met twice, and reviewed cases from patients as far away as Latin America and the Ukraine. The physicians of these patients have elevated the level of care they provide due to the interaction with experts the Board makes possible.

Conclusions: The Pediatric GIST Virtual Tumor Board is transformative because it provides valuable access for patients and doctors who would not be able to attend an in-person clinic due to resources or distance; educates doctors on the most up to date treatment options, trials, and studies; serves as a triage to bring patients to the in-person clinic; and encourages collaborative efforts of leading GIST experts around the world about a rare disease.

October 2015, Volume 2, Number 3, Supplement 3

Discoveries and Innovations on Orphan Drugs (D&IOD) start-up meeting at Mexico, October 13-14, 2015. A platform to expedite orphan drug research and accessibility.

Roldan Emilio JA[1,2], Llera Virginia A[1], Camacho-Molina Alejandra[3], Morales-Blanhir Jaime[4], on behalf of the program organizing committee.

[1]GEISER Foundation, Mendoza, Argentina. info@fundaciongeiser.org
[2]Scientific Direction, Gador SA, Buenos Aires, Argentina
[3]National Institute of Neurology and Neurosurgery, Mexico City, Mexico.
[4] FEMEXER Scientific Advisor.

ABSTRACT

The Discoveries & Innovations in Orphan Drugs (D&IOD) meetings aims to expedite orphan diagnosis and treatments products by creating awareness, a platform for starting-up initiatives, interrelationships and networking's in the orphan products field. The main focus is in those regions in which the affected conditions are not a definite health priority, and research needs to be driven to industrial developing and production. Equity in patient health assistance and accessibility to products which are being manufactured in limited quantities or being distributed at high prices is also a concern. This first experience was developed at Mexico City as part of the Mexican Rare Diseases Global Week, 2015, hosted by both organizations, FEMEXER and GEISER Foundation, at the ISSSTE Buena Vista auditorium. Genetic diagnosis systems, neonatal screening programs, models for statistic and financial support for rare diseases and orphan product commitments, clinical examples of already available drugs and some repositioned options were delivered in 18 consecutive or parallel sessions during the meeting. Hereby the main concepts and outcomes are summarized, exposing areas of demands, further topics having a satisfactory developing and others which request cooperation, improvements of regulations and/or formal long-term planning's. Mainly, data and bio-banks sharing, and rare diseases vs traditional public health concepts were discussed. Known International institutions as IRDiRC, ICORD and NIH (USA) offers bridging opportunities for open collaborations, and Latin America is a region that should be inserted at such levels. The Mexican experiences, mostly at health care programs done in favor of certain diseases can be extrapolated to other countries of the region with caution on the local features. Mexico shows an enormous potential for developing orphan projects and leadership programs in the region.

The Rare Diseases and Orphan Drugs Journal has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n° 305690: RARE-Bestpractices project: www.rarebestpractices.eu. Sole responsibility lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein.

INTRODUCTION

Orphan Drugs are those intended to treat conditions in which the market natural conditions are adverse. Consequently, a huge number of diseases are today not satisfied in diagnosis and treatments options, including those which are rare (1,2), or affects populations with poor resources to purchase medicines (neglected diseases) (3), or are subpopulations not responding to the current available possibilities (clinical conditions with differential pathologic pathways), (4) or those which could be considered as intractable (5).

To revert the current adverse economic environment some countries has promote a number of incentives which in turn makes possibly the appearance of diagnostic and drugs (orphans) (1,6). Likely, more than 400 orphan compounds become available in the last 20 years bringing hopes to patients unattended before (7,8). Some of these orphan drugs have introduced dramatic changes in the prognosis of diseases as the 75% expands of life expectancy in cystic fibrosis patients (9). Nevertheless, some others of these orphan products are still far from modifying desirable clinical end/points as normalizing the affected quality of life. With more importance there still around 6,000 conditions still lacking of any specific treatments. At the current pace it will demand centuries to cover the current health demands in the orphan markets. Moreover, a large portion of orphan options becoming available, are priced at values not accessible to the vast majority of the population (10,11) becoming a challenge for both, the affected and its health care system resources. Hence, more efficacious and accessible alternatives are desirable as well.

At present time biomedical technology is rapidly progressing, mainly after whole human genomic developing (12,13), and current epigenetic, proteomic and pathologic-pathways mapping networking (3,14,15). Many groups of scientists at academia and small or medium biotechnological companies are making big efforts to developed innovative diagnosis and treatments to cover unsatisfied needs, together with the projects and products launched by the big pharma, now involved in the orphan markets. Congruently networking and independent international organizations as ICORD (16), IRDiRC (17), or GEISER Foundation at Latin-America (18) are working to help expediting research and accessibility for orphan products.

As the speed of splitting orphan products information, developing, availability, and accessibility may vary largely in the different countries of the world, being more difficult in the countries in which orphan products are not a health priority, or the socioeconomic conditions are less favorable, the "Discoveries and Innovations on Orphan Drugs" (D&IOD) are intended to bridge innovative researches and developers from all over the world to those regions in which the investigations need to be translated to channels handing the products to the patients. By facilitating these it is expected to accelerate the options for those conditions not satisfied still, and to regulate the oversized cost of some orphan product which may find better conditions in larger markets, with more players being involved or under competitive environments.

Hereby it is reported the main facts and outcomes of the starting D&IOD congress which was held at Mexico Federal District as part of the "Mexican Rare Diseases Global Week" series of rare diseases events performed during October 12-17, 2015.

D&IOD OBJECTIVES

The congress aim was to provide an educative international platform for orphan diagnosis and treatments in the amplest sense. That is, to introduce new ideas and discoveries, innovative developments, pragmatic clinical models for orphan drugs applications, plan for orphan products accessibilities, technological, regulatory and financial support for research and bridging for international cooperation in the field of orphan drugs. In the occasion the program was adjusted to the current Mexican scenario, and in a wider scope to Latin-America needs and possibilities in orphan products.

THE MEETING PROGRAM AT MEXICO 2015

D&IOD was developed during October 13 and 14, 2015, at the auditorium of the Buena Vista Building of ISSSTE, Mexico City, the main outcomes are summarized as follows,

- **Plenary Conference: Trends and opportunities in the field of orphan drugs R&D: An IRDiRC perspective.** Ségolène Aymé (Coordinator for Scientific Secretariat at International Rare Diseases Research Consortium, IRDiRC, France).

Science today offers many opportunities to develop therapies for diseases which were previously never considered as targets for such developments. An appropriate framework is in place in certain regions at the world. Looking at the current landscape, it can be said that the initiatives which were set up have been successful. Despite that, patients 'needs are far from being covered in terms of effective therapies.

The rare diseases community sees to it that no opportunity should be missed through collaborations at an international level and between stakeholders. To ensure data generated by research is optimally used for the benefit of patients, an international consortium- The International Rare Diseases Research Consortium (IRDiRC)- was set up as an initiative of the European Commission and the United Sates ´National Institute of Health.

The Consortium conducted in-depth discussions with all stakeholders on the obstacles to overcome in efforts to accelerate R&D in rare diseases. The brainstorming period resulted in recommendations for funding agencies and researchers to optimize the use of shared data through database and knowledge accessibility and interoperability.

The first contribution of IRDiRC is to ensure that data, independent of the collection location, can be used by any re-

searcher needing to access them. In order to do so, IRDiRC promotes the use of standard ontologies (e.g. Human Phenome Ontology and orphaned Rare Diseases Ontology) to code the clinical expressions of diseases. IRDiRC also supports the adoption of a set of core terms to be included in all terminologies intended to describe rare clinical phonemes, these areas available on the IRDiRC´s website.

Secondly, IRDiRC optimally uses data already collected and electronically accessible to define new R&D opportunities. Therefore, IRDiRC coordinates efforts to develop the use of scientific and clinical data by using dispersed resources, including natural language, for selection of drugs as provisional treatment options for rare diseases. Initiatives, both academic and commercials, have bloomed recently, directed at identifying new therapeutics targets and to repurpose drugs. They leverage on developments in Computational Linguistics and Graph Theory to build a representation of knowledge, which is automatically analysed to discover hidden relations between any drug and any disease. These relationships represent possible Modes of Action for any given pharmacological compound. Their efficacy of this method for selecting drugs as treatments options for rare diseases is already documented and required thoughtful introduction at a larger scale.

The third contribution is to address two problems which are threatening the R&D process: 1- The difficulty in defining reliable and meaningful outcome measures when planning a clinical trial. To accelerate the development of criteria to measure treatment effects that are relevant to patients, so-called patient-centred outcome measures, IRDiRC is federating the efforts of large organizations already involved in the development of patient-centred outcome measures for common diseases, and 2- the difficulty in agreeing and alternative method to conduct clinical trials when the number of patients to be included is small. Several groups are working on alternative methods; the challenge and objective is now to explore how acceptable these methods are for regulatory Agencies. This should contribute to de-risk the R&D process.

All this initiative constitutes IRDiRC roadmap. Participation of stakeholders from Latin-America in these on-going efforts is highly encouraged.

The current trend is the development of a higher number of therapies for patients with rare diseases every year. One major challenge to overcome is the cost of these therapies, which will be too high to allow a wide uptake. It is therefore crucial to identify ways to de-risk the R&D process and decrease the costs.

• Session on Discoveries and Developments in Genetic Diagnosis:

Pharmacogenomics and massive sequencing (panels) in rare diseases. Antoni Mantilla-Duenas (Health Sciences Institute Germans Trias i Pujol, IGTP, Spain). Multiple genome sequencing studies have already uncovered novel relationships for genetic variants with monogenetic Mendelian disorders and complex diseases. Approximately 7.000 well-defined Mendelian disorders are currently know of which the corresponding allelic variants underlying fewer than half of these monogenic disorders have been discovered, and the aetiology of many monogenic diseases is still unknown. Furthermore, genome sequencing enables us to decipher the causes and even to guide treatment of an ever-growing number of "mystery" diseases, of which many cluster in families but can also involve individuals, such as Charcot-Marie-Tooth neuropathy, Millers´ syndrome, and dopa (3,4-dihydroxyphenylalanine)-responsive dystonia. Sequencing has shown the probability of providing a solution in cases where there is and initial inability to make a clinical diagnosis of the disease and in rare cases has been shown to subsequently direct a course of treatment.

Genomic Diagnosis. Mayte Gil-Borja (University of Valencia, Spain). The DNA base sequence of human genes is about 99.9 percent identical among individuals. About 1 of every 1,000 DNA bases varies among individuals, accounting for inherited differences in traits and disease susceptibility. Changes in a DNA base sequence, called mutations, account for inherited gene variations. Mutations may be harmful if they prevent a gene making a normal copy of its specific protein. These mutations can cause an increased susceptibility to specific diseases.

Single-gene diseases are relatively rare diseases that result when a person inherits one gene with a harmful mutation or a pair of genes in which each has a harmful mutation. Inheritance of these mutated genes generally results in a 100 percent chance of developing a specific disease. Single-gene diseases include autosomal dominant diseases (e.g., Huntington disease), autosomal recessive diseases (e.g. sickle cell disease), and X-linked diseases (e.g. Duchenne muscular dystrophy).

Most diseases result from a complex set of both genetic and environmental causes. Inheritance of some harmful gene mutations increases the chance, although it does not ensure, that a person will develop a specific disease. These mutations are called inherited susceptibility mutations.

Genetic research will lead to the development of new predictive and diagnostic genetic tests. It also will lead to the development of new preventive and treatment interventions. Generally, the development of interventions lags years, even decades, behind gene discovery and genetic test development.

Genetic testing for inherited genetic variants is performed for several purposes: diagnosis of individuals with symptoms, determination of future diseases risks in asymptomatic individuals, determination of genetic risks for progeny, guidance of medical treatments, research, and individual identification. Genetic information is information about specific variations in genes or chromosomes learned by genetic testing or by other means.

New testing technologies that will promote genetic testing in health care include DNA chip technology and tandem mass spectrometry.

Pre-symptomatic genetic testing is predictive testing of apparently healthy adults to determine weather they are at risk for a single-gene disorder. These disorders occur with virtually 100 percent incidence in persons who have inherited a specific gene mutation.

• Sessions on the Mexican academies and its contributions to advances in diagnosis and treatments for rare diseases:

Even though Mexico still has a long way to go, progress and actions carried out around the rare diseases subjects are not minor; and it is very important to recognize and move forward to achieve a greater dissemination, knowledge and scope involving all spheres working in favour of rare diseases. The resources, capabilities and experiences at four main Mexican institutions were discussed in two consecutive sessions.

Experience of a lysosomal screening in Mexico. Juana I. Navarrete-Martínez (PEMEX Health Services, Hospital South Central of High Specialties of Mexican Oil Co., Mexico) Neonatal screening is aimed at identifying treatable conditions in presymptomatic newborns in order to avoid premature mortality, morbidity and disabilities. With new or improved treatments options and development of high-throughput screening tests, additional conditions have been proposed for inclusions into the neonatal screening program. Among those there are several conditions with a strong neuropathic component. Some of these conditions have already been added to a few national and international screening programs, whereas others are undergoing pilot studies to determine the test performance metrics. The experience with a neonatal lysosomal screening in Mexico was shared.

Clinic lysosomal storage diseases at INP. Luis Carbajal-Rodriguez (Lysosomal Department at National Institute for Pediatrics (INP), Seguro Popular, Mexico). The clinic for lysosomal storage diseases was founded in 2009, within the National Institute for Pediatrics (INP). This means that professional and timely care for patients with lysosomal diseases is available in our media, as well as an opportunity to diagnose, maintain and improve the quality of life of many patients suffering from orphan diseases, that given its low prevalence, are sometimes forgotten. The more than five years of work were compiled for educational and research purposes.

About orphan drugs in biochemical investigations. Luis F. Montaño-Estrada (Biochemistry Department, Medicine Faculty, National autonomous University of Mexico, Mexico). Orphan drugs may be defined as drugs that are not developed by the pharmaceutical industry for economic reasons but which respond to public health needs. The so called "orphan drugs" are intended to treat diseases so rare that sponsors are reluctant to develop them under usual market conditions. The process from a discovery of a new molecule to its marketing is long (10 years in average), expensive (several tens of millions in euros) and vary uncertain (among ten molecules tested; only one may have a therapeutic effect). Developing a drug intended to treat a rare disease does not allow the recovery of the capital invested for its research. And also, an orphan drug once is finally developed, has to overcome all the filters necessary to re regulated as an authorized drug by the health institutes. Examples from Mexico, for orphan drugs diagnosis and treatments were compiled and discussed.

Molecular diagnosis of rare diseases by massive genomic sequencing. Carmen Alaez-Verson (National Institute for Genomic Medicine, INMEGEN, Mexico). Whole genome sequencing (also known as full genome sequencing, complete genome sequencing, or entire genome sequencing) is a laboratory process that determines the complete DNA sequence of an organism´s genome at a single time. This entails sequencing all of an organism´s chromosomal DNA as well as DANA contained in the mitochondria and, for plants, in the chloroplast.

High-throughput genome sequencing technologies have largely been used as a research tool is currently being introduced in the clinics. In the future of personalized medicine, whole genome sequence data will be an important tool to guide therapeutic intervention. The tool of gene sequencing at SNP level I also used to pinpoint functional variants from association studies and improve the knowledge available to researchers interested in evolutionary biology, and hence may lay the foundation for predicting disease susceptibility and drug response.

• Session on statistics in medical and psychological research:

International charter of principles for sharing bio-specimens and data. Deborah Mascalzoni, CRB Uppsala University and Manuel Posada de la Paz (Carlos III Health Institute, Spain). I'm introducing here the "International Charter of principles for sharing bio-specimens and data" recently published in the EJHG and recently endorsed by IRDIRC. This charter is the result of a careful negotiation of different stakeholders' interest and is built on earlier consensus documents and position statements which provided the general international legal framework.

The need for intensive sharing in order to push biomedical research in the rare disease area is a compelling. There is international agreement on the need to provide greater access to research data and bio-specimen collections to exploit their potential for health discovery: this is especially evident for rare disease research.

Contradictory legal and ethical frameworks across national borders are obstacles to effective sharing: more specifically, the absence of an integrated model proves to be a major logistical obstruction. The charter intent is to fill in the gap by providing both the ethical foundations on which data sharing should be based, as well as a general legal Material and Data Transfer Agreement (MTA/DTA).

The Charter has been formulated to serve as an enabling tool for effective and transparent data and biospecimen sharing and the general MTA/DTA constitutes a mechanism to ensure uniformity of access across projects and coun-

tries, and may be regarded as a consistent basic agreement for addressing data and material sharing globally.

"Accesalud" statistical results and future projects. Paulina Peña-Aragon (Accesalud program, FEMEXER, Mexico). To date, the information, guidance and counseling program "Accesalud" has benefit people with rare diseases from Mexico and other Latin American countries. In this space statistical analysis, projection and future projects of the programs were presented unfold. In addition, Accesalud database results will be serving for current and future research into rare diseases and the advances that have been made to date to create a national registry. At present the program has a partnership with ISSSTE to develop projects.

- **Plenary Conference: Rare diseases epidemiology. A necessary approach to improve the knowledge in this novel field.** Manuel Posada de la Paz and Alonso V, Lopez E, Villaverde-Hueso A, Abaitua I (Institute of Rare Diseases Research, Carlos III Health Institute, Madrid, Spain).

The epidemiology has been always associated to big numbers, mainly observational descriptive studies from populations. However, the modern epidemiology is aimed to analytical studies focus on both the etiology and risks/prognosis factors of diseases.

Descriptive analyses based on person, time and place are still valid because they are the only way to suggest new hypothesis to be tested later on in analytical study designs. The rare diseases field seems to be the opposite of the traditional focus of the epidemiology. Some misunderstanding about concepts like epidemiological methods and the traditional concept of public health could lead us to the idea that the rare diseases is not a public health concern, which should be a big mistake. The low number of cases neither means that the epidemiology is not needed nor is a problem to public health authorities. There are some examples in the clinical epidemiology when the clinical trial N equal to 1 or new adaptive clinical trials designs have been defined to face on how to make conclusions in the situation of small sample sizes. In addition, the epidemiology has adopted several surnames across the years as a process to be fitted with new fields such as cancer epidemiology, molecular epidemiology, genetic epidemiology, etc. hence, Rare Diseases Epidemiology is therefore a new name of this discipline aimed to the implementation of both traditional and new methods in this specific field of the medicine where samples are not so high, cases are spread across different countries and time to collect information is critical due to the high mortality rate and the lack of both treatments and risks factors knowledge.

Rare Diseases registries in their two traditional methods- population based registries and patient outcomes registries come up as important bases for both public health authorities and researchers. While the former need information to make decisions about how to develop health and social plans, the latest need specific and cutting-edge information to find new features that can improve the patients' lives and also the patient lives with quality. (Founding sources: SpainRDR project)

- **Plenary Conference: International cooperation for rare diseases research.** Stephen Groft (National Institute of Health-Rare Diseases Research Office, USA).

International cooperation for rare diseases research and orphan products development activities are evolving to resolve the unmet diagnostic and therapeutic needs of the rare diseases community. An estimated 6% to 8 % of the population has one of the approximately 6500 to 8000 genetic or acquired rare diseases. The exact number remains elusive. Patients, families, advocacy groups, foundations, government research and regulatory scientists, industry, and academic researchers are linked in coordinated, collaborative partnerships. Opportunities exist for global collaborations with these individuals and organizations from all countries. This increased interest in rare diseases is due to several factors including the expanded role of patient advocacy groups as research partners. This relationship has resulted in improved patient recruitment for clinical studies. Increased research emphasis has increased funding for basic, clinical and translational research projects. The number of investigators experienced in multi-center, international clinical trials with small patient populations continues to increase with expansion of international research consortia and networks. Ready access to internet-based information resources, publicity about genetic testing, gene therapy, stem cells, and personalized medicine have all contributed to the increase in public interest along with social media expansion and utilization as a source of information exchange.

Expedited review programs from regulatory agencies such as FDA in the USA and the

EMA in the European Union for serious conditions, including fast track and priority reviews, designation of compounds as breakthrough therapies, and conditional and accelerated approvals with an added emphasis on antibiotics, pediatric populations and repurposing of products add momentum to the development of orphan products. The traditional orphan products development incentives including exclusive marketing privileges, grants for clinical trials, and tax credits for clinical trial expenses have proved to be very useful to the developers of orphan products. Since rare diseases do not respect geographical, political, or historical boundaries, many clinical trials are requiring in multiple global research sites. It is essential to understand the cultural, ethical, legal, and social issues related to data gathering and sharing from diverse populations in multiple countries.

Obtaining the correct diagnosis remains elusive for significant populations of patients with rare diseases. Increased sequencing capabilities will facilitate more accurate diagnosis of most rare and undiagnosed diseases by appropriate interpretation of genotypic and phenotypic data.

The biopharmaceutical and medical devices industry pipelines of potential diagnostics and therapeutic interventions is promising and continues to expand through existing research efforts and mergers and acquisitions of companies with novel interventions or technologies that will complement existing research activities. Developing an orphan product for a rare disease is a difficult and risky venture requiring multiple partners from the rare diseases community. Extensive planning with frequent reviews and collaborations with research and development partners is required to maintain the continuum of product development from discovery through development to public access to approved compounds. The ever-expanding and extensive pipeline of potential therapies continues to offer hope to the millions of patients with a rare disease throughout the world. ICORD-related conferences and workshops provide the forum for potential partners to initiate the global collaborations required to meet these therapeutic and diagnostic needs of the international rare diseases community.

• **Sessions on Immunotherapies.** (Sponsored by Bristol-Myers-Squibb):

Multiple Myeloma, a rare disease and new treatment alternatives. Omar López-Navarro (BMS, Mexico). Multiple myeloma is a cancer that forms in a type of white blood cells called a plasma cell. Plasma cell helps fighting infections by making antibodies that recognize and attack germs. Multiple myeloma causes cancer cells to accumulate in the bone marrow, where they crowd out healthy blood cells. Rather than produce helpful antibodies, the cancer cells produce abnormal proteins that can cause kidney problems. Treatment for multiple myeloma isn't always necessary. If the patient is not experiencing signs and symptoms, may not require a treatment. If signs and symptoms develop, a number of treatments can control the patient multiple myeloma.

Immunotherapy, the new frontier in melanoma treatment. Fernando Aldaco (National Institute for Cancerology, INCAN, Mexico). Immunotherapy is a treatment that uses certain parts of a person immune system to fight diseases such as cancer. This can be done in a couple of ways, by stimulating the own immune system to work harder or smarter, in order to attack cancer cells, or by giving immune system components such as human immune system proteins. In the last few decades, immunotherapy has become an important part of treating schedules for some types of cancer and they all will impact in how cancer will be treated in the future. Immune therapy includes treatments that work in different ways. Some of them boost the body immune system in a very general way. Others help "training" the immune system to specifically attack cancer cells. Immunotherapy works better for some types of cancer that for others. It's used by itself for some of these cancers, but for others it seems to work better when used together with other types of treatments.

Immunity against cancer: Immune-oncology, a new alternative against certain types of cancer, including metastatic melanoma. Xóchitl Gomez-Roel (BMS, Mexico). The immune system has the greatest potential for the specific destruction of tumours with no toxicity to normal tissues and with long-term memory that can prevent cancer recurrence. The last 30 years of immune-oncology research has provided solid evidence that tumours are recognized by the immune system and their development can be stooped or controlled during long-term through a process known as immune-survillance. Tumour specificity of the immune response resides in the recognition of tumours antigens. Viral proteins in tumours caused by viruses and mutated proteins from oncogenes or other genes, as well as non-mutated but abnormally expressed self-proteins found in all tumours, have been shown to be good antigens and good targets for immune-survillance. In many cancers, however, malignant progression is accompanied by profound immune suppression that interferes with an effective antitumor response and tumour elimination. Initially, most of the escapes from immune-survillance was ascribed to changes in the tumour cell themselves (loss of tumour antigens, loss of human leukocyte antigen molecules, loss of sensitivity to complement, or T cell or natural killer (NK) cell lysis), making them a poor target of an immune attack. However, it has become clear that the suppression comes from the ability of tumours to subvert normal immune regulation to their advantage. The tumour microenvironment can prevent the expansion of the tumour antigen-specific helper and cytotoxic T cells and instead promote the production of pro-inflammatory cytokines and other factors, leading to the accumulation of suppressive cell populations that inhibit instead of promote immunity. The best described are regulatory T cells and myeloid-derived suppressor cells. Great conceptual and technical advances in the field of immune-oncology over the past 30 years have provided us with the knowledge and techniques to develop novel immunotherapeutic approaches for the treatment of cancer. These include methods that enhance tumour immunity by blocking inhibitory pathways and inhibitory cells in the tumour microenvironment (e.g. antibodies against cytotoxic T-lymphocytes-associated antigen-4 programmed death 1 or its ligand programmed death ligand 1, or low dose chemotherapy). Of equal importance, they include methods that can enhance the specificity of an antitumor immunity by inducing the expression of T cells and antibodies directed to well-defined tumour antigens (e.g. cancer vaccines, adjuvants, immune-stimulatory cytokines). These approaches are having a substantial impact on the treatment of some patients with advanced, previously untreatable, malignancies as metastatic melanoma. Most exciting of all, these successes provide a rationale to expect that used in various combinations or earlier in diseases, current and future immunotherapies may transform cancer treatment, improving a prognosis for many patients.

• **Session on Familiar Amyloidosis** (sponsored by Genzyme/SANOFI):

Alejandra Gonzalez-Duarte-Briseño (Genzyme, Mexico). Amyloidosis is a condition in which an abnormal protein amyloid builds up in own tissues and organs. When it does, it affects their shape and how they work. Amyloidosis is a serious health

problem that can lead to life-threatening organ failure. Many different proteins can lead to the formation of amyloids deposits, but only a few have been linked to significant health problems. The type of proteins and where it collects determines the type of amyloidosis that can occur. Amyloid deposits may collect throughout the whole body or just in one given area. There are different types of amyloidosis, including: primary systemic amyloidosis (systemic AL), secondary amyloidosis (systemic AA), dialysis related amyloidosis (DRA), senile systemic amyloidosis (SSA) and familiar hereditary amyloidosis (AF). The latter is a rare form that is passed down through families. It is caused by an abnormal amyloid transthyretin (TTR) protein, which is made in the liver. This protein is responsible for the most common forms of hereditary amyloidosis. This is a caused deposit of normal TTR in the heart and other tissues which occurs most commonly in older men.

The perspectives and challenges of a patient having familiar amyloidosis were discussed at the end of the session by Mrs. Adriana Briones-Zabala from the Mexican patients with Amyloidosis Association.

• **Session on Mucopolysaccharidosis and neurology** (Sponsored by Biomarin):

Neurological update in mucopolysaccharidosis (MPS). Alejandra Camacho-Molina (Genetic Dept. National Institute of Neurology and Neurosurgery INNN), Mexico.

Research funded by the National institute of Neurological Disorders and Stroke (NINDS) has shown that gene therapy for vital transmission in animal models of MPS can stop the accumulation of storage materials in brain cells and improve learning and memory. the researchers are planning additional studies to understand how gene therapy stimulates recovery of function in these animal's models. It may take years before this treatment become available for humans.

Advances in pharmaceutical developments and rare diseases. Felipe Navarrera (Biomarin LatinAmerica, Mexico). The pharmaceutical research industry was undoubtedly a key factor in generating new knowledge, which have materialized in drug therapies and providing solutions to the health of millions of people in Mexico and the world. There is a lack of public awareness of rare diseases, and often these patients are left with no hope treatments. The rarity of the disease significantly increases the complexity of clinical development. Usually, there is little knowledge about the diagnosis, and few experts and treatment centres. Every time there is an increased recognition by governments of these patients requires sustainable access to treatments for rare disease. And because of its unique nature, orphan drugs typically receive an expedited review for marketing approval.

• **Session on hereditary angioedema, example of a rare disease** (sponsored by CSL Behring):

Hereditary Angioedema, experiences in diagnosis and treatments. Sandra Nieto (National Institute for Paediatrics, INP, Mexico). Hereditary angioedema is a syndrome characterized by repeated attacks of angioedema that affects the skin and mucosa of the upper airways and digestive tract. This condition is produced by a genetically determined deficiency or dysfunction on chromosome 11, autosomal dominant, the C1 stearase inhibitor (C1 inhibitor) acting on the first component of complement. Without this inhibitor, the complement cascade is activated, generating pharmacologically active mediators (kinins), which produce an increase in vascular permeability and extravasation of fluids, angioedema, in the area where it is generated. In our country (Mexico) there are more than few families diagnosed in relation to the affected population, which implies that there is still a deficiency in diagnosis and lack of information about the disease, which in turn has low prevalence in Mexico.

Hereditary angioedema in Mexico. Treatment guidelines. Maria E Vargas (Mexico). Treatment of hereditary angioedema is stablished by an international consensus. The development of guidelines for the treatment of the disease can drive the use of diagnosis procedures and drugs indications. We describe the pharmacological features of the drugs of use in use at Mexico in the treatment pf hereditary angioedema. Also, its usage and control of the most frequent adverse events as described, and the recommendations of the last international consensus, applicable to formulate a guide for the hereditary angioedema at Mexico.

• **Session on Niemann-Pick** (sponsored by Actelion)

New diagnosis tools for Niemann-Pick type C detection. Leticia Munive-Baez (Mexico). Niemann-Pick diseases is a group of inherited severe metabolic disorders that allows a certain kind of fat accumulation in cells. The fat, sphingomyelin, accumulates in lysosomes (membrane-bound organelles in cells). The lysosomes normally transport materials trough and out of the cell. The prognosis is individual but the severe forms is fata in adulthoods and the milder forms may even have, in some cases a normal lifespan.

The diseases involve dysfunctional metabolism of sphyngo-lipids, which are fats found in cell membranes, so it is a kind of sphyngolipidosis. Sphyngolipidases, in turn, are included in the larger family of lysosomal storage diseases.

Niemann-Pick diseases is inherited in an autosomal recessive pattern, which involves both copies or alleles, of the gene that must be defective to cause the disease. Defective means they are altered in a way that impairs their specific function. Most often, the parents of a child with an autosomal recessive disorder are carriers; they have one copy of the altered gene, but they are not affected because the other copy produces the enzyme. If both parents are carriers, each pregnancy has a 25% chance of producing an affected child. Genetic counselling and genetic testing are recommended for families who may be carries of Niemann-Pick.

• **Plenary Conference: Relevance and outcomes of genomic medicines in relationship with rare diseases.** Gabriel Manuel Lee

(Mexican Institute for Social Integrity, Mexico).

The National Human Genome Research Institute defines genomic medicine as an "emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g. for diagnostic decision-making) and the health outcomes and policy implications of that clinical use". Already, genomic medicine is making an impact in the field of oncology, pharmacology, rare and undiagnosed diseases, and infectious diseases.

The knowledge generated as a result of an extraordinary research effort would be used to advance our understanding of biology and disease and to improve health. The adoption of a "precision medicine", where genomic s, epigenomics, environmental exposure, and other data would be used to more accurately guide individual's diagnosis. Genomic medicine, as defined above, can be considered a subset of precision medicine.

The use of the new discoveries in patient's care takes many years. Based on discoveries over the past five to ten years, genomic medicine is beginning to fuel new approaches on certain specialities that are the leading edge of incorporating genomics, as diagnosis for genetic and genomic markers to guide tailored treatment strategies.

• Session on orphan drugs for pulmonary hypertension treatment:

Clinical and drug experience with congenital hearth disease in Mexican patients. Humberto Garcia (ISSSTE National Medical Centre "20 de Noviembre", Mexico). The ISSSTE has a national reach to 12% of the total population of Mexico. The populations served by the health system is closed population (the service is only for the employees of the Mexican government and its families) so the management of patients with pulmonary hypertension (PAH) is effective, and we have the availability of reference remotely as the health care system provides transportation and accommodation to the affected. The presentations of pulmonary hypertension to our hospital, according to the NICE classification is distributed in 67% PAH associated to heart disease, 24% associated to congenital heart disease, and 9% of other types of PAH.

The clinic of pulmonary hypertension has a behaviour influenced by being a national reference centre for the treatments of congenital heart diseases. Also providing care to adult patients with repaired congenital heart disease and those not repaired. Demographic distribution, in relation to gender, as seen at our files, shows a slight predominance of women (55%). The 84% of the sample population has between 1 and 20 years old, but more than half are younger then 10 years old, justified in a centre for congenital heart diseases. Of the patients with 67% patients with PAH associated to heart disease, are divided in half with repaired and unrepaired or Eisenmenger complex (17%). The presentation of idiopathic PAH correspond to 24% of the sample, in which 8% of patients with familiar PAH are included. A group, 9%, of PAH are patients with bronchopulmonary dysplasia and cystic fibrosis mainly. Regarding the treatment guidelines our institution adheres to the CENETEC guides (www.cenet.salud.gob.mx) for pulmonary artery hypertension in adults. In principle, the guides do not conform to the real situation of each case and the availability of treatment is poor and very variable. For this reason, we use the international guidelines (NICE, 2013). The types of therapies ae distributed in 47% of combination schedules, 43% mono-therapies and 8% in triple therapies. Monotherapies is done with sildenafil in 20% of the cases, and 23% with bosentan. The 5-year survival results: 100% (56/56 cases) during the first year, 97% (99/96 cases) survival after 3 years, and 95% (128/122 cases) after 5 years. Registered causes of morbidity include atrial arrhythmia 12%, hypothyroidism 5%, right heart failure 5%, and depression 4%. Mortality causes are arrhythmia 80%, right heart failure 15% and sudden death 5%. Other programs: in the institution there also programs that extend special situations such as trait and repair program, and rapid initiation with treprostinil among others.

Treatment of pulmonary arterial hypertension. Arturo Gomez (Mexico). Pulmonary arterial hypertension (PAH) is a rare disease that causes an increase in the vascular resistance and an increase in the blood pressure in the pulmonary circulation. The reduced blood flow through the lungs is accompanies by an insufficient supply of oxygen to the body. As a consequence, patients suffer from lethargy, shortness of breath and a drop in their physical performance. If PAH is left untreated for two or three years after the first diagnosis have been made, it will lead to a life-threatening heart failure. Early diagnosis and initiation of a proper treatment are important for the progress of the disease and the quality if life of the patients affected by pulmonary hypertension.

Currently, the primary goal of therapeutic methods is o improve the blood flow in the small (pulmonary) circulation. Improving the blood flow relieves the pressure on the right side of the heart, increases the oxygen uptake and improve the physical performance. It is very important that patients who suffer from PAH have their disorder treated at a centre specialized in PAH.

CONCLUSIONS

This D&IOD starting up meeting was driven through 4 plenary conferences, 5 independent sessions, 6 industry sponsored sessions, plus other 3 satellite sponsored sessions, including 25 speakers from 8 different countries. Opinions from government or official institutions representatives, academia's, public and private health institutions and research services were included. Topics devoted to diagnosis, research and clinical management with orphan products were developed. Examples of international experiences, sharing data and biobanks and of how to deal rare diseases against traditional public health concepts for

priorities were discussed. Moreover, cooperation with procedures and resources in practice at Mexican health institutes were able to be discussed. When dealing with rare diseases which may have available treatments, such as for multiple myeloma, immunotherapies in cancer, a group of lysosomal diseases, familiar amyloidosis, advanced melanoma, Nieman Pick, neurological aspects of mucopolysaccaridosis, hereditary angioedema and pulmonary hypertension, basically, information, training, and expertise at the Mexico City is comparable to the international levels, but the conditions may largely vary within the country and institutions. These unequal situations may be a picture likely described in other regions of the Latin-American continent as well (19,20). Thus more inclusive programs, networking and interactions needs to be developed, ideally motivated by laws or regulations, either at the national and regional levels. Accessibility plans and integral support for the affected by rare diseases and its care givers are being adequately performed by some health institutions. Orphan products research is barely being carried out mainly by individual's initiatives and it's a major pending matter in the region. Internal and external cooperation should be organized.

Next meeting is planned to be carried at Moscow, November 3 and 4, 2016; hosted by "Genetica" Russia and GEISER Foundation. The 2nd D&IOD will include a technological exhibition and experts driven plenary conferences. Independent contributions will be accepted as well. Please contact CIIPT (Center of Innovation and integration programs and technologies) - Ciipt2012@gmail.com. upon your interest in participating and proposals. GEISER Foundation also receives requests for holding future D&IOD meetings world-wide (info@fundaciongeiser.org).

ACKNOWLEDGEMENTS

The following institutions supported the D&IOD meeting at Mexico 2015: The Institute of Security and Social Services for State Workers (ISSSTE, Mexico), GEISER Foundation (Group of Linkage, Research and Support for Rare Diseases, Latin-America), The Mexican Federation of Rare Diseases (FEMEXER, Mexico), "Pide un Deseo" (Lysosomal diseases patients group, MEXICO), The International Conference of Rare Diseases and Orphan Drugs (ICORD).

D&IOD at Mexico, as part of the "Mexican Rare Diseases Global Week" received educational grants for specific session from Genzyme (SANOFI), Shire, Bristol-Myers-Squibb, Actelion, Biomarin, CSL Behring, Sobi and Recordatti Group. All others non sponsored conferences or sessions were free of conflict of interests and the opinion is the sole responsibility of the respective speaker. Institutional founding's, when provided, is mentioned at the end lines of each specific conference abstract.

Authors gives special thanks to Mrs. Julieta Campillo for overall text reviewing; and to Ségolène Aymé, Antoni Matilla-Duenas, Mayte Gil-Borja, Manuel Posada de la Paz, Deborah Mascalzoni, Stephen Groft , Xóchitl Gomez-Roel, Gabriel M Lee, for providing abstract of their conference presentations which were fully included in the present report.

Mrs. Celia Palacios-Gomez-Tagle and Mr. David Peña-Castillo from FEMEXER (Mexico), and Dr. Alina Vlasich de la Rosa (ISSSTE) headed the local staff providing logistic support for D&IOD organization at Mexico. Together with Paulina and Carlos Peña-Aragon provided the warm local atmosphere comforting the plain interaction among attendant, authorities and staff, during the whole meeting development.

REFERENCES

1. Asbury CH. The Orphan Drug Act: the first 7 years. JAMA 1991, 265:893-897.
2. Jacob A, Tandon M, Kumar D. Orphan drug: Development trends and strategies. J Pharm Bioallied Sci 2010, 2: 290-299.
3. Berman JJ. Rare Diseases and Orphan Drugs. Keys to understanding and treating the Common Diseases. Elsevier Inc, London, 2014.
4. Preskorn SH. Treatment options for the patient who does not respond well to initial antidepressant therapy. J Psychiatr Pract 2009, 15.202-210.
5. Tang W, Makuuchi M, Intractable and rare diseases research. Intract Rare Dis Res, 2012, 1:1-2.
6. Seoane-Vazquez E, Rodriguez-Monguio R, Szeinbach SL, Visaria J. Incentives for orphan drug research and development in the United States. Orphanet J Rare Dis 2008, 3:33 doi:10.1186/1750-1172-3-33.
7. Haffner ME, Whitley J, Moses M. Two decades of orphan product developments. Nat Rev Drugs Discov 2002, 1:821-5.
8. Rooswinkel R, Mulder G-J, van Deventer S. acquiring orphans. Nat Biotech 2014, 32: 213-216.
9. Burgel PR, Bellis G, Olesen H, et al. Future trends in cystic fibrosis demography in 34 European countries. Eur Respirat J. 2015. DOI: 10.1183/09031936.00196314
10. Onakpoya IJ, Spencer EA, Thompson MJ, Heneghan CJ. Effectiveness, safety and costs of orphan drugs: an evidence-based review BMJ Open 2015;5:e007199 doi:10.1136/bmjopen-2014-007199.
11. Barak A, Nandi JS. Orphan drugs: pricing, reimbursement and patient access, Int J Pharmac Healthcare Market, 2011, 5:299-317.
12. Califano A, Buttle S, Friend, Ideker T, Schadt E. Leveraging models of cell regulation and GWAS data in integrative network-based association studies. Nat Genet 2012, 44: 841-847.
13. Uhlén M, Fargerberg L, Halström BM, et al. Tissue-based map of the human proteome. Science 2015, 347: 394-403.
14. Menche J, Sharma A, Kitsak M et al Uncovering disease-disease relationships through the incomplete interactome. Science

2015 347: 841-849.
15. Tosi LL, Warman ML. Mechanistic and therapeutic insights gained from studying rare skeletal diseases. Bone 2015, 76: 67-75.
16. Forman J, Taruscio D, Llera VA, et al. The need for worldwide policy and action plans for rare diseases. Acta Paediatr 2012, 101:805-807.
17. Rodwell Ch. Aymé S. Rare disease policies to improve care for patients in Europe. Biochem Biophys Acta 2015, 1852: 2329-2335.
18. Caetano PA. Expedited approval of orphan drugs in Latin America not yet a reality. Reg Focus 2011, 1:27-29.
19. Goncalvez AM, Llera VA, Roldan, EJA. Economic assessment of health technologies in rare diseases and orphan drugs: expert opinions on priorities predominating in Hispano-American countries. Rare J 2014, 1 (suppl 3): 148.
20. Fafaglia A, Llera VA. Background of an educative project for Latin-American and Caribbean (LA&C) health advocates in rare diseases prevention. Rare J 2014, 1 (suppl 3): 178.

Picture 1. Speakers and organizers participating at the Mexican Rare Diseases Global Week 2015, standing at the front stairs of the Bella Vista ISSSTE building, Mexico City, October 12-17, 2015. (photo provided by FEMEXER, Mexico).

October 2015, Volume 2, Number 3, Supplement 3

Report of the 4th Latin-American Congress on Rare Diseases and Orphan Drugs (ER2015LA), Mexico City, October 12, 2015. Identifying the regional priorities.

Llera Virginia A[1], Peña-Castillo David[2,3] on behalf of the program organizing committee.

[1] GEISER Foundation, Mendoza, Argentina. info@fundaciongeiser.org

[2] FEMEXER, Mexico City, Mexico.

[3] Pide un Deseo México City, Mexico.

ABSTRACT

The 4th edition of the Latin-American Conference ER2015LA was successfully developed once again. This time, GEISER, the founder of this Conference, invited the Mexican Federation of Rare Disorders (FEMEXER) as a Co organizer. FEMEXER is the national rare disease nonprofit patient organization in Mexico.

GEISER, pioneer in Latin America, and FEMEXER worked together in order to organized this conference, within the Mexican Rare Diseases Global Week, 2015, including the International scenario through the X ICORD Annual Meeting.

The ER2015LA aim was willing to speed up some achievements about rare diseases in the national and regional levels but also, updating about the state of the art in the continent, explore the particular needs and requests from the different stakeholders. The meeting aspired to serve as a platform to insert the region within international cooperation, with other peer organizations and rare diseases institutions working for globalizing the rare diseases issues. A number of experts participated in conferences and sessions related to laws and regulations, the current scenarios described by patient's groups from different countries, the role and responsibilities of the local industry and health care providers, and the features of the international scenario for cooperation opportunities, were analyzed by regional representatives together with international experts. After the program was accomplished the building of a Latin-American identity in the rare diseases field and orphan drugs policies was found mandatory. This autorecognition is an essential step to collaborate internationally securing impact in the zone and with equity. Accordingly, a position letter was elaborated. At the same time, advanced models of cooperation between the rare disease community at Mexico, its government authorities, and its health care providers were shown as action models which can be adapted and replicated in countries with similar socio-economic conditions. In turn, the regional research and developments should be incentivized and translated to production, in order to balance the differential impact of orphan products among countries which produce and countries which only consume. Hence, the ER2015LA at Mexico settled a basic position in Latin-American rare diseases aspects, which should continue to be reinforced by future agreements and networking.

The Rare Diseases and Orphan Drugs Journal has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n° 305690: RARE-Bestpractices project: www.rarebestpractices.eu. Sole responsibility lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein.

WWW.RAREBESTPRACTICES.EU

INTRODUCTION

Rare diseases are world-wide existing conditions which are not well known, having few medical support due to the lack of specific diagnosis and treatments tools developments (1), among other features which fuse the demands of patients affected by different clinical conditions. Due to the inclusion of these problems in the health agenda has been largely delayed, global international cooperation is now being claimed in order to expedite research and developments, empower assistance programs and balanc e the accessibilities in many countries. Notwithstanding the good wills, the success and equity of cooperation is always subjected to the mutual acknowledgement of the differences and priorities in health, social, economic, and technological resources issues at each particular region. Therefore, each territory should perform their tasks in order to gain self-confident information about their respective state of the art in the field. The health and social resources availabilities, and their country priorities and policies should be weighed, in order to connect the research and assistances programs to the international nets, but ensuing local impacts. The aim of globalization should be to introduce efficient actions at each place, providing integrated solutions to patients with equity, and universality, rather than following a single predominant idea or priorities.

GEISER Foundation, first rare diseases NGO operating with a Latin-American and Caribbean scope, since 2002, started by organizing encounters in different Latin-American countries as Argentina, Chile, Cuba, Columbia, Dominican Republic, Brazil, Panama, Peru, Uruguay. The group further assembled the first two Latin-American Congresses at Buenos Aires (ER-2008LA and ER2010LA), and the third one carried out at Sao Paulo, Brazil (ER2013LA). These early regional meetings were seeking for visibility, awareness and cooperation among the different stakeholders and social players. In parallel, the outcomes of the meetings were introduced at the international scenarios through several bridging platforms as the International Conferences on Rare Diseases and Orphan Drugs (ICORD annual meetings) (2,3), and by encouraging the participation in the World Rare Diseases Day (WRDD) since their beginning. GEISER also linked to medical and social networking; and organized workshops and conferences at many customary medical and patient groups' congresses of different specialties.

In turn, the lysosomal diseases patient group organization of Mexico "Proyecto Pide un Deseo", early approached to GEISER during 2010, and efficiently grow-up at Mexico with influences at international scenarios. With such impulse the Mexican Federation of Rare Diseases Organizations (FEMEXER) was created, receiving outstanding support from private and officials' institutions and performing many imaginative initiatives in the country. Hence both, GEISER and FEMEXER convinced that the coming step was to highlight the regional priorities and needs, decided to ally for the organization of the Mexican Rare Diseases Global Week, during October 12-17, 2015, which included within its events this 4th Latin-American Rare Diseases and Orphan Drugs (ER2015LA) meeting at Mexico City. With the valuable cooperation of the Institute of Security and Social Services of the State Workers (ISSSTE), and of ICORD members, the event was made successfully possible.

Accordingly, ER2015LA was developed at the ISSSTE Buena Vista Building auditorium during October 12, 2015, and hereby the sessions and outcomes are summarized.

THE ER2015LA MEETING PROGRAM AT MEXICO 2015

ER2015LA meeting was co-chaired by Mr. David Peña-Castillo (FEMEXER President) and Dr. Virginia A. Llera (GEISER Foundation President), supported by Mr. José Reyes-Baeza-Terrazas (ISSSTE General Director) and Mr. John Forman (ICORD President).The program was divided into six consecutive sessions, and closed by the co-chairs together with parliament representatives from Mexico (see picture 2).The main aspects are summarized as follows,

Picture 2. Members of the Guanajuato State (Mexico) parliament deputies, together with Dr. Virginia LLera and Mr. David Peña-Castillo, congress co-chairs, and Mr. John Forman ICORD president, at the meeting press conferences reporting the provincial rare disease program.

• **S-I. How Latin America is including the rare diseases community needs into laws and regulations.** Coordinated by Ignacio Burgos-Pérez (Spain).

Lic. Beatríz E. Yamamoto-Cázares (Ex-deputy of the Mexican Parliament) exposed about the initiatives undertaken at the Mexican state of Guanajuato to drive the health assistance of the affected by rare diseases. Likely, Lic. Maria Cristina Gabrili (Deputy of the National Brazilian Parliament), commented that given the characteristics of high complexity and low prevalence of the rare diseases, there is a need to treat them with a global approach, with a clear coordination of the actions at national, regional and local levels, as well as cooperation, diagnosis, treatment and sharing the knowledge and resources on this topic. Likewise, and due to the importance of the social aspects of the rare diseases, the approach of the strategy on the required social assistance is essential. It prevails the design of a strategy of action that includes legislation and incorporation into the government programs in order to assure the coverage and adequate assistance to the affected by rare conditions. Further examples of local initiatives were also given by Lic. Daniel Cedeño (Panama Health Ministry Advisor), remarking the important advances achieved at the Panama Republic to take care of patients with disabilities and seek for sustainable programs for the patients affected by rare diseases. Panama is aware of the need on cooperation and expressed its interest in leading in this field of the human health.

• **S-2. How Latin America is accomplishing its needs. Progresses in regulatory issues.** Coordinated by Mario Alanis-García (México).

Dr. Mario Alanis-García (Federal Commission for the Protection against Health Risks, COFEPRIS, Mexico) updated about the current norms and regulations in force at Mexico, and the achievements in the recent years. The new options and flexibilities were highlighted in order to get faster approvals and availabilities of new drugs in the country. Nowadays, orphan drugs availabilities has been improved. Nearly three times as many drugs for rare diseases are being developed, compared with a decade ago, commented Dr. José V. Coto-Ugarte (National Drugs Department, Ministry of Health, El Salvador). The orphan drug status in Europe and in the United States, in contrast to the legislations in Latin American countries, has made big strides in this regards. With the implementation of new targeted regulation, reimbursement strategies, and drug approvals, accessibility to treatments will be improved for people affected by rare diseases in these developing countries.

• **S-3. Working models in Mexico for rare diseases.** Coordinated by Alina Vlasich de la Rosa (México).

Dr Javier Lozano-Herrera (General Director for Health Services Management, Popular Insurance, Mexico) described the actions and strategies undertaken up to date at the "Seguro Popular" health coverage institution, in order to ensure medical care and access to the treatments of the patients affected by rare diseases. While Dr. Ignacio Ortiz-Aldana (Ministry of Health of the Guanajuato State, Mexico) explained about the cooperation with "Seguro Popular" to organize the best structure in the country caring for patients with rare diseases, specifically for those with lysosomal diseases. Dr. Rafael M. Navarro-Meneses (Chief Medical Director at Institute for Social Security and Services for State Workers, ISSSTE, Mexico) refers to the network stablished at ISSSTE for the prompt care of patients having rare diseases, ensuring specific treatments for such conditions. It is mentioned that since September 2014, it was instituted the Interdisciplinary Clinical Care for the Beneficiaries with an Orphan Disease program, at the National Medical Centre "20 de Noviembre", in order to contribute to the supplementary medical management of patients, and help expediting the intra- and extra-institutional references for specialists and competent laboratories with experience in the subject. A supporting network for patients, and its family, and organizations devoted to rare diseases was also created, being 30 social organizations, 26 of them members of FEMEXER, already participating. Then, Lic. Paulina Peña-Aragon introduced the information, counselling and support program: A proposal for future research. There is an urgent need for inclusion of people with rare diseases to access at a fundamental human right, the right to health. To do this, it is necessary to talk about the specifics features of rare diseases, omissions and exclusions that prevail in diagnosis and access to treatments in these persons, and the lack of psychological support for the people with such diseases; thus "Accesalud" arises. "Accesalud" is an information, guidance and counselling program that aim to consolidate a platform of comprehensive mental health care, meeting the needs of people with rare diseases, facilitating their access to health care, through on-line support. The system not only provides reliable information and guidance related to a given disease, but allows a psychological support to the affected by a rare condition, and to their family group as well. This model aims to provide guidance for the path that patients must follow in order to access to medical treatments, as well as knowing his or her rights and obligations. This program also tries to empower them and provides some certainty about what they can expect from the health institutions. Added to this and considering the particularities of those individuals affected by rare diseases "AcceSalud" was developed to remotely provide enhanced geographical coverage and better support, seeking for the social inclusion of those patients and families living with the rare disease reality through the use of new information technologies and communications tools (ICT´s).

Dr, J. Benítez-Granados J from ISSSTE reported about the institutional process of inclusion of patients with lysosomal disease. ISSSTE provides medical care to patients with lysosomal diseases (LD) through the program called "Programa de Enfermedades Huérfanas (lisosomales)" (PEH). It carries out the following procedure: The patient with suspected LD diagnosis is identified and the case evidence is handled to the health service manager who reports it to the Unit Medical Director, then he submits an inclusive request to the PEH which is sent to the "Subdirección de Atención y Regulación Hospitalaria

"(SRAH). Subsequently the case is transferred to the PEH where they verify that the file is complete and consistent with the diagnosis according to the guidelines for each disease. Once the file is complete it is sent to an interdisciplinary group of medical specialists in each disease, who analyze and review the case in order to express their opinion regarding the diagnostic and treatment. If approved the (Genzyme, Mexico)PEH makes an application to the "Coordinación Administrativa" for funds to be transferred, if the Coordinación has enough budget, the assets will be sent to the corresponding Medical Unit or Town Hall who are responsible of signing up the contract and managing the treatment. The PEH supervise the administration of the therapy, pharmacovigilance, treatment response and the patient follow-up in every Medical Unit.

- **S-4. LA&C national patient organizations round table: What is going on in our countries?** Coordinated by Jacqueline Tovar (México).

The local status needs and priorities at Argentina (F. GEISER), Chile (F. GEISER, FECHER and "Derechos a la Vida"), Colombia (FECOER), Guatemala (Bene Asociation), Panama (Niños de Cristal) and Mexico (FEMEXER) were reviewed by delegates from the respective patients groups. Basically the predominant scenarios at Latin-America are the existence of many and growing individual efforts, driven by medical services, health care institutions, researchers or patient's groups. In addition, many laws and regulation has been approved by now meaning the official recognition of the rare diseases impact in the health programs. In spite of some commendable achievements, there are no national plans regulated by laws, or being sustained with consistent financial support. Accessibility and equity is a major concern, and comprehensive educational programs, free of conflicts of interest should be installed at the short term. Definitively, rare diseases are not a health priority in the Latin American countries, and the socio-sanitary system creates vulnerabilities within the affected, not matching with the conditions working in mode developed countries. NGOs initiatives are barely supported by government resources and undesirable dependences may likely occur.

During the following day, satellite session were hold devoted to the challenges at Mexico, formation of reference centres, empowerments of patients associations, supporting health care programs (Accesalud), positioning from Fundacion GEISER for Latin-America, prospects and challenges, and further meetings with parliament representatives and journalists.

- **S-5. About the role of the regional industry and private health care providers. Responsibility, cooperation and accessibility.** Coordinated by Emilio Roldán (Argentina).

Dr. Jose Rivelino-Flores-Miranda (Regulatory Affairs and Innovation Director at the National Chamber of Pharmaceutical Industry of Mexico, CANIFARMA) updated the current state of the art in research & developments of the Mexican pharmaceutical industry, highlighting the quality and efficiency to solve most of the health requirements of the country. He was followed by Dr. Emilio Roldán (invited by the Latin American Association of Pharmaceutical Industries, ALIFAR). ALIFAR is an NGO in which 320 companies from 14 regional countries join, aiming to empower and support the development of the regional industry. In the last years (2008-2014) a 42.5% units increase in sales, and a 57.1% increase in values (IMS Health Argentina), reflects the growing economy of the region and a net inclusion of more pharmaceutical goods consumers. Indeed, at an average price of 8.09 U$D per unit (2014 data) the regional production is adapted supplying medications affordable for the majority of the population. Many facilities approved by over-seas high standard agencies, and fast growing exportation figures also means that the quality of the products has been significantly improved. At present the regional industry is prepared and competitive for further challenges as the Orphan Drugs (ODs) market. ODs are a world-wide growing market, and due to its high prices is challenging the health economy of many countries. The impact is still under control in the Latin American and Caribbean region essentially because the market is still under development. Nevertheless, Latin America is a huge continent. Awareness and diagnosis need to be best worked-out. Complex health assistance systems and a variety of social and cultural realities demand experience and know-how to progress with efficiency. It can be estimated that today not more than 10% of the affected by rare diseases are identified (based on extrapolated prevalence figures, and/or sales figures in US or European markets). Nevertheless, the scenario will rapidly change compelled by an increasing demand, the introduction of better diagnosis tools and the increase of many new ODs approved at both FDA and EMA. To minimize the high impact of the expensive ODs, policies of discount or tired-prices formulas (multiple price schemes) are being offered by the manufacturer, according to the economic indicators (purchasing power) of the different countries. The formula looks fine for the ultra-rare conditions, and/or special situations, but there are further options for all other rare diseases. In reference to tired-formulas, the region is still not always prepared for ODs "Access programs" and some regulatory agencies raise involuntary barriers. In parallel, some financial measures to rescue payer's organizations with additional taxes seem to be far from satisfying the needs that will be invariably demanded. So the region will need to face the ODs defies, and the regional industry is well prepared to offer competitive options. Moreover the local pharma industry can duly develop innovations to supply to international markets and in this way compensate the importing expenses by producing high-value exportations. Beyond such goodwill, today there is no Orphan Drug Act in force in the region. That is clearly disadvantageous in comparison with US or European developers. Tax and grants facilities, vouchers (bonus), clearer ODs regulatory rules, certainties in the market (epidemiological accuracy of data, awareness) needs to be promoted. In addition, links with specific academic programs and industry programs, among others, should be smoothed and planned together, in order allow the regional industry similar conditions to the international one. Already available RDs laws are well welcome, but there is a need for an ODs law balancing demand and offer, ideally harmonized in the whole continent. In conclusion the pharmaceutical industry is willing and ready to

develop solutions and accessibility to the Latin American population, as well as innovations for the affected all over the world. But following the models performed at US and Europe the RDs interested community should set clear rules with transparency and open the scope to all the actors interested in the field. Governments, industry, academia and patients groups should work together. Finally, ODs is not a problem of minorities only; it is a serious social challenge and at the same time a technological opportunity for the region. Latin America have the infrastructure, Latin America have the patients, but needs fiscal, economic and regulatory incentives to invest in OD and RD in the same way Europe and USA are doing. The cost of such incentives is infinitely cheaper than the cost of non-treating the patients.

- **S-6. The new scenarios for R&D for orphan drugs in Latin America. International opportunities.** Coordinated by Celia Palacios (México).

After the expression of goodwill and cooperation with Latin-America, Mr. Peter Saltonstall (President and CEO at the National Organizations for Rare Diseases, NORD, USA), Mrs Paloma Tejada (Senior Manager at Rare Diseases International, France) exposed about the advancements on the Rare Disease International (RDI) project promoted by EURORDIS (European Organization for Rare Disease). Dr. Virginia A. LLera (President of GEISER Foundation, Latin-America), highlighted the differential priorities of rare diseases in the Latin-American countries, and the need of cooperating within global organizations after having identify the local situations, needs and priorities. International partnerships are highly desired, with balance of opportunities and actions at the different parts of the world.

In this sense a more regional communicational tool was developed, and its impact was measured comparing with global tools used by the organizations in LA&C. An advertising campaign in social networks in order to discover and make visible the realities of the Latin American and Caribbean countries was developed by GEISER Foundation through August to October 2015. Same was based on a football (soccer) balloon named "Gemma" which was the tool selected to do an "un common passed" by different rare diseases organizations or individual patients from Mendoza City, Argentina, to Mexico City at a glance. At the Mexican Rare Diseases Global Week events, the ball was signed by most of the key leaders of opinion in rare diseases supporting the Latin-American claims to set its regional claims and priorities (see picture 3). Accordingly, the nomination of August 13 as a Latin-American Day for Rare Diseases, precisely aimed to focus in the local features, and efficiently interact and support the EURORDIS World Rare Diseases Day (February 29), was the expected outcome of this pilot campaign.

Picture 3. Gemma, the football (soccer) balloon signed by experts in rare diseases which carries the expectancies of the Latin American people affected by rare diseases, their care givers and organizations.

CONCLUSIONS

The governmental intervention to respond to patient groups claims is considered essential by legislators, in both national and provincial levels at Latin-America. Some initiatives are underway with success. Regulations to expedite approval for orphan drugs is being improved, facilitating studies and availabilities, notwithstanding there is no harmonization in the region. Regarding assistance to patients with rare diseases there are good examples of health care companies at Mexico, as ISSSTE, "Seguro Popular" and "AcceSalud" programs, collaborating with health ministries, legislators and patient's groups, driving patients with certain rare diseases, expediting diagnosis and treatments as available. This serve as working models which can be adapted to further Latin-American environments. The regional pharmaceutical industries in both Mexico and the rest of Latin-America are well equipped and with enough know-how to interact with competitive and innovative projects in orphan drugs. Incentives are claimed in order to balance the opportunities of the Latin American commitments with those coming from US and Europe. During the closing ceremony of the congress, the following Mexican parliament members: Lic. Beatriz Yamamoto-Cázeres, Lic. Adriana Elizarraraz, Lic. Alejandra Gutiérrez, Lic. Lorena Alfaro, and Lic. Alejandra Reynoso signed

with Mr. David Peña-Castillo a memorandum of understanding to develop rare diseases program at Guanajuato province, which in turn is the introductory law-supportive plan to be applied in the country. Dra. Virginia Llera closed remarking the positioning of the Latin-American rare diseases stakeholders and the will of being inserted at the international networking as peers and with the inclusion of the local features, needs and priorities. A supporting letter to each Latin-American country was issued, and the ICORD positioning letter "The declaration of Yukiwariso" (1) was translated into Spanish and distributed to authorities as well.

Next Latin American meeting (ER2017LA) is planned to be carried at Panama City, during the second half of 2017; hosted by "Niños de Cristal" patient organization and GEISER Foundation. This 5th congress will include in its program due spaces for members of the governments, academia, industry, patient's groups and social security experts. International experts interested in global cooperation are also welcome. Independent contributions will be accepted as well. To interested parties or to propose activities, GEISER Foundation secretariat should be contacted at info@fundaciongeiser.org

ACKNOWLEDGEMENTS

The following institutions supported the ER2015LA meeting at Mexico 2015: The Institute of Security and Social Services for State Workers (ISSSTE, Mexico), GEISER Foundation (Group of Linkage, Research and Support for Rare Diseases, Latin-America), The Mexican Federation of Rare Diseases (FEMEXER, Mexico), "Pide un Deseo" (Lysosomal diseases patients group, MEXICO), The International Conference of Rare Diseases and Orphan Drugs (ICORD).

Authors gives special thanks to Mrs. Julieta Campillo (GEISER Foundation) for her dedication with the text reviewing and program coordination from the Argentinean secretariat; and to Mrs. Celia Palacios-Gomez-Tagle, Paulina and Carlos Peña-Aragon and the whole "Pide un Deseo" staff of volunteers are acknowledged as key persons for the meeting planning organization and success.

Parts of the manuscript were provided by the participating speakers and included in the present report after text adaptation. None of the speakers were payed and participated at ER2015LA with each own opinions. Although backed by the Mexican Week of Rare Diseases organization, the ER2015LA meeting was financed with support from ISSSTE and donations from the volunteer's staff of FEMEXER and GEISER Foundation. The entire program was built free of conflict of interest and following institutional compliance rules. FEMEXER and GEISER Foundation reserves the right of the material and images produced during the event.

REFERENCES

1. Forman J, Taruscio D, Llera VA, et al. The need for worldwide policy and action plans for rare diseases. ActaPaediatr 2012, 101:805-7.
2. Roldan E. Proceedings from the VIII International Conference on Rare Diseases and Orphan Drugs (ICORD). St. Petersburg (Russia), October 31-November 2, 2013. Rare J 2014, 1 (suppl1): 1-46.
3. Roldán E, Larsson A, Gavhed D. Proceedings from the IX International Conference on Rare Diseases and Orphan Drugs (ICORD). Ede (TheNetherlands), October 7-9, 2014 Rare J 2014,1 (suppl3): 133-191.