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RE(ACT)CONGRESS

9-12 March 2016 BARCELONA

3RD INTERNATIONAL CONGRESS ON RESEARCH
OF RARE AND ORPHAN DISEASES

9TH TO 12TH MARCH 2016
CROWNE PLAZA BARCELONA – FIRA CENTER, BARCELONA, SPAIN

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SWISS FOUNDATION FOR RESEARCH ON ORPHAN DISEASES
SCHWEIZERISCHE STIFTUNG FÜR DIE FORSCHUNG SELTENER KRANKHEITEN
FONDATION SUISSE POUR LA RECHERCHE SUR LES MALADIES ORPHELINES
FONDAZIONE SVIZZERA PER LA RICERCA SULLE MALATTIE ORFANE

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Introduction

It is with great pleasure that I have the chance to introduce the Abstract Section dedicated to the 3rd RE(ACT) Congress – International Congress of Research on Rare and Orphan Diseases (http://www.react-congress.org) – in the present issue of *Molecular Syndromology*.

Collaboration between researchers is particularly important to avoid duplication of studies in a field where financial resources are very limited and patient population is small. Since 2012, the efforts of the BLACKSWAN Foundation (http://www.blackswanfoundation.ch/) have been focusing on the implementation of the RE(ACT) Initiative, a project that aims at facilitating cooperation in research and increase knowledge sharing.

The Initiative comprises the first international scientific congress on research of rare and orphan diseases, RE(ACT) Congress, and the development of the online platform RE(ACT) Community (http://react-community.org/). The platform aims to help researchers find new collaborations, exchange information and start crowdfunding campaigns for their projects.

These international activities are of fundamental importance for the scientific community, especially in the field of rare diseases. With this in mind, we established strong partnerships with other international organizations such as E-RARE, Eurordis and IRDiRC.

The third edition of the Congress in Barcelona, Spain, held March 9–12th, 2016 is organized by the BLACKSWAN Foundation and E-RARE, the European Research Consortium on Rare Diseases. The 2016 RE(ACT) Congress will focus on: drug repositioning and personalized medicine, next-generation sequencing (NGS) technology and undiagnosed rare diseases, pathophysiology, bringing treatments to the clinic, neurological diseases, patients and research. The unique feature of the RE(ACT) Congress is that specialists from different fields of research come together to address rare diseases and treatments across the boundaries of their own disciplines.

The conference also wants to promote research on rare and orphan diseases among the general public, the industry and policy makers. In fact, to date, these diseases do not represent a public health priority, and little research is performed despite the fact that all together these conditions affect half a billion people in the world – not to forget that most of them are children. The adoption of incentives for the pharmaceutical industry have stimulated the development of treatments for rare diseases; however, much remains to be done, since effective therapies still are not available for more than 95% of the patients. Increasing awareness, international cooperation and the active participation of patients in research are key prerequisites to secure success in this field.

The BLACKSWAN Foundation has recently started a new program that promotes a global and comprehensive strategy and ensures rare diseases are recognized as a public health and research priority. The program has three separate components which run in parallel, namely: (a) Awareness and Advocacy, (b) Support for Research (grants), and (c) Strengthening of the RE(ACT) Initiative.

We believe that a stronger engagement at an international level is fundamental to attract more resources, create new incentives for research and develop therapies for millions of patients. At the same time, it is essential to

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directly support research projects and prove that investing in research is also cost effective for the health systems and often bring new discoveries and treatments for more common diseases to the benefit of a larger population.

On the occasion of the 3rd RE(ACT) Congress, the BLACKSWAN Foundation wants to launch an online petition to advocate for research on rare diseases.

We believe that public policy plays a crucial role in advancing rare disease research. The Orphan Drug Act of 1983 in the US and the European Regulation n. 141/2000 demonstrate the impact that policy decisions can have in driving forward innovative research and show the successful outcomes that public policy intervention can achieve. However, much more international attention and incentives are needed to push forward research and increase prevention, diagnosis and treatments for rare disease patients.

The petition will include the most important points that deserve the attention of institutions and international organizations; it will be prepared as a position paper and finally, officially presented to Rare Disease International (RDI; http://www.rarediseasesinternational.org) during the 2017 Rare Disease Day. This document will assist RDI in advocating for rare diseases at the United Nations, the World Health Organization and other international parties.

The petition will be available online after the Opening Ceremony of the RE(ACT) Congress. Please share it with your contact and become an ambassador – signing can do very much for this challenging field of research (http://www.blackswanfoundation.ch/en/petition/).

Olivier Menzel

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Drug Repositioning and Personalized Medicine

A003_2016

Pinging the Transcriptome: Mining the Pharmacopeia for Rare Inherited Disorder Therapies

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The genetic analysis of monogenic disorders has over the past 3 decades resulted in the identification of thousands of genes which either cause or impact these conditions; most of these disorders have no therapies. The modulation of the transcripts and proteins encoded by these genes might be anticipated to have therapeutic utility, either by their upregulation (e.g. of mutated recessive disease genes encoding proteins with residual enzymatic activity, of genes that are sequentially similar to, and that functionally recapitulate, mutated recessive disease genes or of genes that cause disease when haploinsufficient) or downregulation (e.g. of mutated dominant genes which confer a gain of pathologic function or of genes which, when present in increased number, cause disease). Moreover, it is known that small molecules including clinically approved drugs can affect the human transcriptome. Given the number of genes that cause or effect inherited human conditions and the substantial subset of the transcriptome that is impacted by drugs, we believe that there are likely genes which are both modifiers of rare disease and responsive to pharmacologic modulation. The enhanced CARE for RARE project in Canada is therefore exploring whether previously unknown off-target effects of clinically approved drugs may lead to new therapies. We have screened ~80 rare conditions, (haploinsufficient, rescuing paralogous genes and hypomorphic mutation with residual function) using this approach. There are currently 5 conditions which show some induction *(GLUT1, SMAD3, DDHD2, NEU1, HPRT)*; the most promising results and lessons learned from this approach shall be presented.

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A004_2016

Genetic Editing with the CRISPR/Cas9 System for Huntingon's Disease

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Huntington's disease (HD) is a neurodegenerative disorder caused by a pathological CAG expansion at the 3′ end of the first exon of the huntingtin gene *(HTT)*. Currently, there is no efficient treatment for HD. Editing of the mutant *HTT* gene with the clustered regularly interspaced short palindromic repeats (CRISPR) system represents a new and promising approach. Recognition of the HTT target sequence by a single-guide RNA sequence (sgRNA) and the CAS9 protein is inducing DNA double-strand breaks (DSB), which activate endogenous cellular repair pathways. Non-homologous end joining (NHEJ) will introduce small insertions/deletions (indel) that alter the reading frame of the *HTT* gene, while homology-directed repair (HDR) is activated in the presence of a DNA template. To validate the approach and optimize the delivery of the CRISPR system with viral vectors, we first targeted artificial sequences containing fluorescent reporter genes in HEK 293T cells. An efficient gene disruption was measured and associated with a loss of fluorescence in neurons, astrocytes, in vitro and in vivo. Furthermore, we developed multiple strategies to disrupt the mutant *HTT* gene. Quantification demonstrated a high rate of indels, leading to a strong reduction of HTT protein in HEK 293T cells, mouse cortical neurons and human iPS-derived neurons. Blocking *HTT* expression in vitro HD models is improving several physiopathological parameters. We are currently evaluating the impact of allele- or nonallele-specific mutant *HTT* editing in human neurons from HD patients. Altogether, these data demonstrate the potential of the CRISPR technology as a therapeutic strategy for HD.

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A005_2016

Repurposing Losartan to Ameliorate Dystrophic Epidermolysis Bullosa

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This talk will focus on an emerging conceptual approach to alleviate symptoms in recessive dystrophic epidermolysis bullosa (RDEB), a rare skin fragility disorder characterized by injury-driven blister formation, progressive soft tissue fibrosis, and a highly elevated risk of early-onset aggressive skin cancer. Since RDEB is caused by genetic loss of collagen VII, gene/protein-based strategies have been in the focus of most efforts for RDEB therapy. However, major hurdles have to be overcome before such therapies can be implemented in the clinics. Since RDEB is largely driven by progressive secondary disease mechanisms, a 100% efficiency of causal therapies cannot be expected, and alternative approaches need to be pursued. From our and other investigators' research, it has become evident that although the mutations and the protein at fault differ, common disease mechanisms are at play in a range of genetic connective tissue disorders, including RDEB. Targeting these mechanisms provides means to slow down disease progression, reduce its burden, and facilitate clinical implementation. We took an evidence-based approach for a first symptom-relief therapy for RDEB. Based on findings that TGF activity is elevated in injured RDEB skin, we repurposed the angiotensin II type 1 receptor antagonist losartan to treat RDEB in a preclinical setting. The drug has been used in other connective tissue disorders to ameliorate fibrosis, but the data cannot be automatically transferred, since the effects are tissue-, context- and disease specific. In the

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RDEB mouse, losartan efficiently limited TGF activity and attenuated fibrosis, as seen by lower fibrotic markers, longer and fewer fused toes and softer skin. To gain better knowledge on mechanisms determining disease progression in RDEB and mechanisms of action of losartan, we employed global unbiased mass spectrometry-based proteomics. This revealed molecular events linked to tissue inflammation as major drivers of disease progression. Our recent research revealed a new mechanism by which RDEB tissue becomes malignant and new druggable therapeutic targets. Treatment of 3D organotypic RDEB skin cultures with inhibitors of TGFβ signaling, lysyl oxidase, or integrin β1-mediated mechanosignaling-limited tumor cell invasion. In conclusion, our studies suggest that limiting unrestrained responses to tissue damage poses a relatively risk-free approach to reduce disease burden in RDEB.

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A006_2016

Autophagy Induction as a Potential Treatment for Lysosomal Diseases

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Lysosomal storage disorders (LSDs) are genetic diseases caused by the abnormal accumulation of non-degraded macromolecules into lysosomes, leading to a biochemical cascade that results in the impairment of the autophagy flux and the prevention of lysosomal clearance in most cases. Recent studies have demonstrated that the induction of autophagy in LSDs could decrease the abnormally stored material by enhancing lysosomal exocytosis. Bicalutamide is a synthetic non-steroidal antiandrogen molecule reported to be involved in the induction of autophagy in human prostate cancer cells. The aim of our work was to evaluate the potential benefits of bicalutamide treatment, and its enantiomers (R and S), in skin fibroblasts derived from patients affected by 7 different LSDs. Treatment response was evaluated in cultured fibroblasts by monitoring lysosomal exocytosis, substrate accumulation and cell viability. Treatment with (S)-bicalutamide enantiomer was able to ameliorate the altered biochemical parameters significantly in all the cell lines, while the response to (R)-bicalutamide, the racemic bicalutamide or ciclodextrin (a previously described autophagy inductor in LSDs), was less effective. Moreover, we have studied the molecular mechanism underlying bicalutamide's action, and we found that bicalutamide acts through the activation of the transcription factor TFEB. This transcription factor enhances the transcription of genes involved in autophagy and lysosomal biogenesis, leading to the subsequent increase of the autophagy flux and the lysosomal exocytosis. These results are encouraging as this approach circumvents the primary enzyme deficiency responsible for these diseases by exploiting the ability of lysosomes to expel their content into the extracellular space, resulting in the clearance of the pathogenic stored material.

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A007_2016

BBrm02, a Read-Through Repurposed Drug for Nonsense Mutations, Shows Proof of Efficacy in Treatment of Spinal Muscular Atrophy (SMA)

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Background: The administration of read-through agents (e.g. aminoglycosides) acting on the stop codon located at exon 8 of the survival of motor neuron (SMN-del7) protein was found to be effective in inducing a higher level of functional SMN protein. Prior attempts to translate these agents into therapeutic candidate drugs were hampered by prohibitive toxicity. Bioblast Pharma is currently developing a proprietary therapy for spinal muscular atrophy (SMA), using FDA-approved macrolide antibiotic drugs as read-through agents, known as the BBrm family. **Results:** BBrm02, intrathecal formulation of azithromycin, increased SMN protein expression levels and function (shown by nuclear GEMs presence) in SMA patients' cell lines. Intracerebroventricular (ICV) administration of BBrm02 to the well-known delta7 mouse model caused an increase in SMN expression levels in brain, spinal cord and muscle at 2.1-, 2.4- and 5.7-fold, respectively, above vehicle-treated animals. The unique PK profile of BBrm02 enabled a sustained effect in this model on body weight, motor function and increased survival, following a single administration, especially at low dose. Moreover, 30 days following a single ICV administration of BBrm02 to the Regeneron C/C mouse model (the Jackson Laboratory) demonstrated a statistically significant increase in both tail length and body weight, phenomena that are indicative of an effective intervention in this mouse model. Combination of BBrm02 therapy with ASO therapy resulted in a synergistic effect on the delta7 mouse model. Toxicological studies with intrathecal administrations to rats and dogs have been completed, showing no observed adverse effect level (NOAEL). **Conclusions:** Our encouraging combined results demonstrate a proof of efficacy of the Bioblast approach for the treatment of SMA using its lead molecule, BBrm02. The completion of safety studies enables Bioblast to initiate a Phase I clinical study in the near future.

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A008_2016

Teaching an Old Dog New Tricks? Lessons on Using N-of-One Trials to Repurpose Treatments for Rare Diseases: The Example of Ephedrine for Myasthenia Gravis

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Background: During the first edition of the RE(ACT) Congress, we reported on the development of an n-of-one trial service for rare diseases to examine the efficacy and safety of off-label treatments. An n-of-one trial is an efficient method because a patient can be his own control, using a crossover design. We now describe the results of the first series of n-of-one RCTs, using ephedrine, a drug (previously) used for asthma in some countries, for autoimmune myasthenia gravis (MG) as a case study, and the regulatory implications of these results. Ephedrine may postpone or abolish the need for immunosuppressive therapy when added to acetylcholinesterase inhibitors or low-dose prednisone, but its effect in MG has not been systematically evaluated. **Objectives:** To study the effect and safety of ephedrine as add-on treatment for MG in a Cochrane systematic literature review and a series of n-of-one trials, and to examine how this treatment can be made available to patients via the current regulatory frameworks for market approval and reimbursement. **Results:** Our review reported on 53 nonrandomized studies including 308 patients but showed that there was no evidence from RCTs. Our series of 4 n-of-one RCTs found a small but statistically significant improvement in all 4 patients (1.0 point improvement on the Quantitative Myasthenia Gravis score) and minimal adverse effects. The Netherlands Medicines Evaluation Board (CBG) and National Health Care Institute (ZIN) were asked to advize on how these results can be used to make this treatment available to patients. CBG stated that data of n-of-one trials could be sufficient to warrant registration as a last resort option for rare diseases under certain conditions such as fast onset of the effect. However, both ZIN and CBG considered the clinical relevance of the effect inconclusive. A different study design (e.g. a parallel group trial with longer treatment duration) was suggested. Currently, only companies have the means to apply for market approval. Investments in old drugs may cause companies to raise prices of rediscovered drugs beyond cost-effectivity. **Conclusion:** N-of-one RCTs can provide evidence of efficacy of treatment for rare diseases, particularly when repurposing existing treatments where companies can expect little return on investment. It seems warranted to use public funding for evidence development for such drugs to ensure reasonable prices.

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A009_2016

Mild Inhibition of Alanine-Glyoxylate Aminotransferase Translation as a Possible Treatment of Primary Hyperoxaluria Type I

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Background: Primary hyperoxaluria type 1 (PH1) is a kidney stone disease, often leading to ESRD, caused by absence, deficiency or mistargeting of the liver peroxisomal alanine-glyoxylate aminotransferase (AGT), encoded by AGXT. The most frequent mutation in the *G170R* gene, responsible for 30% of PH1 cases in Caucasians, results in aberrant mitochondrial localization rather than catalytic inactivity. Modulating AGT maturation and folding has long been perceived as a therapeutic approach. Yet, numerous attempts over the years failed to rescue AGT mutants. We propose mild translational inhibition as a novel approach to improve folding and localization of AGT mutants. **Methods:** Our model is CHO cells transfected with appropriate vectors as well as hepatocytes from PH1 patients with a mutated *G170R* and WT AGT. We used the FDA-approved drug emetine as a translation inhibitor. To ensure selective and specific discrimination between the mitochondrial (major) and the peroxisomal (minor) subpopulations of a mutated *AGT*, we developed the GlowAGT system based on the recently described self-assembly split GFP approach. Only those GlowAGT molecules (WT or mutant) that are localized in peroxisomes are fluorescent. **Results:** WT-AGT, but not G170R-AGT was detectable by GlowAGT fluorescence due to mitochondrial mislocalization of the mutant. However, both variants were visible by indirect immunofluorescence. Treatment of G170R-AGT with emetine showed a statistically significant increase of fluorescent subpopulation of G170R-AGT. GFP fluorescence was exclusively codistributed with the peroxisomal staining in all cases. Treatment of G170R-AGT human hepatocytes with emetine had rescued the elevated level of oxalate excretion by human hepatocytes. **Conclusions:** We show that mild translation inhibition by emetine is a novel therapeutic approach for PH I caused by AGT misfolding/mislocalization. We suggest that mild translation inhibition could be used as a therapeutic approach for many conformational diseases.

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A010_2016

Novel Therapeutic Perspectives for Sarcoglycanopathy by Assisting Protein Folding

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Sarcoglycanopathy, the collective term for 4 forms of limb-girdle muscular dystrophy (LGMD 2C-2F), is a rare genetic disorder

affecting mainly the proximal musculature. Defects in any one of the genes coding for α-, β-, γ - or δ -sarcoglycan (SG), forming a key structural tetramer in the sarcolemma of striated muscles, strongly affect the SG-complex formation/stability. Disease severity is strictly related to the residual level of sarcoglycans in the sarcolemma, with the most severe forms characterized by the almost complete loss of the proteins. Most of the sarcoglycan defects are missense mutations producing a full-length but folding-defective protein. We have proven that the primary pathological event in sarcoglycanopathy occurs in the endoplasmic reticulum, where the quality control system, by proof-reading newly synthesized sarcoglycans, recognizes and directs the folding-defective mutants to the proteasomal degradation. This event causes the secondary loss of the wild-type partners. We have also demonstrated that many missense mutants retain their function and that the entire complex can be properly rescued by blocking the degradation of these mutants. These findings opened new perspectives for the therapy of this neglected disease allowing to design small molecule-based approaches aimed not only to merely inhibit sarcoglycan mutants degradation, but particularly to help their folding so that, structurally stabilized, these mutants can skip disposal and traffic at the proper site of action. To this intent, we have tested several small molecules, known as protein-folding correctors screened for the treatment of cystic fibrosis, in both cell models expressing folding-defective forms of α-SG and primary myogenic cells isolated from a patient suffering of LGMD2D (human samples have been provided by the Neuromuscular Bank of Tissues and DNA samples of the Italian Telethon Foundation.) We have observed, by Western blot and immunofluorescence analyses that treatments with these compounds lead to the accumulation of different *α-SG* mutants that are competent to assemble with the wild-type partners and traffic to the cell membrane. Although the mechanism of action of CFTR correctors on sarcoglycans is still unknown and needs to be clarified, these data represent the proof of principle of a 'protein-repair strategy' that can be developed to treat LGMD2D, utilizing well-known and available small molecules correcting mutant folding.

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A011_2016

Human Brody Disease and Its Animal Model Cattle Pseudomyotonia: From Understanding the Pathogenetic Mechanism to Identification of Novel Therapeutic Approaches

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Human Brody disease is a rare inherited myopathy clinically characterized by an exercise-induced impairment of muscle relaxation due to a deficiency of the sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA1), resulting from a defect of the *ATP2A1* gene coding for SERCA1. In skeletal muscle fibers, SERCA1 allows relaxation by removing Ca^{2+} from cytosol to restore resting Ca^{2+} concentration. Brody disease is transmitted as an autosomal recessive trait and is genetically heterogeneous. SERCA1 deficiency has been attributed to a reduction either in SERCA1 protein content at sarcoplasmic reticulum (SR) membranes of pathological fibers, or in Ca^{2+}-ATPase activity. Large animals have emerged as genetically relevant models for human inherited diseases. Cattle congenital pseudomyotonia (PMT) is a muscular disorder characterized by stiffness and delayed muscle relaxation. All PMT-affected animals are homozygous for the *ATP2A1* gene mutations and, like Brody disease, cattle PMT turned out to be genetically heterogeneous. Bovine pathological muscles are characterized by a selective reduction of SERCA1 protein. Clinical symptoms, genetic and biochemical findings clearly demonstrated that cattle PMT is the true animal model of Brody disease. Using both HEK293 cells overexpressing *SERCA1* mutants and biopsies from cattle pathological muscles (collected in conformance with the institutional guidelines for the care and use of animals), we provided evidence that *SERCA1* mutants were polyubiquitinated and prematurely degraded by the ubiquitin-proteasome system. The treatment with proteasome inhibitors rescued the expression level of mutated *SERCA1* at SR membranes, both in the HEK293 cell model and in muscle fibers from PMT-affected animals. Although corrupted in proper folding, SERCA1 retained the catalytic properties; therefore, by monitoring Ca^{2+} re-uptake, we demonstrated that the recovered SERCA1 was able to re-establish resting cytosolic Ca^{2+} concentration. At present, no specific therapy exists for Brody disease. We have found that small molecules known as 'CFTR correctors' are able to reverse the Brody pathological phenotype by promoting correct folding and proper targeting at SR membranes of the mutated misfolded SERCA1. So, a possible pharmacological therapy could be hypothesized for the specific population of Brody patients in which *ATP2A1* mutations impair SERCA1 protein folding causing its rapid degradation but leave the Ca^{2+}-ATPase activity of the protein unaffected.

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A012_2016

Repositioning and Rare Diseases: A Fast Drug Development Process

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Background: Drug repositioning is the process in which a drug already used for a certain condition is used to treat other diseases, expanding the range of use of the medicine. An advantage over traditional drug development is that a repositioned drug has already passed toxicity and clinical trials (such as Phase I); its safety is well known, and the risk of failure for reasons of adverse toxicology is reduced. Thus, they can bypass much of the early cost and time, representing a profitable way to achieve success. Computational chemistry is a promising strategy in drug repositioning. SOM Biotech's approach is drug based and, in particular, based on chemical similarity. Orphan diseases are also attractive as there is a focus in unmet needs; facilitated development and availability of the drug through priority review, accelerated approval, fast track designation, breakthrough therapy designation, and market exclusivity period; small clinical trials, and a targeted commercial footprint. SOM is devoted to combine these 2 concepts in order to avoid the safety risks, costs and time needed to bring the drug onto

the market. **Methods:** SOM's discovery platform is a proprietary, ligand-based virtual screening software which identifies new drug activities. It compares physicochemical properties of a selected reference compound, with those of a database of marketed products plus products that have reached clinical research. As a result, products with potential similar biological activity but with different structure than the reference compound are identified. Once a new activity is determined in silico, disease relevant in vitro and in vivo studies are performed to confirm it and protect it with an international patent. Experimental validations are carried out by consortia partners or outsourced when appropriate. **Results:** Among the different projects on orphan diseases carried out since 2009, two of them reached clinical phases. SOM0226 has been demonstrated to be effective for transthyretin amyloidosis in a 20-patient proof-of-concept trial. SOM3355 showed to be effective in preclinical experiments for the treatment of chorea associated to Huntington's disease and a clinical proof-of-concept is ongoing. **Conclusion:** SOM's technology showed to be effective in repositioning drugs for rare diseases as successful cases demonstrate. The company is devoted to obtain fast potential cures for orphan diseases, diseases with a very high medical need and with no treatment available.

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A013_2016

A New Chance for Cystinosis Therapy

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Cystinosis is a rare autosomal inherited disease caused by a functional deficit of the lysosomal cystine transporter cystinosin, coded by the *CTNS* gene. The accumulation of cystine crystals causes impairment of several organs, in particular, end-stage kidney failure and ocular complications in the first decade of life, if not treated early with cysteamine. Oral and ophthalmic cysteamine therapy postpones the need for renal transplantation and ocular complications, respectively. However, the resulting side effects of cysteamine therapy adversely affect the lifestyle of patients and their relatives. Large-scale drug screening was performed on immortalized proximal tubule epithelial cells of patients (ciPTEC *CTNS*$^{-/-}$) to find molecules that improve the cystinotic phenotype. Prestwick Chemical Library, collecting 1,200 small molecules 100% FDA and EMA approved, was assayed at 10 μM for 24 h on ciPTEC *CTNS*$^{-/-}$. Two drugs were identified by crosschecking positive hits found by quantification of the intracellular cystine level measured by HPLC, and by determining the apoptosis, assessed as caspase 3/7 activation state in an automatized platform. Molecule 4176 was chosen for its bioavailability and molecular stability. Pharmacokinetics studies in ciPTEC *CTNS*$^{-/-}$ showed that molecule 4176 reduced intracellular cystine more efficiently than cysteamine, in a dose ranging from 0.1 to 20 μM. This result was confirmed in PBMCs of patients. Furthermore, an addictive effect was observed when molecule 4176 and cysteamine were combined in a ratio 1:1. Molecule 4176 reduced ROS significantly by about 25% and by about 50% in combination with cysteamine. Finally, an in vitro cystine crystallization assay showed the capability of molecule 4176 to reduce the formation of crystals in a supersaturated cystine aqueous solution. The preclinical experimental evidences show that repositioning of molecule 4176, used alone or coupled with cysteamine, could represent a potential therapy for systemic and topical treatment of cystinosis.

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A014_2016

In vitro Model of Proximal Tubular Dysfunction in Cystinosis

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Background: Cystinosis is a homozygous recessive lysosomal storage disorder caused by mutations in cystinosin *(CTNS)*. Patients with this disease develop a severe renal phenotype with polyuria and proteinurea at the age of 6 months (renal Fanconi syndrome) and kidney failure before the age of 10. The current therapies are not able to restore proximal tubular function or improve water and protein reabsorption by the kidneys. **Aim:** The aim of this study is to develop a high-throughput in vitro assay that can be used to evaluate the cystinostic proximal tubular cell function for drug testing **Methods:** We used conditionally immortalised proximal tubular cells (ciPTEC) from both cystinosis patients and healthy controls. To evaluate the protein uptake, we compared the uptake of labelled bovine serum albumin (BSA-FITC) or receptor-associated protein (RAP-GST), both ligands of the megalin mulitiligand receptor which is responsible for protein reabsorption in the proximal tubules. Next, we evaluated the colocalisation of the internalised protein with the endosomes (EEA1 staining) or lysosomes (LAMP1 staining). Images were taken with the CV7000 high-content imager to get high-resolution confocal images. **Results:** RAP-GST showed a clear vascular pattern that overlapped with the endosomal and lysosomal compartment. BSA-FITC binding showed high background staining and was not used for further analysis. RAP-GST colocalised well with EEA1 and LAMP1 after 1 h incubation, compared to no overlap on ice. Protein uptake experiments showed that protein degradation was delayed in cystinotic cells as compared to the controls. Furthermore, the lysosomes were less regularly distributed on the cell surface in cystinotic cells and prone to forming larger clumps. This phenotype was used to grade the cystinotic phenotype and will be used as a model to select for drug candidates that may have a positive effect on the proximal tubule function in cystinotic patients. **Conclusion:** The in vitro model of human proximal tubular cells shows a clear defect in lysosomal patterning and protein degradation which we can use as a functional readout to identify drug compounds that can improve cystinotic proximal tubular function.

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A015_2016

Endogenous Metabolic Profiling as a Fundament in Personalized Theranostics

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Metabolomics has grown into an established tool in research as: (1) diagnosis, i.e. classification, (2) identification of biomarkers in relation to e.g. diseases, and (3) dynamic studies, i.e. to identify effects from e.g. medical treatment, changes in food intake, or environmental or genetical changes to a living species such as human, animal, or plant. In this presentation, the use of metabonomics as a tool in drug discovery and theranostics will be highlighted. In the first part, the differences in biochemical profiles between healthy volunteers and persons with the diagnosis rheumatoid arthritis (RA) are discussed as well as the identification of novel biochemical pathways for understanding the underlying factors of the disease. In the next part, a comparison of different animal models is made in order to identify the most relevant factors describing the disease in humans for the evaluation of novel treatments, which can be drugs, nutrition, etc. In the last part, we will make an attempt to understand the origin of the endogenous metabolites we observe in the circulating blood, i.e. the biochemical pathway used to identify enzymes involved in the disturbed metabolic pattern caused by a mal condition, which is the basis for developing treatments of rare diseases such as Battens.

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A016_2016

Back to the Future – How Drug Repositioning Has and Will Create Treatments for Unsolved Diseases

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There are at least 7,000 unsolved diseases in the world affecting as many as 500 million people. The majority of these are rare or neglected diseases affecting people who have little or no access to effective medical solutions. The global for-profit medical research industry can create 15–40 new drug treatments per year, with only a few of them focused on rare diseases. When industry does create a treatment for a rare disease, the yearly cost can exceed USD 100,000 per patient. At this rate, if all we can depend on is industry to create treatments for unsolved diseases, we are likely to leave most patients without a treatment and our economies depleted. We need to find a way to supplement the good work of industry to create more effective treatments and bring down the cost of healthcare. The good news is that there is a simple and cost-effective solution to unsolved diseases, if we can only create the economic and other incentives to support it. This solution is drug repositioning. There are thousands of inexpensive and relatively safe drugs and nutriceuticals already human approved or human used that can be quickly repositioned to provide affordable and effective treatments and cures for these unsolved diseases. We know drug repositioning works for 2 reasons: (1) There are hundreds of examples of approved drugs that have already received further regulatory approval for a new disease indication, from thalidomide repositioned for the rare diseases leprosy and multiple myeloma, to colchicine repositioned for gout to the rare disease Mediterranean fever. (2) Physicians prescribe off-label treatment to between 18–90% of their patients, depending on their treatment specialty, with rare diseases, pediatrics, oncology, pain and mental health having the highest rates of off-label prescribing. This presentation will discuss the historical successes of drug repositioning, examine the current landscape of drug repositioning in industry, bioscience, academia and clinical care, and hypothesize about how we can improve patient outcomes and reduce healthcare costs in the future, if we are able to create the right incentives for drug repositioning.

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A017_2016

Drug Repositioning for the Personalized Therapy of Cystic Fibrosis

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Discordance in patient's responsiveness to treatment complicates the assessment of efficacy of new candidate drugs and entails the need to enroll thousands of people in large clinical trials with the result that a great proportion of individuals may take medications that do not help them. Personalized approaches that focus on individual and not average responses to therapy are encouraged. Cystic fibrosis (CF), the most common lethal recessive disease in Caucasians, is a paradigm of heterogeneity in patient response rates to treatments. Mutation-specific highly expensive treatments, aiming at directly targeting the mutant CFTR protein, are available for a small fraction of CF patients with a rare channel-dead mutant but are only marginally effective in rescuing CFTR function in the vast majority (70–90%) of CF patients bearing the most common class II *F508del-CFTR* mutation. Emerging mechanistic target-driven discovery programs aim to identify novel targets for therapeutic intervention by targeting the proteostasis network perturbed by the lack of a functional CFTR. For this purpose, drug-repositioning strategies for affordable patient-centered therapies that are able to restore the CFTR function are required to fill the gap between basic research and clinical application and favor a personalized approach to CF therapy. A target-driven drug-repositioning strategy led to the discovery that a combination of 2 molecules which target 2 major nodes of the hub-dysfunction in CF, disabled autophagy and CK2 overactivation, may circumvent a F508del-CFTR defect. The repurposed drug cysteamine, FDA

approved for the treatment of cystinosis, which reestablishes autophagy, synergizes with the over-the-counter flavonoid epigallocatechin gallate (EGCG), which inhibits the overactive CK2, thereby rescuing and stabilizing a functional F508del-CFTR, both in mice and in primary nasal cells from F508del homozygotes, and restores CFTR function in vivo in a pilot clinical trial on CF patients. Personalized medicine should benefit the patient and not the disease by targeting the right medicine, to the right patient, in the right time frame, provided that proper biomarkers are available to either predict individual patient's responsiveness to treatments or to monitor the early stages of disease reversion during treatment. Thus, new 'mechanistic' drug discovery programs and affordable predictive tests of responsiveness to treatments are required for a patient-centered medical approach to CF.

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NGS and Undiagnosed Rare Diseases

B001_2016
An Effective Approach for Diagnosing Rare Genetic Diseases within the Saudi Population

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Personalized medicine enables the convergence of information from the population to the individual level, necessary for making optimal decisions for screening of high-risk mutations, diagnosis, or optimal treatment, relative to an individual's unique genetic architecture. Time- and cost-effective solutions have been tested within the Saudi population, which carries one of the highest incidence rates of rare disorders worldwide. Here, we provide a summary of clinical genomics measures within the spectrum of preventive, diagnostic, and screening for rare disorders within Saudi Arabia. The Mendeliome, a set of 13 next-generation sequencing-based multiplexing assays that encompass ~3,000 known Mendelian genes have been tested within the Saudi population because of undiagnosed diseases suspected to be of genetic origin. A total of 2,357 patients suspected to have a genetic disease were examined. A likely causal mutation was identified in 1,018 patients, giving an overall clinical sensitivity of 43% versus ~25% reported by several large clinical whole exome sequencing (WES) studies. Only 11% of negative cases were consequently identified by WES to harbor a likely causal mutation in a known disease gene not included in the current assays. Although the Saudi population is enriched for consanguinity, 24% of solved cases were autosomal dominant and 4% were X-linked, suggesting that this approach is also applicable to outbred populations. The high degree of consanguinity allowed observation of many variants in homozygosity as a result of autozygosity. Observing them at a relatively high-population frequency strongly argues against their asserted disease link. Arab-specific versus Caucasian-specific mechanisms have been detected and will help elucidate future population genomic studies worldwide. 342 HGMD variants at high frequency [minor allele frequency (MAF) >1%] in the Saudi in-house database, including 133 variants with MAF >5% are rare in the Human variome database. Of these variants, 137 are listed in the 1000 Genomes Project with a MAF <1%, highlighting the unique distribution of variants in various populations. Finally, 433 novel disease alleles from a total of 788 variants were identified, the largest to be reported in a single study. The Mendeliome assays can account for a large proportion of suspected genetic disorders and provide significant practical advantages over clinical WES.

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B002_2016
MAGEL2 as a Gene Responsible for the Opitz C Syndrome

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Opitz C syndrome (OTCS; MIM 211750) is a rare (with less than 60 cases described in the literature) and heterogeneous genetic disorder characterized by severe malformations such as trigonocephaly, variable mental and psychomotor retardation and variable cardiac defects with a high mortality rate. OTCS shows a phenotypic overlap with Bohring-Opitz syndrome (BOS; MIM 605039), a disorder with more severe features, and it has been suggested that there is a gradient of spectrum between them rather than being separate syndromes. Different patterns of inheritance and high genetic heterogeneity have been suggested for this syndrome. In this context, next-generation sequencing technologies represent a valuable tool in investigating the molecular basis of this disease. The purpose of this study is to find the gene or genes responsible for the OTCS and BOS syndromes. We studied a cohort of 17 patients from 14 unrelated pedigrees with OTCS or BOS phenotype. Whole exome sequences (WES) of 4 nuclear families and 2 additional patients have been analyzed. We have found a mutation in the *MAGEL2* gene in an 18-year-old girl (OC7) diagnosed with OTCS. *MAGEL2* is an imprinted gene located at 15q11q13, within the Prader-Willy region, and it is maternally silenced. Patient OC7 was found to be a carrier of a de novo nonsense mutation (p.Q638*) in this gene. By means of a methylation-sensitive restriction followed by PCR amplification [Schaaf et al., 2013, Nat Genet], we have demonstrated that the mutation was in the paternal chromosome. Recently, mutations in *MAGEL2* have been associated with a Prader-Willy-like syndrome named Shaaf-Yang [Schaaf et al., 2013, Nat Genet; Soden et al., 2014, Sci Transl Med] and, independently, with severe arthrogryposis [Mejlachowicz et al., 2015, Am J Hum Genet] (references to be obtained by the author). The OC7 patient presented with severe mental retardation and seizures as well as trigonocephalia, micrognatia, hypotelorism, scoliosis, arthrogryposis, and hypotonia; these symptons are con-

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sistent with those present in Shaaf-Yang and severe arthrogryposis patients. *MAGEL2* is being analyzed in the remaining patients of the cohort, but no other mutation has been found so far. These results provide the first molecular genetic basis for OTCS and indicate that there is an overlap between OTCS and other syndromes. This result also emphasizes the high genetic heterogeneity in this syndrome. In this sense, WES has become a reliable tool in the diagnosis of these patients.

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B003_2016

A Novel Splicing Mutation in the *IQSEC2* Gene that Modulates the Phenotype Severity in a Family with Intellectual Disability

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The *IQSEC2* gene is located in chromosome Xp11.22 and encodes a guanine nucleotide exchange factor for the ADP-ribosylation factor family of small GTPases. This gene is known to have a significant role in cytoskeletal organization, dendritic spine morphology and synaptic organization. Variants in *IQSEC2* cause moderate to severe intellectual disability in males and a variable phenotype in females because this gene escapes from X-chromosome inactivation. Here, we report on the first splicing variant in *IQSEC2* (g.88032_88033del; NG_021296.1) that cosegregates in a family diagnosed with an X-linked form of ID. In a percentage of the cells, the variant activates an intraexonic splice acceptor site that abolishes 26 amino acids from the highly conserved PH domain of *IQSEC2* and creates a premature stop codon 36 amino acids later in exon 13. Interestingly, the percentage of aberrant splicing seems to correlate with the severity of the disease in each patient. The impact of this variant in the target tissue is unknown, but we can hypothesize that these differences may be related to the amount of abnormal IQSEC2 transcript. To our knowledge, we are reporting a novel mechanism of *IQSEC2* involvement in ID. Variants that affect splicing are related to many genetic diseases and the understanding of their role in disease expands potential opportunities for gene therapy. Modulation of aberrant splicing transcripts can become a potent therapeutic approach for many of these diseases.

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B004_2016

Exome Sequencing Revealed Mutations in *NADK2* in a Patient with Clinical Improvement upon Lysine Restriction and Pyridoxal Phostate Administration

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We report a 10-year-old Spanish female with mutations in *NADK2*. Antenatal CNS abnormalities showed ventriculomegaly, colpocephaly and hypoplasia of the corpus callosum. At birth, axial hypotonia along with uncoordinated movements, microcephaly and generalized cerebellar atrophy were detected. Metabolic investigations revealed high lysine, lactate and pipecolic acid levels in blood and cerebrospinal fluid. Pyruvate carboxylase and pyruvate dehydrogenase activity in fibroblasts were normal. Since the newborn period, she received biotin, thiamine and carnitine supplementation. A lysine-restricted diet was started at one month of age. As pipecolic acid was high, pyridoxine was added to the treatment. Later on, at 3 years of age, astatic myoclonic epilepsy appeared with no response to levetiracetam. We switched pyridoxine to pyridoxal phosphate with electroclinical improvement. Because the activity of mitochondrial respiratory chain complexes III and IV were slightly low in muscle, other cofactors such as ubidecorenone, idebenone, vitamin E, and creatine were added to the treatment. At 8 years of age, plasma acylcarnitines were performed and high levels of C10:2 were found. Whole exome sequencing identified a homozygous splice site mutation in *NADK2* (c.468 + 6T>C; p.Trp156Cysfs*21). This substitution generates an exon skipping, leading to a truncated protein. In fact, NADK2 mRNA and the corresponding protein were almost absent. Now, at 10 years of age, she presents ataxia and incoordination. She has oral-motor dysphasia but is able to understand flowing language and is a very friendly girl. We hypothesize that clinical improvement could be due to the lysine-restricted diet together with cofactors and pyridoxal phosphate administration, a cofactor of several enzymes in the CNS. The rationale for this treatment was the fact that the pipecolic acid level was high in CSF; consequently, its product – piperideine-6-carboxylate –could also be high. Since it is known that piperideine-6-carboxylate inactivates pyridoxal phosphate by a Knoevenagel reaction, we provide a potential explanation for the clinical improvement of our patient upon pyridoxal phosphate administration.

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B005_2016

Interactive Software for the Integrated Analysis and Identification of Rare and Undiagnosed Diseases Using NGS Data

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The growing number of known rare diseases is estimated to be larger than 7,000, with more being discovered each day. However, for only half of these diseases, the underlying genes are not known. Often, rare disease patients go for long periods of testing without a diagnosis. Recent advances in next-generation sequencing (NGS) have revolutionized genomics allowing physicians and scientists to examine patients at a level that allows finding the proverbial 'needle in a haystack'. The current challenge with NGS technologies is no longer the development of equipment, but rather the interpretation and analysis of data. Here, we present an integrated solution that facilitates analysis and identification of potential causing mutations in rare and undiagnosed diseases from NGS-based genome-sequencing studies. The application is made of several steps covering the whole analyses workflow, from raw data to a final report. All complex analysis steps are abstracted from the end user and results are presented in an intuitive and interactive way. The application annotates identified variants with over 50 properties, including descriptive statistics, prediction scores, frequencies from public databases (e.g. 1000 genome, ExAC), and information from disease-related databases (ClinVar, OMIM, BIC). In order to support researchers with finding the disease-causing mutations, an interactive filtering, prioritization, and classification mechanism is included offering unprecedented ways to analyze variants. Family studies can be collectively analyzed using sophisticated querying and filtering methods including graphical representations of the relationships. The whole system is available as a web-based application integrated into the Platomics platform, which offers powerful features for heterogeneous data handling of samples, performing analysis runs using optimized parameter settings, and tracking of previously completed analyses. As a proof of principle, using the new software, we have analyzed targeted sequencing data in a cohort of patients with primary immunodeficiency disorders (PIDs) of unknown molecular origin. PIDs are a diverse group of congenital disorders affecting both naïve and adaptive immune response resulting in severe, life-threatening, and early-onset defects. Therefore, the new application will contribute to fast and reliable diagnosis, which could have a major impact for the PID patient treatment as well as for personalized medicine.

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B006_2016

Exome Sequencing Reveals Two Autosomal Recessive Variations in the *BTD* and *NLGN1* Genes in Two Intellectual Disability and Autistic Monozygotic Twins Born of Healthy First-Cousin Parents

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Intellectual disability (ID) and autism are serious medical and social problems and establishing their cause is essential. Exome sequencing has been proven to be a powerful tool in the identification of their genetic causes, and the strategy using trio analysis that compares the genomes of the proband and the parents is thought to give a diagnostic rate of 15–40%. In this line, this study was designed to find out the genetic causes of ID and autism in families with at least 2 male brothers affected. Here, we present 2 monozygotic twin brothers born with a normal phenotype of healthy first-cousin parents. They have repeatedly presented with significant psychomotor developmental delay and autistic features including repetitive movements. They also have an atypical symbiotic behavior. On recent assessment at 15 years of age, their motor skills had improved significantly as well as their knowledge, but they still have social interaction difficulties and learning disability. The Ampliseq Exome kit was used to enrich the exon regions of the genomes, which were sequenced using the Ion Proton sequencing system with 200 bp single-end reads Hi-Q Chemistry. NGS was performed by Genetracer Biotech Company and mutations found by NGS were verified by Sanger sequencing in our laboratory. In both brothers, 2 autosomal recessive changes have been found in homozygous condition. Sanger sequencing of their parents confirmed that both variations were inherited: (1) A c.G1330>C (p.Asp444His) missense change was found in the *BTD* gene (Biotinidase). A well-documented mutation (D444H) in individuals with a mild form of biotinidase deficiency, but our patients do not have any symptoms of this deficiency, and their levels of biotinidase are similar to those described for heterozygotes. (2) A c.74T>A nonsense variation was found in the *NLGN1* gene (neuroligin-1) which has not been described to date, resulting in a truncated protein (p.Leu25*) predicted to be deleterious in in silico prediction programs. In fact, multiple members of the NL family (including *NLGN1*) have been linked to autism and ID. In addition, *Nlgn1*-knockout mice exhibit a dramatic increase in repetitive, stereotyped grooming behavior. So, we consider that this mutation is highly suggestive to be the cause of the condition of these monozygotic twin brothers.

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B007_2016

Improving the Management of Inherited Retinal Dystrophies by Targeted Sequencing of a Population-Specific Gene Panel

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Background: The aim of this study was the development of an efficient next-generation sequencing (NGS)-based diagnostic tool for the identification of causative mutations in a Spanish cohort with diverse inherited retinal dystrophies (IRD). **Methods:** We implemented a custom panel of 64 retinal genes and 3 disease-associated intronic regions for the molecular diagnosis of 32 families with a wide range of IRD. Targeted bases were captured and sequenced on the Illumina MiSeq platform. Subsequently, bioinformatics and cosegregation analyses were performed to identify causative variants. **Results:** The mutation detection rate of this panel was 100%, with 99% of target bases covered >70×. Pathogenic mutations were found in 73% (22/30) of IRD patients ranging from 50% (4/8) for autosomal dominant cases, 75% (6/8) for syndromic cases, 83% (10/12) for autosomal recessive cases, and 100% (2/2) for X-linked cases. Two cases unsuccessfully studied by exome sequencing were resolved by applying this panel. Moreover, the phenotype and genotype were not in full agreement in 6 probands, which led to the refinement of clinical diagnoses. Furthermore, intra- and interfamilial phenotypic variability was also observed in 2 cases, respectively. **Conclusions:** To our knowledge, this is the first study to apply a population-specific panel to seek for causative mutations in a cohort of unselected patients with IRD. Our results demonstrate that this approach is highly efficient for the diagnosis of this heterogeneous hereditary condition. The molecular information found in this study has aided clinical diagnosis in some cases and has improved family counseling and patient management in others.

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B008_2016

HIPBI-RD: Harmonising Phenomics Information for a Better Interoperability in the Rare Disease Field

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Background: Rare disease (RD) research is a field of medicine increasingly reliant on information technology, with the advent of low-cost whole genome sequencing revolutionising the discovery of genetic causes of disorders. Detailed phenotype data, combined with genomic data, have an enormous potential to accelerate the identification of clinically actionable prognostic or therapeutic implications and to improve our understanding of RD. The harmonisation of phenomics information, including disorders and phenotype traits that are stored in different contexts in a non-standardised way, is a cornerstone for producing sound data to foster research. **Summary:** HIPBI-RD (harmonising phenomics information for a better interoperability in the rare disease field) is a 3-year project starting in 2016 funded via the E-Rare 3 ERA-NET. This project builds on 3 resources largely adopted by the RD community: Orphanet, its ontology ORDO (the Orphanet Rare Disease Ontology), HPO (the Human Phenotype Ontology) and PhenoTips, with the support of outstanding bio-ontologies players, the European Bioinformatics Institute, and the Garvan Institute. The project aims to provide the community with an integrated, RD-specific bioinformatics ecosystem that will harmonise the way phenomics information is stored in databases and patient files worldwide, and thereby contribute to interoperability. This ecosystem will consist of a suite of tools and ontologies, optimised to work together, made available through commonly used software repositories. **Conclusion:** The HIPBI-RD ecosystem will contribute to the interpretation of variants identified through exome and full genome sequencing by harmonising the way phenotypic information is collected, thus improving diagnostics. The ultimate goal of HIPBI-RD is to provide a resource that will contribute to bridging genome-scale biology and a disease-centred view on human pathobiology.

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B009_2016

A Next-Generation Sequencing Approach for Molecular Diagnosis of Primary Immunodeficiencies

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Primary immunodeficiencies (PIDs) are a group of rare genetic diseases that can affect all arms of the immune system. Heterogeneity in the severity, frequency and anatomical distribution of

the symptoms highly contribute to the difficulty in clinical interpretation. Indeed, clinical presentations often vary within a specific disease, and different diseases have overlapping features, challenging the establishment of a clear diagnosis and potentially delaying access to appropriate treatments. To meet the need for molecular diagnosis, we have designed a blueprint to identify variants associated with undiagnosed phenotypes, by combining high-throughput technology to scientific knowledge and clinical assessment of PID patients. We used next-generation sequencing to screen DNA from peripheral blood samples harvested from individuals presenting with clinical features of PIDs. Patient-specific libraries were created from a unique panel of 361 candidate genes involved in pathways for disorders of the immune system, based both on scientific and clinical knowledge. The primer pool design allowed targeting 5,477 specific amplicons and was highly customized to allow the coverage of 97% of targeted exons. Bar-coded libraries were pooled, amplified using the emulsion PCR-based technology and templates were sequenced with the semiconductor Ion PGM instrument. More than 1 million reads per patient were analyzed with dedicated softwares in a 2-step approach involving: (1) the annotation of genetic variants, in terms of SNPs and Indels, shared between the patients' family members, and (2) the assessment of their biological impact by applying appropriate filters to reveal their potential functional role in the targeted protein. This strategy will help associating clinical relevant variants to precise clinical features. We expect this strategy to yield confirmation of known genetic etiologies in patients with atypical clinical phenotypes as well as identification of new key molecules involved in mechanisms causing PIDs and, ultimately, point the way towards new therapeutic targets.

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B010_2016

Tracking Mitochondrial Diseases through Next-Generation Sequencing

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Mitochondrial disorders are a genetically heterogeneous group of individually rare, highly incapacitating human diseases for which no effective treatment is available. The large number of more than 250 clinically similar mitochondrial disorders together with the multisystemic nature of mitochondrial diseases makes molecular diagnosis difficult, as many different medical specialties are involved and many physicians are discouraged by the complex phenotypes. The introduction of whole exome and whole genome sequencing in clinical practice of medicine has dramatically improved diagnostic success for mitochondrial diseases and moved investigative efforts from mitochondrial DNA to the nuclear genome. The increasingly broad application of sequencing is not only allowing us to better diagnose well-established Mendelian syndromes, but also to discover new disease genes and define new syndromes. Moreover, it has expanded the phenotypic spectrum of established conditions.

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B011_2016

Usher Syndrome – Challenges for Diagnosis and Treatment

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The Usher syndrome (USH) is the most common form of inherited deaf-blindness. Hearing impairment is the first symptom to develop and is detected by the newborn screening at birth. In contrast, visual symptoms (retinitis pigmentosa, RP) manifest before or during puberty. This variable onset of the clinical symptoms makes diagnosis of USH challenging. Clinically, USH is divided into 3 clinical types (USH1, USH2, and USH3) depending on the age of onset, severity and progression of the symptoms. However, additional atypical forms have been described due to the genetic heterogeneity of USH. To date, 10 causative genes, 3 additional loci and genetic modifiers have been identified. To date, the diagnosis 'Usher syndrome' is normally established in the second decade of life. However, an earlier diagnosis would support parents in their choice for cochlear implants instead of learning sign language. Cochlear implants can successfully compensate the hearing deficiency, especially when they are implanted as early as possible. In <1 year of age, the auditory pathway can mature normally resulting in close to normal speech development as well as hearing abilities. In contrast, there are currently no effective cures for the retinal phenotype available. Although gene addition is in the focus for many hereditary retinal disorders, the size of genes and the expression of various splice variants with yet undefined functions hamper gene addition approaches for USH. Patient screenings conducted over the last years have provided insights into USH-causing mutations revealing that ~11% of all USH-causing mutations are nonsense mutation. For patients carrying a nonsense mutation the so-called translational read-through therapy is a promising therapeutic option. Nonsense mutations generate a premature termination codon in the coding sequence of genes, leading to early termination of protein translation resulting in non-functional proteins that manifest in USH. Translational read-through-inducing drugs allow the translation machinery to suppress a nonsense codon and consequently result in the synthesis of full-length protein. Recent research has raised hope for the usage of translational read-through therapy as a gene-based pharmacogenetic therapy for a variety of hereditary retinal disorders caused by nonsense mutations.

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B012_2016

A Genetic Approach to Complement Newborn Screening for Actionable Genetic Conditions

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Background: Newborn screening is a public health program for the detection, diagnosis and intervention of genetic disorders that may otherwise produce serious clinical consequences. In the last years, tandem mass spectrometry allowed for expanded programs in most developed countries. While the sensitivity and specificity of the method can be up to 99% for metabolic disorders, they are lower for cystic fibrosis or hypothyroidism. Thus, new challenges are reducing false positives and avoiding false negatives by using fast and appropriate second-tier tests. In order to shorten diagnosis time and provide genetic diagnosis and counseling, we are evaluating the use of next-generation sequencing as second-tier test. **Methods:** We use dried blood spots from newborns with positive results in the newborn screening from Spain to isolate DNA and subject it to NGS library preparation. We have developed a panel of 71 known genes commonly affected in the disorders detected by this program. A bioinformatic pipeline has been designed to identify genetic variants that may be disease causing. We have retrospectively analyzed ~100 samples to establish the sensitivity and specificity. In a second phase, we will analyze positive hits from the screening in real time and will assess the turnaround time and the cost-effectiveness. In all cases, we generate a report with the genetic variants identified and classified according to the American College of Medical Genetics and Genomics guidelines. **Results:** Samples in the retrospective phase have been sequenced. Preliminary results show high specificity and sensitivity. Two candidate variants were identified in 88% of the 100 retrospective samples, and in 7%, 1 candidate variant was found. In samples where previous genetic diagnosis was available (n = 16), 100% concordance was found. These values will have to be confirmed by analyzing the entire retrospective series. We have currently enrolled 2 screening centers for the prospective phase. **Conclusion:** We have successfully developed an NGS panel that allows a sensitive and specific genetic diagnosis of diseases included in newborn screening in Spain. Our preliminary data show that genetic testing could be a valid and useful strategy to bypass confirmatory biochemical tests. This could lead to a faster and more accurate diagnosis which will help provide faster treatment to patients.

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B013_2016

De novo Mutations in Intellectual Disability: From Gene to Genome and from Research to Diagnostics

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Germline coding de novo mutations have recently been indicated to play an important role in moderate to severe forms of intellectual disability (ID). The frequent occurrence of new deleterious mutations in the germline may explain why these disorders with a severe effect on fitness remain so frequent in our population. Widespread application of unbiased methodologies, such as genomic microarrays, and more recently exome and genome sequencing of patient-parent trios now provides us with a detailed insight into the presence, distribution, frequency, and role of de novo mutations in these disorders. In this presentation, I will describe our recent work on using both family-based exome and genome sequencing to detect and interpret de novo mutations in patients with severe ID. Our data and those of other groups indicate that de novo germline mutations (SNVs, indels as well as CNVs) may explain the majority of all sporadic forms of severe ID. This has great implications for the diagnostic process of patients with ID and for estimating the recurrence risk within families. These studies provide fundamental insight into the mutational processes ongoing during spermatogenesis and oogenesis and reveal risk factors that increase the number of de novo mutations in the offspring (e.g. advanced paternal age). Moreover, the detection of recurrent de novo mutations in genes as well as noncoding regulatory elements gives an enormous boost to our understanding of the underlying biology of ID. Also, I will discuss our progress with the implementation of exome sequencing as a routine diagnostic test for genetically heterogeneous disorders and our plans to implement genome sequencing in diagnostics.

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Pathophysiology

C002_2016

Dyskeratosis Congenita and Related Diseases of Telomeres

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Dyskeratosis congenita (DC) is a pleotropic syndrome. In its classical form, it is characterised by mucocutaneous abnormalities, bone marrow failure (BMF) and a predisposition to malignancy. BMF is the principal cause of mortality and patients display features of premature aging. Studies over the last 2 decades have led to significant advances with 11 disease genes *(DKC1*, *TERC*, *TERT*, *NOP10*, *NHP2*, *TINF2*, *USB1*, *TCAB1*, *CTC1*, *RTEL1*, and *ACD)* having been characterised. Ten of these are important in telomere maintenance. DC is therefore principally a disease of defective telomere maintenance, and patients usually have very short/ and or abnormal telomeres. The genetic advances have also led to the unification of DC with a number of other disorders. This includes the multi-system disorder Hoyeraal-Hreidarsson as well as a subset of patients with aplastic anaemia (AA), myelodysplasia, leukaemia, liver disease and pulmonary fibrosis. This wide spectrum of diseases ranging from classical DC to AA can be regarded as disorders of defective telomere maintenance, 'telomeropathies', highlighting the importance of telomere maintenance in humans. Correct diagnosis is important as haematopoietic failure associated with this group of disorders is unlikely to respond to immunosuppressive agents and is more likely to respond to drugs such as oxymetholone and danazol. For patients who are unresponsive to these agents, haematopoietic stem cell transplantation using fludarabine-based low-intensity protocols is producing encouraging results. Some cases of DC remain uncharacterised. Using whole exome sequencing, we recently identified novel biallelic mutations in the poly(A)-specific ribonuclease *(PARN)* gene in families exhibiting severe DC. PARN is an exonuclease whose deadenylation activity in part controls mRNA stability and therefore regulation of a large number of genes. The mutations identified affect key domains within the protein and studies on patient cells show reduced deadenylation activity. This deficiency causes an early DNA damage response and reduced cell viability upon UV treatment. Individuals with biallelic *PARN* mutations have reduced RNA levels for several key genes associated with telomere biology. They also possess very short telomeres. Collectively, these results identify a role for *PARN* in telomere maintenance and demonstrate that it is a disease-causing gene in a subset of cases with severe DC.

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C003_2016

Of Fish and Men – Using Zebrafish to Study Rare Genetic Disorders of Hemostasis

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We are studying human genetic disorders of hemostasis, in particular fibrinogen deficiencies. These are rare and affect either the quantity or the quality of circulating fibrinogen, which is the precursor of the major protein component of the blood clot, fibrin. My laboratory identified the gene and the first causative mutations for complete deficiency of fibrinogen, afibrinogenemia, in 1999. Fibrinogen is a hexamer comprising 2 copies of 3 polypeptides encoded by the fibrinogen alpha, beta and gamma genes clustered in human chromosome 4. Mutations in the fibrinogen genes lead to a deficiency of fibrinogen by several mechanisms: at the DNA level, at the RNA level by affecting messenger RNA splicing or stability, or at the protein level by affecting protein synthesis, hexamer assembly or hexamer secretion. Interestingly, complete fibrinogen deficiency is associated with a variable bleeding phenotype, which may be influenced by environment and genotype. We sought to use the zebrafish as a model for fibrinogen disorders because of its accessible vasculature and because the coagulation system proteins are generally conserved throughout vertebrates. Targeted mutations were introduced into the zebrafish *fga* gene using zinc finger nuclease technology. Animals carrying 3 distinct frameshift mutations in *fga* were raised and bred to produce homozygous mutants. We observed hemorrhaging in *fga* mutants and reduced survival compared to control animals. This first transmissible zebrafish model of a defined human bleeding disorder validates the use of zebrafish for thrombosis and hemostasis research and will now serve in the search for afibrinogenemia-modifying genes or agents.

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C004_2016

Epigallocatechin Gallate Effect on a Williams-Beuren Syndrome Mouse Model

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Background: Williams-Beuren syndrome (WBS) is a rare neurodevelopmental disorder caused by a heterozygous deletion of 26–28 genes in chromosome band 7q11.23. Patients display a characteristic cognitive and behavioral profile, including intellectual disability, increased general anxiety, overfriendly personality, and visuospatial deficits. The complete deletion (CD) mouse model carries the same deletion found in WBS patients, and it recapitulates most of the neurocognitive phenotype, including low levels of Bdnf and alterations in the PI3K signaling in the hippocampus,

particularly the dysregulation of the regulatory subunit of PI3K (Pik3r1). Therefore, it is a useful tool to evaluate novel therapeutic approaches. Epigallocatechin gallate (EGCG) is the major polyphenolic compound found in green tea. It is associated with various neurological benefits, including cognitive improvement. Although the exact mechanism is unknown, it has been related to the PI3K signaling pathway. In addition, EGCG treatment in a mouse model of Down syndrome restored abnormal levels of Bdnf, an important synaptic plasticity marker. **Objective:** We hypothesized that EGCG treatment could improve the neurocognitive deficits observed in these mice. Animals were fed either with EGCG or water during one month. We compared the effect of these diets using some behavioral tests, RNA expression studies and neuroarchitecture analysis in the hippocampus. **Results:** Although mRNA levels of Pi3kr1 were not normalized, levels of Bdnf in the hippocampus of CD mice were completely restored after the treatment. However, CD mice fed with EGCG presented the same behavioral alterations as control CD mice, including hypersociability, abnormal levels of anxiety-like behavior and an impaired working memory. In addition, neuroanatomical findings such as alteration in spine density and dendrite length of hippocampal CA1 neurons were not normalized after the treatment. **Discussion:** Although EGCG was able to normalize the levels of Bdnf in CD mice, we could not find any effect on behavioral or neuroanatomical aspects. This could be due to: (1) duration of the treatment or the behavioral tests used was not appropriate, or (2) the alterations seen in CD mice are not exclusively dependent on normalization of mRNA levels of Bdnf and other mechanisms might be involved. Therefore, further analyses are needed to determine the specific effect of EGCG on WBS.

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C005_2016

New Tools for Mapping Molecular Pathways Altered in Kindler Syndrome

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Kindler syndrome (KS; OMIM 173650) is an autosomal recessive skin disorder caused by mutations in *FERMT1* and characterized by skin blistering, photosensitivity, premature aging, and skin cancer predisposition. However, the known functions of *FERMT1*, involved in cell adhesion, do not suffice to fully understand the pleiotropic nature and clinical variability of this genodermatosis. Oxidative stress and mitochondrial disfunction have been recently related to this disease by our group. The complexity underlying this pathology promotes the development of new tools in order to deeply understand Kindler syndrome. For this reason, our group has developed a skin-humanized mouse model that fully recapitulates the histological phenotype of KS patients. We have also performed expression analysis arrays that allow the screening of the potential genes that are altered in KS keratinocytes in order to understand the pathogenesis of the disease.

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C006_2016

Bardet-Biedl, Alström and Related Ciliopathies Pathogenesis: From Ultra Rare Diseases to More Common Diseases

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Bardet-Biedl (BBS), Alström and related syndromes are defined as a group of rare disorders due to the dysfunction of the primary cilia, a major organelle found in almost all cell types. Most of them share an early-onset retinal degeneration, renal dysfunction and/or obesity as well as many other complications such as intellectual disability and polydactyly for BBS, or type 2 diabetes and cardiomyopathy for Alström syndrome. The challenge working with this group of disorders is to understand the general and organ-specific pathogenesis to better target future therapies. The first clue is gene identification; although most genes have now been identified, pieces are still missing in the jigsaw puzzle of various networks identified for ciliopathies. Ultra-rare ciliopathies gene identification may still lead to pinpoint key players of various pathways. This will be illustrated by a few examples. Moreover, the most severe clinical manifestations demand the recognition of the causative mechanism. Retinal degeneration is a common, highly disabling manifestation due to photoreceptor dysfunction at the level of the ciliary connecting structure with altered transport of proteins leading to apoptosis. We will highlight the pathogenesis of the retinal degeneration taking into account ciliary networks. The potential metabolic consequences of ciliopathies, such as obesity or diabetes, are studied and show the importance of these actors in various processes, providing novel insights that can be useful for the understanding of common diseases.

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C007_2016

RASopathies – The Other Face of RAS Signaling Dysregulation

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RAS proteins are small monomeric GTPases that function as molecular switches controlling a major intracellular signaling network that, depending on the cellular context, guides diverse biological functions, such as proliferation, migration, survival, cell fate determination, differentiation, and senescence. Within this

network, signal flow through the RAF-MEK-ERK pathway, the first identified mitogen-associated protein kinase (MAPK) cascade, mediates early and late developmental processes, including determination of morphology, organogenesis, synaptic plasticity, and growth. Signaling through the RAS-MAPK cascade is tightly controlled, and its enhanced activation has been known for decades to represent a major event in oncogenesis. Activating somatic RAS gene mutations occur in ~30% of human cancers, and upregulation of this signaling pathway also results from enhanced function of upstream signal transducers and RAS effectors as well as from defective negative control of feedback mechanisms. Unexpectedly, discoveries derived from a massive disease gene-hunting effort performed in the last 15 years have established a novel scenario in which the upregulation of this signaling cascade underlies a group of clinically related developmental disorders, collectively known as 'RASopathies', characterized by facial dysmorphism, a wide spectrum of cardiac defects, reduced growth, variable cognitive deficits, ectodermal and musculoskeletal anomalies, and an increased risk for certain malignancies. These disorders are caused by mutations in an increasing number of genes encoding RAS proteins, regulators of RAS function, modulators of RAS interaction with effectors, or downstream signal transducers. While individually rare, RASopathies constitute the most common family of non-chromosomal disorders affecting development and growth, with an estimated aggregate prevalence of 1:1,500 live births. The largely collaborative research performed in the recent years has provided novel molecular tools for a prompt diagnosis, new data for a more effective patient management and risk assessment, and insights for efforts directed to the development of therapeutic intervention to treat postnatal complications of these disorders. These discoveries have also significantly contributed to deepen our understanding of the complex biology of RAS signaling and the multifaced functional role of several signal transducers with a function in this network.

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C008_2016

DNA Repair Syndromes: A Key for Understanding Aging

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The molecular basis underlying ageing and ageing-related diseases is one of the main unsolved questions in biology. Ageing in various model organisms appears remarkably plastic: e.g. suppressing insulin signaling extends lifespan in worms, flies and mice. On the other hand, virtually all premature aging syndromes in man provide a link with genome instability. We have generated mouse models which strikingly mimic human DNA repair deficiency syndromes and display wide-spread accelerated aging. For instance, DNA repair-deficient *Ercc1*$^{\Delta/-}$ mice defective in 3 or more repair pathways show numerous accelerated aging features limiting lifespan from 4 to 6 months. Simultaneously, they exhibit an anti-aging 'survival response', which suppresses growth and enhances maintenance, resembling the longevity response induced by dietary restriction (DR). Interestingly, subjecting these progeroid, dwarf mutants to actual DR resulted in the largest lifespan increase recorded in mammals. Thirty percent DR tripled median and maximal remaining lifespan and drastically retarded numerous aspects of accelerated aging, e.g. DR animals retained 50% more neurons and maintained full motoric function. Repair-deficient *Xpg*$^{-/-}$ mice also showing many premature aging symptoms responded similarly to DR, extending this observation beyond *Ercc1*. The DR response in *Ercc1*$^{\Delta/-}$ mice resembled DR in wild-type animals including reduced insulin signaling. Interestingly, ad libitum *Ercc1*$^{\Delta/-}$ liver expression profiles showed gradual preferential extinction of expression of long genes, consistent with genome-wide accumulation of stochastic, transcription-blocking lesions, which affect long genes more than short ones. DR largely prevented this decline of transcriptional output, indicating that DR prolongs genome function. We will present phenotypes of conditional DNA repair models targeting aging to selected organs, striking parallels with Alzheimer's disease. Our findings strengthen the link between DNA damage and aging, establish *Ercc1*$^{\Delta/-}$ mice as a powerful model for identifying interventions to promote healthy aging, reveal an untapped potential for reducing endogenous damage, provide new venues for understanding the molecular mechanism of DR, and suggest a counterintuitive DR-like therapy for human progeroid genome instability syndromes and DR-like interventions for preventing neurodegenerative diseases.

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Bringing Treatments to the Clinic

D001_2016

Innovative Tools for Drug Development and Disease Modeling

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There are fewer than 400 approved treatments for ~7,000 rare diseases affecting more than 30 million Americans. The NIH have more than 30% of promising medications that have failed in human clinical trials because they are determined to be toxic despite promising preclinical studies in animal models, and another 60% fail due to lack of efficacy. The challenge of accurately predicting drug toxicities and efficacies is in part due to inherent species differences in drug-metabolizing enzyme activities and cell-type specific sensitivities to toxicants. These challenges are particularly acute for rare diseases, where adequate tools and resources are severely lacking. To address this challenge in drug development and regulatory science, the Tissue Chips program aims to develop alternative approaches that would enable early indications and potentially more reliable readouts of toxicity or efficacy. The goal of this program is to develop bioengineered microdevices that mim-

ic functional units of the 10 major human organ systems: circulatory, respiratory, integumentary, reproductive, endocrine, gastrointestinal, nervous, urinary, musculoskeletal, and immune. The opportunities for significant advancements in the prediction of human drug toxicities through the development of microphysiological systems requires a multidisciplinary approach that relies on an understanding of human physiology, stem cell biology, material sciences, and bioengineering. This unique and novel in vitro platform could help ensure that safe and effective therapeutics are identified sooner, and ineffective or toxic ones are rejected early in the drug development process. These microfabricated devices are also useful for modeling human diseases, especially for studies in rare diseases as well as precision medicine, environment exposures, reproduction and development, infectious diseases, microbiome and countermeasures agents.

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D002_2016

Non-Targeted and Targeted Gene Therapy Approaches in Fanconi Anemia

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Fanconi anemia (FA) is an inherited disease mainly characterized by congenital abnormalities, progressive bone marrow failure, and cancer predisposition. In contrast to other hematopoietic disorders already treated by hematopoietic gene therapy, marked proliferation and differentiation defects have been observed at the stem cell level both in FA experimental models and FA patients. This characteristic FA stem cell phenotype implies significant difficulties for collecting clinically relevant numbers of hematopoietic stem cells (HSCs) from FA patients. On the other hand, the proliferation advantage of gene-corrected FA HSCs may facilitate the hematopoietic reconstitution of the patient by a low number of transduced HSCs. To facilitate the collection of HSCs from FA patients filgrastim and plerixafor have been used as mobilizing agents. Small aliquots of mPB CD34+ cells have been transduced with a lentiviral vector carrying the *FANCA* gene under the regulation of the PGK promoter and a mutated *WPRE** sequence. This vector efficiently reverted the hematopoietic phenotype of these cells both in vitro and also after transplantation into immunodeficient mice. Using an FA mouse model, we have also demonstrated the long-term phenotypic correction of their hematopoiesis after gene therapy, without noting genotoxic insertions, as deduced from the polyclonal HSC repopulation pattern, the absence of dominant integrations and active HSC turnover. In addition to conventional gene therapy, we have also investigated the possibility of generating gene-corrected FA HSCs by conducting untargeted and also targeted gene addition approaches on FA fibroblasts that were subsequently reprogrammed to generate hematopoietic progenitor cells. Improvements of gene editing tools, mainly engineered nucleases and donor constructs, have allowed us to attempt the targeted insertion of *FANCA* in primary HSCs from FA patients. An update of data obtained in our preclinical and clinical studies will be presented.

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D003_2016

Challenges and Experiences of Conducting a Randomized, Double-Blind, Placebo-Controlled Trial for a Rare Genetic Disorder: Intranasal Insulin in Phelan-McDermid Syndrome

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Phelan-McDermid syndrome (PMS) is a rare neurodevelopmental disorder caused by a 22q13.3 deletion. Patients have a moderate to severe developmental delay, often accompanied by behavioural problems. An exploratory study by Schmidt et al. in 2009 (reference to be obtained by R.J. Zwanenburg) suggested a beneficial effect of intranasal insulin on development and behaviour in 6 children with PMS. From March 2013 to June 2015, we conducted a randomized, double-blind, placebo-controlled trial in 25 children with PMS to validate this possible positive effect. Setting up a clinical trial for this rare chromosomal disorder was challenging but also rewarding for various reasons. First of all, the biological effects and local distribution of intranasal insulin were not yet known, so we had to rely on previous studies in animal models and patients with other disorders. Secondly, at the preparations of the trial, Dutch patients with a 22q13.3 deletion were scattered across the country and only few patients had been diagnosed at our department, so a recruitment strategy had to be developed. Thirdly, we had to choose a study design that would be able to both allow all patients to benefit from the potential treatment and simultaneously detect effects in a small study group. Fortunately, our efforts and strategies have resulted in a good collaboration between Dutch departments of clinical genetics, an excellent relationship with and commitment from the parents and a growing number of new referrals to our centre. Moreover, this has contributed to an increased knowledge about this rare disorder and has led to new research projects. The results of our clinical trial show a promising and clinically relevant improvement of developmental functioning with intranasal insulin, but results did not reach statistical significance for most items in this small study group. We would like to share our experiences in setting up a clinical trial for a rare genetic disorder such as PMS. We will also discuss the role of the clinical geneticist and the project group in this process, and the importance of staying connected with parents.

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D004_2016

OrphanDev, a French National Platform Dedicated to Rare Diseases Clinical Trials

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Less than 100 orphan drugs are available in Europe in 2016 for more than 7,000 rare diseases. Despite the implementation of incentives and the involvement of research teams and health industries in rare diseases, the number of therapeutics available for patients remains inadequate. Furthermore, these incentives remain unfamiliar in the academic sector while it is often at the origin of the proof of concept and the creation of start-ups or SMEs. The development of orphan drugs remains a challenge – the barrier of the therapeutic evaluation being one of the main difficulties to overcome. Specific constraints of rare diseases (small number of patients, heterogeneity of patients, poorly documented etiology, lack of previous clinical trials, etc.) are added to the usual constraints of clinical trials. OrphanDev is a unique academic structure in France and in Europe completely dedicated to rare diseases, able to support health industries, researchers and physicians in the elaboration and the conduction of clinical trials. Created in 2009, this platform is labeled by FCRIN (French Clinical Research Infrastructure Network) since 2012, the French component of ECRIN. OrphanDev offers a set of custom services, adapted to the issues of each project. (1) Regulatory support for orphan designation applications and protocol assistance is an important step in the development of drug candidates, bringing them to the clinic in the best conditions. (2) Recruitment of patients in clinical trials is a key point and represents a real challenge in rare diseases. OrphanDev, after an analysis of the constraints and objectives of the clinical trial, offers a global recruitment strategy of the patients to anticipate and overcome this difficulty (choice of inclusion criteria, constraints of study, methodological choices, early involvement of patients' organizations, etc.). We develop communication tools and prescreening tools to decrease the screen failure and optimize the recruitment. (3) OrphanDev also proposes information tools (newsletters, 'OrphanDoc' educational sheet) and organizes training courses: – 'Orphan Drug & Rare Disease Seminar', a European meeting destined to health professionals; 'Explain-me clinical trials', aiming to better understand the development of drugs, especially the clinical trials, destined to representatives of patients' organizations with rare and chronic diseases.

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D005_2016

Chronic Non-Bacterial Osteitis: IL-β Dysregulation and EQ5D-5L Validation of Health Outcome Status

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Introduction: Chronic non-bacterial osteitis (CNO; OMIM 259680) is a rare autoinflammatory disease of the bone marrow of unknown etiology. The term autoinflammatory syndrome was coined by Kastner (references to be obtained by S. Sathyanandan) to include disorders that did not fit into the classical groups of autoimmune diseases. The main difference between these diseases is that neither autoantigens nor autoantibodies are involved. **Objectives:** (1) to validate Iyer et al. clinical criteria with radiographic and immunohematological feautures of a CNO case and (2) to allow immunomapping status of chromosome 18q21.3 and the *Pstpip2* mutation in CNO murine model. **Methods:** A longitudinal case study with conversion to a double-blind, randomized control trial. Study setting: Multicentric trial with the Trivandrum Medical College, Tata Memorial Centre & PGIMER. Study period: a 5-year period (since 2011–ongoing). Patient registry: Patient registered with EUROFEVER Project & E-RARE – Pediatric International Trial Organization (PRINTO). **Results:** In 2011, a 9-year-old female child presented with a hypointense rim of the right shoulder indicating sclerosis with a post contrast enhancement suggestive of subperiosteal infection (TIM and T2WI MRI). A bone biopsy revealed a chronic inflammatory infiltrate with predominant monocytes. Bacterial culture and mycobacterial RT-PCR were negative. This is in conformance with Iyer et al. criteria for CNO. Molecular evaluation was negative for HLA-B27 with a negative ANA-profile. CRP was negative with an elevated ESR. The EQ5D-5L (European Quality of Life) index as a mean of assessment of generic health outcome is 0.722 (max. value for positive health is 1). Transgenic CNO murine model: The mouse *Lupo* (I282N) mutation in the *Pstpip2* gene leads to a reduced expression of *Pstpip2* associated with a macrophage-mediated disease CNO. Data pooling allowed us to immunomap 18q21.3q22 with the *Pstpip2* mutation in CNO mice, which also have high levels of macrophage inflammatory protein 1-α and IL-6. In CNO monocytes, the effect of attenuated TLR4/MAPK signaling and IL-10 polymorphism with reduced Sp1 recruitment and attenuated H3S10 phosphorylation contributes to central pathophysiology along with IL-1β dysregulation. TPMT assay is withheld, considering the financial situation of the patient. A treatment protocol with anti-TNFα inhibitors and immunomodulatory therapy is initiated for severe disease with a poor health outcome. Assessment of *1L10, TNFα, IL-1β*, and *TNSALP* gene mutation (metabolic defect with hypophosphatasia involving the NLRP3 inflammasome) were evidence-based, optional cytogenetic tests. Gene marker: NGS technique with a rare allele of marker D18S60. **Conclusion:** Iyer et al. criteria sufficiently can aid in starting an immunomodulatory therapy for CNO after gene sequencing and immunohematological studies. Murine

models do suggest association of the *Pstpip2* mutation, but it was found unrelated in CNO patient.

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D006_2016

Generation of Tools for Disease Modeling of Primary Hyperoxaluria by Cell Reprogramming

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Disease models are essential to understand the molecular mechanisms that drive pathogenesis and enable the development of novel therapies. In particular, cell reprogramming offers a valuable tool to develop patient-specific disease models that, after subsequent differentiation into the cell type of interest, allows the study of diseases that were previously inaccessible. In this work, we describe 2 different strategies to develop in vitro disease models of type 1 primary hyperoxaluria (PH1) by cell reprogramming, one generating patient-specific induced pluripotent stem cells (iPSCs) and a second one by direct transdifferentiation. In particular, we show the generation and characterization of the first iPSC lines derived from peripheral blood mononuclear cells (PBMCs) and dermal fibroblasts of a PH1 patient homozygous for the p.I244T mutation, which is highly prevalent in Canary Islands due to founder effect. On the other hand, direct reprogramming has been described as a potential source for the generation of hepatocytes from non-hepatic cell sources. We have developed a system to obtain hepatocyte-like cells from human fibroblasts using hepatocyte-specific transcription factors and a hepatocyte-defined culture media. We have applied this procedure to PH1 fibroblasts, and we have obtained PH1-deficient cells expressing hepatocyte markers. Cells obtained from either strategy are being used to develop an E-Rare-3-funded project (ERAdicatPH) which aims at the generation of disease models for PH1 that allow the development of synergistic novel therapeutic approaches.

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D007_2016

Therapies and Treatment for (Very) Rare and Genetically Heterogeneous Disorders: Why (Not) CDG?

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Congenital disorders of glycosylation (CDG) are rare inborn errors of glycosylation. With more than 70 different types and a number of cases constantly growing, CDG becomes an impressive group of metabolic diseases. However, because of the complex nature of glycosylation defects, the number of patients that receive effective treatment is small. Several cellular and animal models have been prepared for the study of the pathophysiology of the different types of CDG, but the challenges for the development of therapies remain huge: CDG is clinically and genetically heterogeneous, and the deficiencies reside in cellular compartments that cannot be reached by, e.g. enzyme replacement therapies. Neither is gene therapy a good option because of the methodological challenges and small numbers of patients. Cell therapy may well come of age eventually, but at this stage, it is not easily conceivable for CDG (apart from bone marrow transplants that may be considered in specific patients).Thus, it would be good to explore other lines of research on therapies for CDG. First, PMI-CDG and PGM1-CDG are characterized by the deficit of sugar intermediates for glycan synthesis. The oral application of mannose and galactose, respectively, to a small group of patients was shown to result in biochemical and clinical improvements. However, better galenic formulations and/or combinations of these sugars might improve the therapeutic benefit. Second, for PMM2-CDG and other types of CDG which are characterized by a low residual activity of the mutant protein, chaperones and other pharmacological agents might alleviate the enzymatic deficiencies. Third, a few types of CDG are caused by intra-compartmental pH and ion alterations. The patients may benefit from drugs that alter the intracellular environment. Evidently, even if these approaches look attractive, money is needed to test the different hypotheses. On the other hand, one may wonder whether causal treatments and cure must be the primary aim. In CDG, there is room for optimization of the classical, supportive therapies to improve the patients' life and alleviate the burden for the parents and families. Unfortunately, studies of the natural history of the disease, and funds to involve the parents and primary caretakers in collecting the data, are not often included in research grants and applications. Nevertheless, in the field of CDG, clinical and basic researchers are joining forces to try and reach at least some of these aims.

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D008_2016

Needs and Opportunities from Congenital Disorders of Glycosylation (CDG): Results from the First World Think Tanks

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CDG are a rapidly growing family of rare genetic life-limiting diseases with about 70 and 110 types identified since the first clinical description in 1980. Despite the rapid expansion of our understanding of the genome, regulatory incentives, and advances in the development of new therapeutic modalities for most CDG types, there are still no treatment options for the disease. Consequently, children and adults are patients for life. This unique and innovative study aims to elicit the expert views of patients, families and practitioners to explore, and gain an understanding of, the main needs of the CDG community. Solutions to overcome these needs are also discussed. The study resorts to a think tank methodology used, for the first time with the CDG community, at the Second World Conference on CDG in Lyon, France, in August 2015. This study revealed that some of the most common unmet needs faced by CDG are: (1) late or missed diagnosis, (2) limited access to reliable information, (3) limited awareness of professionals and lack of access to specialist expertise and knowledge, (3) differences in the availability to diagnostic techniques across countries, (4) differences on the care delivered within and between countries, and (5) psychological distress. The study highlights the need to coordinate resources and deliver information and care in a patient-friendly manner. Online platforms were proposed as beneficial for CDG. Overall, these findings help delineate the factors impacting negatively on the development of one of the most urgent needs expressed by CDG families: a medication that could bring hope for children and adults with CDG. Our findings have important policy and practice implications. It is recommended that clinicians and policy decision-makers place greater emphasis on the wide range of needs experienced by the CDG community and the solutions proposed by this population to overcome them.

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D009_2016

Fast Skeletal Troponin Activation for Restoring Muscle Strength in Mouse Models of Nemaline Myopathy

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Nemaline myopathy (NM) is a rare and fatal neuromuscular disorder with an estimated prevalence of 1 in 50.000 live births. The main clinical feature of NM is muscle weakness, which impairs swallowing and causes severe respiratory problems. In children suffering from NM, the diaphragm is often severely affected, leading to suffocation. There is currently no treatment for NM, and efforts are directed at alleviating symptoms and compensating for disabilities as far as possible. Our E-Rare 1 project NEMMYOP has yielded important results on: (1) the pathophysiology of muscle weakness in NM, (2) new NM biomarkers, and (3) in vitro effects of troponin activators on muscle fibres of NM patients. The insights gained in NEMMYOP have provided the first indications for a possible treatment for NM. To build upon this promising finding, TREAT-NEMMYOP will determine the efficacy of tirasemtiv, a fast skeletal troponin activator, in 4 NM mouse models. TREAT-NEMMYOP will make the next pivotal step towards clinical trials and future treatment of NM. To reach our aim, TREAT-NEMMYOP will assess the effect of tirasemtiv on: (i) muscle function, (ii) energy metabolism and (iii) NM biomarkers. To obtain an in-depth evaluation of tirasemtiv efficacy, we will combine measurements of in vivo and ex vivo muscle strength, noninvasive magnetic resonance imaging (MRI) and spectroscopy with analysis of the involved signalling pathways and proteome. This also enables us to better understand the pathology of NM and the molecular mechanisms by which compounds such as tirasemtiv increase muscle strength in NM patients. TREAT-NEMMYOP is a powerful consortium of 3 academic groups and complementary collaborative partners, including the developer of tirasemtiv (Cytokinetics Inc.). The consortium has access to 4 unique NM mouse models and a high-end infrastructure that enables thorough assessment of muscle- and whole-body performance. This makes TREAT-NEMMYOP well equipped to assess the efficacy of this highly promising treatment option for NM.

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D010_2016

Deciphering Immunological Aspects of Congenital Disorders of Glycosylation (CDG): A Model for Common Diseases

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Glycosylation is a reaction in which antennas formed by sugars attach (glycans) to proteins and others glycoconjugates. Congeni-

tal disorders of glycosylation (CDG) are a group of serious, life-altering disorders caused by the incorrect or absence synthesis of sugar antennas (glycans). Glycosylation of cell surface proteins has a key role in all interactions between cells and between cells and their environment. Since the immune response lays on innumerable contacts between cells and molecules, there is a great probability that glycans or glycopeptides may have a significant role in a variety of more common diseases such as cancer, inflammation, Alzheimer's disease, diabetes, and so forth. The aspects of immune deficiency associated with CDG still remain unknown. CDG has a childhood mortality of 15–25% in the first 2 years of life due to severe infections or organ failure. Under the scope of the first worldwide established CDG Professionals and Patient Associations Working Group (CDG-PPAWG), our current research project aims at: (1) boosting patient centered CDG research, (2) uniting expertise from and liaising different laboratories and patient advocacy groups to increase the knowledge in the field of glycoimmunology for CDG and related human glycosylation diseases, and (3) collecting the existing clinical evidence in literature about the impairment of the immune response reported in CDG, using PubMed as source of information. Our results show that immunological dysfunction is a minor or a major part of the phenotype in a minority of CDG. CDG with major immunological involvement are ALG12-CDG, MAGT1-CDG, MOGS-CDG, SLC35C1-CDG, COG6-CDG, and PGM3-CDG. Overall, our results about the immunological aspects of CDG will help us to understand and treat these pathologies and other more common diseases.

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Neurological Diseases

E001_2016
Mitochondrial Diseases: State of the Art

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Mitochondrial diseases, or diseases of the oxidative phosphorylation system, consist of a group of disorders originated by a deficient synthesis of ATP. This system is composed of proteins codified in the 2 genetic systems of the cell, the nuclear and the mitochondrial genomes and, therefore, the mode of inheritance of these disorders could be either mendelian or maternal. They are in general multisystemic and show a large phenotypic variability with symptoms that affect different organs and tissues. Sometimes, it is possible to define specific syndromes but, in general, overlapping symptoms and a large variety of phenotypes are found. All this makes diagnosis of these disorders very complicated and requires the participation of specialists from different areas. These disorders collectively affect ~1/6,000 births. Human mtDNA is composed of 16,569 bp that encode 37 genes: 2 rRNAs, 22 tRNAs and 13 polypeptide components of 4 of the 5 OXPHOS complexes. There are several mtDNA copies per mitochondrion and many mitochondria per cell. The basic features of the mitochondrial genetic system, the mode of replication and transcription, and the proteins that encode were described in the 1980's. The location of mtDNA in a cytoplasmic organelle has conferred genetic features that distinguish it from nuclear DNA. The main genetic features of this genome are: maternal inheritance, polyplasmy (homoplasmy and heteroplasmy), mitotic segregation, threshold effect, and a high mutation rate. mtDNA diseases are also unique inasmuch as different mutations in the same or in different genes might give rise to the same phenotype, just as the same mutation can give rise to very different phenotyes. NGS has enabled us to associate different nDNA mutations with these diseases. Cellular models (transmitochondrial cybrids and transfected fibroblast) are used to determine the pathogenicity of the mutations. Recently, there are several proposals of therapy to cure or avoid the transmission of these diseases.

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E002_2016
ER and Post-ER Quality Control of MLC1 by the Adhesion Molecule GlialCAM and the Ubiquitin Ligases CHIP and Ubr1

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Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare leukodystrophy, which is caused by mutations in the gene encoding the glia/astrocyte-specific MLC1 molecule, an integral plasma membrane (PM) protein, or the adhesion molecule, GlialCAM. Although the exact function of MLC1 remains unknown, it has been postulated to be involved in cellular/endosomal ion homeostasis and cell-volume regulation. In this study, we investigated membrane trafficking and ubiquitination of the wild-type MLC1 and its disease-associated mutations in relation to GlialCAM at multiple cellular locations, using HeLa and U251N glial cells as heterologous expression systems. Unexpectedly, we found that GlialCAM association with both native and mutant MLC1 can enhance the forward trafficking from the endoplasmic reticulum (ER). This was attributed to the permissive role of GlialCAM in MLC1 biosynthetic maturation at the ER. Depletion of GlialCAM expression induced rapid degradation of MLC1 in the ER via the ubiquitin proteasome system, providing a plausible explanation for the MLC1 cellular phenotype in GlialCAM deficiency. At the PM, GlialCAM restricts the lateral diffusion of WT and mutant MLC1, without influencing the preferential ubiquitination and rapid ESCRT-dependent turnover of mutant MLC1s. We show that the non-native MLC1 represents a substrate for CHIP- and Ubr1-dependent ubiquitination in concert with molecular chaperone recognition. Depletion of CHIP was able to partially revert the rapid lysosomal targeting of MLC mutants. The loss in Ubr1 expression was also accompanied by reduction of mutant MLC1 ubiquitination at the PM/endosomes, hence decreasing

the consequential lysosomal targeting. The Ubr1 role in the peripheral quality control of MLC1 is supported by its endosomal localization, demonstrated by immunocolocalization. These observations, jointly, demonstrate novel insights into the molecular regulation of MLC1 trafficking. First, the adhesion molecule Glial CAM regulates MLC1 biosynthetic secretion positively by enhancing its escape from the ER QC, followed by restricting its diffusion at the PM to subdomains, where peripheral protein quality control removes non-native MLC1 relying on CHIP and Ubr1 E3 ubiquitin ligases activity.

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E003_2016

Delving into the Complexity of Spinocerebellar Degenerations: How Next-Generation Sequencing Improved Our Knowledge

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Spinocerebellar degenerations are clinically and genetically heterogeneous neurodegenerative disorders. Their genetic diagnosis has been improved by next-generation sequencing techniques. Novel types of mutations or transmissions in known genes are constantly being identified. The phenotypic spectrum associated with a single gene constantly gains in complexity. Numerous novel genes have been identified; some have been implicated in these diseases in addition to being responsible for other diseases. Novel pathological mechanisms have been identified. All these factors make genotype-phenotype correlations particularly difficult. Some, but not all, of this variability can be explained by different pathophysiological consequences (loss of function, gain of function, variable levels of haploinsufficiency) but also raises the question of modifier genes.

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E004_2016

Mitochondrial Haplogroup Analysis in Autism Spectrum Disorders

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Autism spectrum disorders (ASDs) are known in patients younger than 3 years of age. The most important signs of these diseases are: impairment in social interactions and verbal and nonverbal behaviors, failure to develop relationships and respond to normal teaching methods, repetitive behaviors, pragmatic language impairment, and severely limited activities. ASDs are considered neurodevelopmental disorders. Diseases such as Asperger's syndrome, Rett syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS) or childhood disintegrative disorder (CDD), Tourette syndrome and Down Syndrome are accompanied by autistic behaviors. A mitochondrial haplogroup is a cluster of phylogenetically related mitochondrial genotypes (haplotypes). These haplogroups are defined by ancient mutations. These changes appeared and survived; therefore, they could not be deleterious mutations. Most of them probably did not have a phenotypic effect and were neutral. Some of them had a beneficial effect and were positively selected. However, this positive effect was related to a particular environment and nowadays, in other environmental conditions, may have different effects on the phenotype. To investigate the involvement of mitochondrial DNA (mtDNA) haplogroups in determining susceptibility to ASD, we sequenced the mtDNA HVS-I of 30 Iranian ASD patients. We examined the relationship between ASD and each of 9 major mitochondrial haplogroups in Iranian ASD patients. In this study, we found a significant association of haplogroup H with ASD in Iranian patients. Therefore, our finding suggests that a mitochondrial genetic background plays a role in modifying an individual's risk for ASD.

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E005_2016

Prevalence of Rare Hereditary Neurodegenerative and Neuromuscular Disorders in Poland

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Hereditary neurodegenerative and neuromuscular disorders represent a large group of diseases heterogenic in terms of transmission, molecular etiology and phenotype. Although rare, they are also characterized by diverse frequencies in different populations. The study concerns disorders caused by dynamic mutations: several types of spinocerebellar ataxias (SCAs), Huntington's disease (HD) and muscular dystrophies type 1 and type 2 (DM1 and DM2), and congenital Thomsen/Becker myotonia (CM) resulting from point mutations and microrearrangements. The aim of this study was to assess the relative prevalence of some rare hereditary movement disorders molecularly confirmed in Poland. During 20 years of molecular investigation, 2,317 mutation carriers belonging to 1,452 pedigrees were identified in 4,276 patients suspected of HD or at-risk individuals. Testing for SCAs resulting from dynamic mutations revealed pathogenic expansions in 632 subjects out of 3,102 individuals. Identified SCA mutation carriers belong to: 200 SCA1, 38 SCA2, 1 SCA3 (of German origin), 2 SCA7, 51 SCA8, 3 SCA17, and 7 SCA36 pedigrees. The Institute of Psychiatry and Neurology is in cooperation with the Polish HD Association and the Association of Families with Spinocerebellar Ataxia. Over 10 years, molecular analyses for myotonic dystrophies type 1 and type 2 performed in 1,370 individuals resulted in the identification of 278 DM1 pedigrees with 476 mutation carriers, and 203 DM2 pedigrees with 276 mutation-positive subjects. The latest

molecular investigation on CM – corresponding to testing for DMs – has been carried out so far for 80 probands with DM1 and DM2 previously excluded. The preliminary data obtained for 8 patients revealed 5 heterozygotic and 2 homozygotic deletions (14 bp; c.1437_1450) within exon 13 of the *CLCN1* gene, and in one subject, the same heterozygotic deletion in exon 13 and 2 point mutations in exon 5 (c.568G>T, c.569G>C) were found. The clinical diagnosis of CM has been confirmed up till now for 3 patients: 2 cases of recessive Becker myotonia and 1 patient with dominant Thomsen myotonia. Contrary to the highest worldwide SCA3 frequency, SCA1 is the most common genetic type of SCA in Poland with the relative frequency of 66% (among all genetically confirmed SCAs). The tentative data of congenital myotonia investigation revealed the presence of a relatively frequent (10%) recurrent deletion within the exon 13 of the *CLCN1* gene.

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E006_2016

Monitoring Nucleolar Activity as a Marker of Disease Progression in Models of Huntington's Disease

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Inhibition of rRNA synthesis and consequent disruption of nucleolar integrity – nucleolar stress – is an emerging mechanism in neurodegenerative disorders, including Huntington´s disease (HD). The expansion of CAG repeats in the mutant huntingtin protein impairs, among other fundamental cellular functions, the transcription of rRNA genes causing nucleolar stress. To dissect its contribution to the onset and progression of HD, we mimicked nucleolar stress in striatal medium spiny neurons (MSNs) in mutant mice for the first time. This was achieved by conditional ablation of the nucleolar transcription factor *TIF-IA* gene, crucial for the recruitment of the RNA polymerase I to the rRNA promoters. With this strategy, we could specifically induce nucleolar stress-dependent responses showing that this triggers pathophysiological and molecular similarities with HD. These results suggested an important role of nucleolar stress in HD. Hence, we performed a systematic analysis of nucleolar activity and integrity in cell and mouse models of HD at different stages and in different brain regions to establish whether nucleolar activity is a marker of disease progression. To this end, we optimized molecular and histological methods to measure nucleolar activity in distinct cells and in tissue sections. In parallel, to dissect the function of nucleolar stress in disease progression, we induced nucleolar stress in a slowly progressive mouse model of HD and investigated its impact on neuropathology at early stages. Concomitantly, we showed that the phosphatase PTEN is upregulated upon nucleolar stress and in a cellular model of HD expressing mutant huntingtin, playing a potential neuroprotective role. The results allow us to better understand the mechanisms of HD and indicate a novel approach to identify disease modifiers linked to altered nucleolar activity also in other disorders.

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E007_2016

The New Role of Medical Genetics in Clinical Guiding

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Genomic testing takes first place as a disruptive technology in medicine, even before telecommunication and imaging technology. Nearly all concepts currently known to play a role in personalized medicine are based on genomic analysis of individual patients. This is a challenge for Medical Genetics as it moves away from pedigree analysis towards identifying novel genes or even away from testing for specific mutations in affected individuals towards genetic screening. This has been made possible by the recent developments in NGS technologies. In less than 5 years, this technology has become a part of routine diagnostic in the clinical setting. However, even if the technical part of genome sequencing has been solved widely, the extent of interpretation of individual genome data in clinical practice is still a matter of debate. Most of the current approaches are thus focusing on symptom-based genetic diagnosis groups using targeted enrichment of genes, the so-called gene panels. However, depending on the diagnosis, these panels may cover as many as 1,000 genes (for instance, intellectual disability, ID). Knowing that today only about 50% of the genetic causes of ID are being identified and at the same time that extensive data sets are being generated, which are for the most parts not yet classified for their pathogeneity, geneticists are 'playing back' comprehensive variant sets to the clinicians. Currently, 'Mendeliome' enrichment strategies are in testing, basically allowing us to test all proven disease genes in one analysis. However, with this huge data information, the specificity of the data is reduced with generating 'unwanted' information at the same time. This raises a new ethical dimension whether geneticists should be allowed or even requested to play back genetic data with clinical implication for disease prevention (cancer, cardiomyopathy, etc.).

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E008_2016

Rare Neurogenetic Disorders: The Clinician's Perspective

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The clinician investigating rare genetic disorders interfaces not only with patients and families, but with numerous other professionals that form a team. Several pitfalls in communication and management of cases are discussed in this talk and illustrated by case reports. The following potential pitfalls will be high-

lighted: (1) Delineation of neurogenetic disorders start with a careful phenotypic description, this process may be complicated by lumping together unrelated symptoms or vice versa. (2) Establishing a tentative mode of inheritance depends on understanding culture-dependent definitions of relatedness. (3) The process of filtering sequencing data should be clear to the clinician as several assumptions derived from the clinical data go into the process. (4) Once a list of possible causative variants has been assembled, the discussion of which pathways are relevant to the patient's symptoms should be informed by the clinician. (5) Reaching a molecular genetic diagnosis is not the end of the patient-clinician relationship, and expectations should be set accordingly.

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E009_2016

Therapeutic Potential of Thyroid Hormone Analogs Triac and Ditpa in Allan-Herndon-Dudley Syndrome

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Allan-Herndon-Dudley syndrome (AHDS) represents a rare form of psychomotor retardation characterized by severe intellectual deficits, pronounced neuromuscular impairments, and abnormal thyroid hormone (TH) concentrations in the circulation. This syndrome is caused by inactivating mutations in the X-linked *SLC16A2* gene that encodes the monocarboxylate transporter 8 (MCT8), a highly specific TH transporter. Since TH is essential for proper brain development, MCT8 deficiency leads to insufficient neural TH supply and, consequently, to abnormal neural differentiation. However, up to date the exact pathogenic mechanisms underlying AHDS remain largely unknown. Worse still, there is currently no treatment for AHDS patients. We have recently established a mouse model for AHDS – namely the 'Mct8/Oatp1c1 dko mice' – that fully replicates both the endocrinal abnormalities and neurological phenotypes of the patients. By taking advantage of these mice, two TH analogs, Triac and Ditpa, both of which are not transported by MCT8, but are able to activate TH receptors, were tested to evaluate their therapeutic potential for treating AHDS patients. Animals were injected with these substances during the first 3 postnatal weeks and neurodevelopment was followed by immunohistochemistry and by performing locomotor tests. In addition, the thyroidal state of peripheral tissues was analyzed in order to assess any thyrotoxic side effects of this treatment. Our data provided experimental evidence that postnatal application of Triac (400 ng/g bw) was sufficient to normalize 3 key processes that are compromised in AHDS patients and in Mct8/Oatp1c1 dko mice: (i) cerebellar development, (ii) myelination, and (iii) differentiation of GABAergic interneurons in the cerebral cortex. Moreover, only Mct8/Oatp1c1 dko mice treated with Triac displayed normal locomotor function, while Ditpa treatment was less effective. Finally, Triac treatment efficiently suppressed endogenous TH production by downregulating hypothalamic *TRH* and pituitary *TSH* expression. Overall, our data suggest that Triac may represent a promising therapeutic option for patients with *MCT8* mutations, particularly if treatment is initiated early in life.

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E010_2016

An Update on Leukodystrophies

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Leukodystrophies are rare genetic disorders primarily affecting the white matter of the central nervous system (CNS). When the studies on leukodystrophies started in 1987, only a limited number of disorders was known, and it was estimated that over 60% of the cases remained with a specific diagnosis. With MRI pattern recognition, an increasing number of disorders could be defined, and for the most prevalent disorders, the basic genetic defect was determined by genetic linkage studies. Despite this progress, the percent of unsolved cases was still found to be 50% in 2010. The problem was that the remaining cases comprised numerous exceedingly rare disorders, which escaped disease definition by clinical and MRI observations and gene identification by conventional genetic linkage. The introduction of massive parallel sequencing, allowing whole exome and whole genome sequencing (WES and WGS) changed the situation completely and allowed disease definition and gene identification in very small groups of patients and even in single families and individual patients. A recent retrospective study showed that now 80% and probably soon 90% of the leukodystrophy patients can receive a specific diagnosis. Disease definition and identification of the gene defect underlying the disease is essential for all further studies on clinical insights, disease mechanisms and therapy development. One example is megalencephalic leukoencephalopathy with subcortical cysts (MLC), a disease first described in 1995. Genetic linkage helped identify the first gene, *MLC1*, harboring recessive mutations in ~70% of the patients. MLC1-protein interaction studies led to the identification of *HEPACAM/GLIALCAM* as a second gene, harboring recessive mutations in ~10% of the patients and dominant mutations in ~20% of the patients. The recessive disease was classical, but the dominant disease had an improving phenotype. Since then, it has become clear that the loss of *MLC1* function is central in the disease. GlialCAM is a chaperone of *MLC1* to ensure its normal location in astrocytic endfeet at the blood- and CSF-brain barriers. *MLC1* has been shown to be involved in volume regulation by astrocytes. Mouse models for MLC have been developed allowing further studies on disease mechanisms and therapy.

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E011_2016

Generation of iPSC Models to Study the Neurodevelopmental Disorders Caused by Reciprocal 7q11.23 Rearrangements: Williams-Beuren Syndrome and Autism Spectrum Disorders

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The main limitation in the study of human neurodevelopmental diseases is the inability to analyze the brain in detail, the organ directly involved. Despite knowing the genetic cause of many diseases with neurological dysfunction, it is difficult to study the mechanisms whose alterations cause abnormal brain function and, therefore, the pathogenesis of the disease. This lack of knowledge limits the possibilities for diagnosis, prevention and treatment for these diseases. The recent research advances in induced pluripotent stem cells (iPSC) have opened new perspectives for modeling human disease 'in vivo', generating patient-specific iPSCs and differentiating them into neural progenitors in the case of neurodevelopmental disorders. Williams-Beuren syndrome (WBS) and autism spectrum disorder (ASD) are 2 neurodevelopmental diseases with opposite phenotypic features in the areas of communication and sociability. WBS is caused by a hemizygous deletion of 26–28 contiguous genes in the 7q11.23 region, while the reciprocal duplication of the same locus causes a syndrome commonly associated with ASD. Initially, we generated iPSC cells from those reciprocal genetic models from skin fibroblast of 2 patients with 7q11.23 deletion and 2 patients with 7q11.23 duplication. Next, we derived these iPSCs to neural progenitor cells (NPC) and differentiated them to dopaminergic neurons, using a serum-free neuronal induction medium. We evaluated the efficiency of the neuronal differentiation process by quantitative RT-PCR analyses (panel including Nurr1, TH and FOXA2 expression) and qualitative immunocytochemistry studies using neuronal markers (TH, TUJ1 and FOXA2). Phenotypic evaluation of dopaminergic differentiation process followed by time-lapse microscopy pointed up some divergences between models, including the number and the morphology of interactions between neurons. Transcriptional analyses (GeneChip® Human Gene 2.0 ST Array) of the entire differentiation process were carried out in order to understand the pathophysiology of such genetic diseases and also to determine appropriate therapeutic targets and biomarkers. Currently, we are generating iPSCs from 4 additional patients to replicate the initial results and to determine the model specificity of the alterations observed. As a final point, all these generated models will be used as an 'in vivo' cellular model to test new therapeutic strategies.

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E012_2016

Drug-Resistant Epilepsy in a Young Male with Cat Eye Syndrome

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Background: The 22q11 region is susceptible to chromosomal rearrangements, leading to various types of congenital malformation and intellectual disability. Several genomic disorders have been described, including cat eye syndrome (CES) caused by extra copies of the most proximal region, DiGeorge/velocardiofacial syndrome due to deletion of 22q11.21, 22q11.2 duplication syndrome, and distal 22q11.2 microdeletion/microduplication syndrome. We present a clinical observation of a 28-year-old male with a tetrasomy of the region 22q11.1q11.21, corresponding to the CES region. **Methods:** The patient underwent clinical, neurophysiological and neuroradiological examination. Laboratory studies included array-CGH, conventional cytogenetic and FISH analysis. **Results:** A 28-year-old male patient was born to nonconsanguineous parents after a normal pregnancy. His weight at birth was 3,350 g. At birth, a total anomalous pulmonary venous connection of the heart was diagnosed and a surgical correction was required. Developmental milestones were severely delayed: first steps without help after 3 years and no development of language. A nasal fistula was corrected surgically during infancy. Since the past 2 years, the patient has developed daily atypical seizures, characterized by loss of contact and motor stereotypies, which are refractory to treatment. Seizures became more and more frequent with ageing (up to 1–2 episodes a day). Further results are as follows: (1) Clinical examination: turricephaly, spastic tetraparesis more marked on the right side; (2) Brain MRI: thinning of the corpus callosum, hypomyelination of the oval centers; (3) 24-hour EEG: spikes/polyspikes and waves more marked on the left side during sleep; (4) Cognitive phenotype: severe learning disabilities and specific language impairment, IQ at WAIS was undetectable for severity, and (5) Behavioral phenotype: presence of ritualistic and stereotyped behaviors, lethargy, and lack of eye contact. Array-CGH detected the tetrasomy of about 1.55 Mb on chromosome 22q11.1q11.21, due to the presence of a bisatellited, small dicentric supernumerary chromosome, as demonstrated by karyotype and FISH analysis. **Conclusion:** Although seizure characterization is lacking in CES, in the present case, epilepsy emerged as a main disturbance in the clinical picture of CES.

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E013_2016

A New Generation of Potent Transthyretin Amyloid Inhibitors

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The aggregation of proteins into insoluble amyloid fibrils is the hallmark of many highly debilitating human pathologies such as Alzheimer's and Parkinson's disease, or rare neurodegenerative diseases such as familial amyloid polyneuropathy (FAP). FAP is an amyloid disease caused by mutations in the protein transthyretin (TTR) and characterized by progressive peripheral and autonomic polyneuropathy, starting with loss of temperature and pain sensation in the lower limbs and evolving to severe autonomic dysfunction, usually resulting, if untreated, in the death of patients 10–15 years after the onset of the first symptoms. TTR is a homotetrameric protein found in the plasma, cerebrospinal fluid and the eye and is synthesized in the liver, choroid plexus and retina, respectively. Liver transplantation (LT) was the standard treatment option for FAP for nearly 2 decades. In recent years, tafamidis meglumine was introduced to the European and Japanese markets, demonstrating improvement of symptoms in ~60% of FAP patients enrolled in an 18-month phase-III clinical trial. The need for more efficacious solutions to the treatment of FAP, and principally of nonresponsive FAP patients, as well as the need to provide therapeutic solutions for FAP-associated comorbidities of the central nervous system (CNS) and the eye, and other TTR-associated amyloidoses, is of the utmost importance. Here, we report on successful efforts to discover new chemical entities (NCEs) with high amyloid inhibitor profiles in vitro and high TTR stabilization activity ex vivo, in particular, in plasma of carriers of the most common amyloidogenic *TTR* mutation.

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Patients and Research

F001_2016

LA&C: Opportunities and Challenges to Rare Diseases Research

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The first step necessary to understand the opportunities and limits of our region regarding rare diseases research is to have a closer look at the different aspects influencing the research results: (1) The background of the researchers is of importance (basic research made by universities vs. clinical trials made by clinicians without any academic training in research; lack of communication between basic and clinical trials; GCP and ethics only as a formal procedure, so there is a lot of sensitive information; the gap between people's needs and the 'academic vision'; the market growth vs. the unmet needs). (2) The patients are not aware of the benefits of research (less proactive attitude, more lost opportunities for all). (3) The regulatory policies are building barriers instead of favoring opportunities caring for citizens, etc. Even if most of these aspects are similar around the world, in a more detailed view, they are particular in our region. On the other hand, interest in this field of research from public policies and local industries is growing. The researchers are initiating first steps toward translational criteria. The knowledge of all these aspects helps us to find strategies and solutions to develop the maximum opportunity for research in our region. These specific strategies and suggestions could arise from an international collaboration. International collaboration speeds up creativity and better solutions. As an example, there are many collaborative programs between Europe and LA&C, but there is no one devoted to develop educational programs on this specific item. GEISER Foundation proposes to include rare diseases research programs in the international collaboration. As it is a sensitive issue, for this reason and in order to be more efficient, the start might be a round table including all the stakeholders, delivering an educational program proposal to maximize the efforts and to concentrate on the concerns of the affected citizens. GEISER Foundation proposes a draft agenda to be considered as a first step for an international collaboration program for rare disease research, articulating all the current initiatives and the new ones to come from the developing countries.

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F002_2016

Crowdfunding Primary Rare Disease Research: Bootstraps and Biobanks

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The RE(ACT) Community aims to promote both scientific knowledge-sharing and to allow all interested stakeholders an innovative and targeted tool to raise funds for rare disease research projects. In 2014, I initiated the first crowdfunded project on this platform. Our lab proposed to collect biological resources nationwide concerning the large congenital giant nevus for our current and prospective research. With the support of multiple patient advocacy groups and individuals worldwide, we have reached our fourth milestone at over thirty-six thousand euros to date, research is underway, and results are coming in. This talk will share some of our experiences, both disappointing and encouraging, so that others can gauge how crowdfunding approaches could kick-start their own original scientific endeavors.

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F003_2016

The Power of Social Media for Karyotype-Phenotype Analysis of Rare Chromosome Disorders

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This presentation is the direct result of a study that was performed on request of a Facebook Group of parents of children with a chromosome 6 disorder. The successful use of social media in this study demonstrates how eager parents are to give and receive information about the condition of their child. In our study, we initially focused on isolated 6q deletions. Through social media including Facebook and Twitter, we were able to collect more and more detailed information than available in literature within a short period of time. This allowed for a better description of the 3 main groups of 6q deletions: proximal (6q11q16), intermediate (6q15q25), and distal (6q25qter). Moreover, smaller deletions could be further characterized and smallest regions of interest defined. For example, a Noonan-like phenotype could be assigned to deletion 6q25.1. All patients with deletions in this region had a highly resembling appearance and shared many clinical features, including short stature and heart defects, predominantly involving the cardiac valves. A detailed analysis of all 6q data allowed the confirmation or identification of candidate genes for specific features, e.g. congenital heart defects. The results of our social media pilot, prompted us to initiate the development of an interactive online database system based on the intelligent collection, combining and presentation of information for chromosome 6, in collaboration with the Chromosome 6 Facebook Group, Unique, ECARUCA and Cartagenia. The online database system will consist of a multilingual patient questionnaire that is currently being validated, an automated data interpretation program, for which the prototype is ready, a program that allows combining the database information with data available from other sources, and an interactive query and information program suitable for families, primary caretakers and professionals. Eventually, the system can be applied to all chromosome disorders.

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F004_2016

Telethon Foundation Fighting Rare Diseases alongside Patients

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The Telethon foundation is an Italian charity-funding biomedical research focusing on the cure of rare genetic diseases (www.telethon.it). All its funding decisions are made by an international scientific committee through a peer review-based selection system. After 25 years of activity, the results achieved by Telethon-funded research are globally acknowledged; the Foundation has placed itself among the main players in the world in the field of biomedical research for rare genetic diseases [Hum Gene Ther 2015;26:183–185]. Telethon-funded research, tackling the challenge of genetic diseases from diagnosis to basic and clinical science, is constantly moving forward toward the development of therapies for an increasing number of pathologies including metabolic, hematological and neuromuscular disorders. The Telethon research portfolio includes intramural research led by the 3 Telethon Institutes: TIGET (San Raffaele Telethon Institute for Gene Therapy, Milan), TIGEM (Telethon Institute of Genetics and Medicine, Pozzuoli, Naples) and DTI (Dulbecco Telethon Institute, a career program), and extramural research funded by several funding programs. Telethon participates in several national and international collaborations and alliances, such as the European RD-connect project, the International Rare Diseases Research Consortium (IRDiRC), the European NeuroMuscular Center (ENMC), and coordinates the EuroBioBank Network. The close relationship with many patient organizations is the basis of the Telethon strategic plan, and over the course of years, it has led to the implementation of several initiatives: the Telethon-Uildm Call for clinical neuromuscular research, the Telethon Network of Genetic Biobanks (TNGB, http://biobanknetwork.telethon.it/), the Call for Exploratory Projects, and the fledgling Undiagnosed Diseases Program. Moreover, to provide patients with information on research on their genetic diseases, Telethon joined Europe PubMed Central as a funder to offer open access to the results of the Telethon-funded research and has set up activities such as the 'Filo diretto' and the network of the 'Italian Patient Associations Friends of Telethon' and has promoted patient empowerment on research topics through the organization of several meetings.

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F005_2016

Detectable Clonal Mosaicism in Blood DNA as Early Marker of Cancer in Fanconi Anemia Patients

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Background: Mosaicism, the coexistence of cells with a different genetic composition within an individual, has been associated with aging and cancer. Mosaicism for chromosomal events >500 kb affecting ≥10% of cells can be detected using SNP array of DNA from all tissues. Fanconi anemia (FA) is a genetic disorder characterized by congenital defects, bone marrow (BM) failure and cancer susceptibility, caused by poor repairing of DNA interstrand crosslink (ICL). Due to the high risk for hematological and mucosal cancers, a strict follow-up protocol is recommended including,

among other exams, periodic BM testing. We have studied the prevalence of clonal mosaicism in blood DNA of young FA patients and whether mosaicism could be used as an early marker for cancer. **Methods:** Blood DNA samples of 129 FA patients (0–50 years old), obtained for diagnostic purposes, were analyzed by SNP array (Illumina 1M or Infinium HumanCore). Copy-number and copy-neutral chromosomal mosaic events were detected with the MAD software and experimentally validated by microsatellite and MLPA analyses. DNA from an anal squamous cell carcinoma (SCC) sample from one FA patient was also studied. **Results:** We detected 45 mosaic events in blood of 14/129 FA patients (10.8%) and validated 94.7% of them by microsatellite and/or MLPA analysis. Compared to 11,944 age-matched controls, FA subjects under 18 years of age had a 220× rate, while young adults (18–50 years of age) had a 109× rate of detectable mosaicism (4.39/0.02%; $p = 2.2 \times 10^{-7}$ and 29.4/0.27%; $p = 4.1 \times 10^{-17}$). Considering events, there was a 243× increase in FA patients, with an average of 0.34 mosaic events/patient and 0.0014 events/control. The risk of developing cancer 0–10 years after DNA extraction was 5.2× higher in FA patients with mosaicism compared to FA patients without mosaicism (85.7/16.5%; $p = 5.7 \times 10^{-7}$). A uniparental disomy of 6p was detected both in blood and in the SCC of FA013 – diagnosed 10 years later – suggesting an early embryonic origin of the mosaicism. **Conclusions:** We have shown that SNP arrays can detect mosaicism for chromosomal rearrangements in an important proportion of FA patients, and that mosaicism detection is associated with a higher risk of hematological and solid cancer. Although further studies are required to establish the sensitivity and specificity of the method, detection of clonal mosaicism using SNP arrays from blood (and/or buccal) DNA could be used as early markers for cancer risk in these chromosomal instability disorders.

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F006_2016

Rare Diseases Registries as Tools for Clinical Research

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The double-blind randomized controlled trials (RCTs) are accepted by medicine as objective scientific methodology that, when ideally performed, produce knowledge untainted by bias. These complex, expensive studies can involve hundreds or even thousands of patients. In common conditions, such as hypertension, the population is so large that it is not difficult to select those patients who fit the enrollment criteria. On the contrary, clinical trials in rare diseases (RDs) have to deal with the geographic spread of patients but also with the strong heterogeneity within the same condition. Different patient subsets and a fluctuating disease course can often be documented. Patient registries and databases are useful tools in the field of RDs, and they are sometimes the only way to pool data in order to achieve a sufficient sample size for clinical research. In order to better characterize patients and establish long-term prognosis, patient-specific data are most often collected in registries linked to biorepositories. The Clinical Research Center for Rare Diseases of the Mario Negri Institute has gained great experience in implementing rare disease registries, and the results of our studies emphasize the clinical importance of such an effort. Examples showing the utility of registries are moreover numerous in scientific literature and must lead to overcome difficulties encountered in their implementation and maintenance. The approval process of orphan drugs by regulatory agencies may also have to deal with limitation inherent to the small populations. Patient registries are often a mandatory item (requested by regulatory authorities such as the US FDA or the European EMA) to capture long-term safety and efficacy data of new drugs in the post-marketing phase. Genotype-phenotype correlations in patients with genetic RDs enrolled in registries may allow us to identify different subgroups of subjects responsive to targeted treatments. Over the last 20 years, RDs have received more attention from health authorities and from the public at large. To date, a lot of experience has been gained in Europe as far as forwarding information to patients and coordinating patient support groups is concerned. Actions to collect relevant information about the patients, with registries linked to biorepositories, as a mean to implement clinical research and treatment possibilities should be considered a priority for the near future.

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F007_2016

Opening Ceremony

Catalyzing Translational Innovation

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The process by which observations in the laboratory or the clinic are transformed into demonstrably useful interventions that tangibly improve human health is frequently termed 'translation'. This multistage and multifaceted process is poorly understood scientifically, and the current research ecosystem is operationally not well suited to the distinct needs of translation. As a result, biomedical science is in an era of unprecedented accomplishment without a concomitant improvement in meaningful health outcomes, and this is creating pressures that extend from the scientific to the societal and political. To meet the opportunities and needs in translational science, NCATS was created as NIH's newest component in December 2011, via a concatenation of extant NIH programs previously resident in other components of NIH. NCATS is scientifically and organizationally different from other NIH Institutes and Centers. It focuses on what is common to diseases and the translational process, and acts a catalyst to bring together the collaborative teams necessary to develop new technologies and paradigms to improve the efficiency and effectiveness of the translational process, from target validation through intervention development to demonstration of public health impact. This talk will provide an overview of NCATS mission, programs, and deliverables, with a view toward future developments.

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