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ICORD

International Conference on
Rare Diseases & Orphan Drugs

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SIXTH FRAMEWORK PROGRAMME

Support from the EU to Research on Rare Diseases

Recognising the importance to stimulate rare disease research activities at the European level, the European Union provides direct financial support for selected research projects through its Sixth Framework Programme for Research, Technological Development and Demonstration Activities (FP6). Like former Framework Programmes, the aim of FP6 – running from 2002 to 2006 – is to develop and exploit European research. Support to rare disease research will mainly be from Thematic Priority 1 – Life Sciences, Genomics and Biotechnology for Health – where a wide range of projects will be funded in both basic and clinical research.

Priority 1 includes a sub-area dedicated to 'Combating cardiovascular disease, diabetes and rare diseases', whose aims are "to improve the prevention and management of important causes of mortality and ill-health in Europe and to pool Europe's research resources for tackling rare diseases". Other sub-areas of Priority 1, or other parts of the Sixth Framework Programme, such as the Coordination of Research Activities (ERA-Net scheme) or Research for policy support, also dedicate some financial support to research on rare diseases. FP6 so far allocated more than 60 million Euros to research on rare diseases.

The participation of small and medium-sized enterprises (SMEs) is encouraged in Priority 1 as a way of stimulating European innovation. This is particularly evident in the context of rare diseases, which offer industry the opportunity of developing 'niche' markets.

FP6's new and innovative research instruments, Integrated Projects (IP) and Networks of Excellence (NoE), mark a move towards coherent and long-term research activities and partnerships in an attempt to achieve critical mass and tackle fragmentation in the European Research Area. Funding of research projects is also through more traditional types of instruments: Specific Targeted Research Projects (STREP), Coordination Actions (CA) and Specific Support Actions (SSA).

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FP6 homepage: http://fp6.cordis.lu/fp6/home.cfm
Priority 1 homepage: http://www.cordis.lu/lifescihealth/home.html

Office of Rare Diseases

The Office of Rare Diseases National Institutes of Health

Department of Health and Human Services
Bethesda, MD USA

The Office of Rare Diseases (ORD) was established in 1993 within the Office of the Director of the National Institutes of Health (NIH). On November 6, 2002, the Office was established in statute (Public Law 107-280, the Rare Diseases Act of 2002). A rare disease (also called an orphan disease) is a disease or condition affecting fewer than 200,000 persons in the United States. An estimated 25 million people in the United States have a rare disease.

The goals of ORD are to stimulate and coordinate research on rare diseases and to support research to respond to the needs of patients who have any one of the more than 6,000 rare diseases known today.

To leverage its resources, stimulate rare diseases research activities, and foster collaboration, ORD works with NIH Institutes or Centers to support

1) a grants program to establish a network for research on rare diseases, including the training of rare diseases researchers,

2) an intramural center for patients with undiagnosed rare conditions, and programs to stimulate clinical research on rare diseases including the training of researchers interested in rare diseases, and providing support for Bench to Bedside research projects

3) a scientific conferences program to stimulate research where little exists, where research progress may have stalled, or in response to scientific opportunities;

4) regional workshops to assist patient advocacy groups to become partners with the NIH and better understand NIH research programs and gaining better access to NIH research opportunities,

5) an information center and other information dissemination activities to supply reliable and useful information on the rare diseases to the public, researchers, and health care providers, including various databases to provide access to information at the ORD web site on genetic testing, clinical trials, patient travel to the research and treatment sites, patient advocacy groups, and research resources for the rare diseases research community.

Welcome to Stockholm and ICORD 2005

We are very pleased to welcome you to a most exciting meeting on Rare Diseases and Orphan Drugs, The 1st International Conference on Rare Diseases and Orphan Drugs (ICORD 2005). We have been very fortunate to be able to present a list of outstanding speakers, covering a wide range of important issues with regard to rare diseases and orphan drugs including Diagnostics, Prevention and Treatment of rare diseases.

The ICORD 2005 will focus on the improved possibilities for the development of novel treatments, following the Orphan Drug legislations in the US and EU. Speakers and participants are invited from academia, pharmaceutical industry, funding and patient organizations, the European Commission, National Institutes of Health and other policymaking organizations.

The ICORD 2005 aims to stimulate and facilitate interactions among researchers, in order to promote knowledge on how to develop new treatments for rare diseases. The conference will serve to support the society in general to be part of this process. In addition, it will encourage the pharmaceutical industry to participate in the development of orphan drugs. Most of all, ICORD 2005 will combine forces and strengths with the same ultimate goal, novel treatments for rare diseases, to work in the most efficient and rational way for the society as a whole.

Accordingly, ICORD 2005 is a meeting place for Academia, Industry, Patients and Society representatives. In another dimension, it is also a meeting place in the international perspective, being the 1st International Conference on this topic.

In addition to enjoying the formal part of the program, we hope that you will enjoy the social part of your stay in Stockholm. There will be a Welcome Reception in the evening of February 14 at the Stockholm City Hall, the venue for the Nobel Prize Banquet, including a stand-up buffet and a guided tour. In the evening of February 15, we are pleased to invite you to a Banquet in the Main Hall of The Vasa Museum, to dine in a unique setting along the 50-meter hull of the famous restored 17th-century royal warship Vasa.

We are also very honoured that Her Majesty Queen Silvia will join ICORD 2005 for the Opening Ceremony. On behalf of the Organizing Committee, we wish you Warmly welcome to Stockholm to participate, network and get inspired!

Jan-Inge Henter, M.D., Ph.D.
Chairman of the Organizing Committee

Maria Wästfelt, Ph.D.
Coordinator of Organizing Committee

Programme overview

	Monday February 14	Tuesday February 15	Wednesday February 16
Morning		**08.30** **Official Opening Ceremony** in the Presence of **Her Majesty Queen Silvia** **09.00-12.30** Morning Theme: **Historical Problems snd Present Opportunities** Rare Diseases and Orphan Drugs Experiences in the US, and a Global Perspective Rare Diseases and Orphan Drugs Experiences in the EU	**08.30-10.30** Morning Theme: **From Disease to Therapy (Session III)** Pharmaceutical Companies' Views **11.00-12.00** **From Disease to Therapy (Session IV)** Facilitating Clinical Studies on Rare Diseases
Afternoon	**Guided Tour of Karolinska Institutet** **14.30** Grand Hôtel **14.50** Tour of Campus of Karolinska Institutet **15.15** Visit at Nobel Forum, refreshment will be served **16.20** Visit at Department of Molecular Medicine **17.00** Bus leaves for the Stockholm City Hall	**14.00-16.20** Afternoon Theme: **From Disease to Therapy (Session I)** Academic Research Investigators Views **16.50-19.10** **From Disease to Therapy (Session II)** Academic Research Investigators Views (continued)	**13.30-15.00** Afternoon Theme: **Interaction Academia - Industry - Society: Cooperation between Academia and the Pharmaceutical Industry.** Role of Patient Support Groups in Rare Diseases and Orphan Products **15.30-17.30** Where do we go from now, and how
Evening	**17.30-20.00** Welcome Reception in Stockholm City Hall	**20.00** Banquet Dinner at the Vasa Museum	**Thursday February 17** Swedish satellite meeting

Programme in detail

Monday February 14

TOUR Karolinska Institutet and
WELCOME RECEPTION in Stockholm City Hall

14.30-17.30 Tour of Karolinska Institutet

17.30-18.00 Entrance to the City Hall is open

18.00-20.00 Welcome, gathering, light meal, guided tour (starts 18.00 sharp)

Tuesday February 15

Morning Theme:
HISTORICAL PROBLEMS AND PRESENT OPPORTUNITIES

08.30 **Official Opening Ceremony**
in the Presence of **Her Majesty Queen Silvia**

In respect for this special session, please arrive in advance of the meeting to ensure that all delegates are seated before the ceremony.

Chairman: Prof **Jan-Inge Henter**, Chairman, Organizing Committee
Prof **Jan Carlstedt-Duke**, Dean of Research, Karolinska Institutet

9.00-10.00 **Rare Diseases and Orphan Drugs Experiences in the US, and a Global Perspective**

09.00 **Keynote lecture**: Dr **Stephen C. Groft**, Director, Office of Rare Diseases, NIH, USA
Aims of NIH with regard to Rare Diseases and Orphan Drugs

09.40 Dr **Hans Hogerzeil**, Acting Director Essential Drugs and Medicines Department, World Health Organization (WHO), Geneva, Switzerland
Orphan drugs in a global perspective

10.00-10.30 Refreshment Break and Networking

10.30-12.30 **Rare Diseases and Orphan Drugs Experiences in the EU**
Chairman: Prof **Gunnar Alvan**, Director General, Medical Products Agency, Sweden

10.30 Mr **Thomas Lönngren**, Executive Director, European Medicines Agency (EMEA), UK
The role of the EMEA in Orphan Drug development

10.50 Prof **Josep Torrent-Farnell**, Chairman COMP (Committee for Orphan Medicinal Products); Fundació Doctor Robert, Barcelona, Spain
Five years with the Orphan Drug Directive in the EU: Achievements by the COMP

11.10 **Dr Kerstin Westermark**, Medical Products Agency, Sweden; COMP-member,
Wilson's Disease, an Orphan Disease, from a COMP perspective

11.30 Mr **John F. Ryan**, Health and Consumer Protection Directorate-General, European Commission, Luxembourg
European Community Networks in the field of Rare Diseases

11.50 Dr **Per Nilsson**, CHMP (Committee for Human Medicinal Products), and Medical Products Agency, Sweden
Application for marketing authorization of Orphan drugs - the European experience

12.10 Dr **Marlene E Haffner**, Director, Office of Orphan Drug Development, FDA, USA
The Orphan Drug Act, the Rare Diseases Act and their implications today in finding cures

12.30-14.00 **LUNCH**

Afternoon Theme:
FROM DISEASE TO THERAPY (Session I)

14.00-16.20 **Academic Research Investigators Views**
Chairman: Prof **Jan Carlstedt Duke**, Dean of Research, Karolinska Institutet

14.00 **Keynote Lecture**: Prof **Alain Fischer,** Department of Pediatric Immunology, Necker Hospital, and French Institute for Rare Diseases Research, Paris, France
The journey from idea to practise: personal experiences and goals for the future

14.40 Dr **William Gahl**, National Human Genome Research Institute, National Institutes of Health, USA
Early oral cysteamine therapy for nephropathic cystinosis, and the investigation of nitisinone in the treatment of alkaptonuria

15.10 Dr **Jean-Pierre Hugot**, Fondation Jean Dausset and Hopital Robert Debre, Assistance publique, Hopitaux de Paris, Paris, France
Genotype-phenotype correlation in inflammatory bowel disease, and the way to therapy

15.40 Dr **Elisabeth Holme**, Sahlgrenska University Hospital, Gothenburg, Sweden
Tyrosinemia: From defect to therapy

16.00 Prof **Jan-Inge Henter**, Dept of Pediatrics, Karolinska Institutet, Stockholm, Sweden
Successful therapy and clinical studies in hemophagocytic lymphohistiocytosis: Academia and patient organizations in collaboration

16.20-16.50 Refreshment Break and Networking

16.50-18.40 **FROM DISEASE TO THERAPY** (Session II)

Academic Research Investigators Views (continued)
Chairman: Dr **Giovanna Spinella**, Office of Rare Disease, NIH, USA

16.50 Prof **Leena Peltonen-Palotie**, Dept of Medical Genetics, Helsinki, Finland
Population screening aspects and the potential impact of identification of gene defects

17.20 Dr **Bruce Trapnell**, Children's Hospital, Cincinnati, USA
The Rare Lung Diseases Consortium: Disorders, defects and developing novel therapies

17.50 Dr **Giovanna Zambruno**, Laboratory of Molecular and Cell Biology, Istituto Dermopatico dell'Immacolata IRCCS, Rome, Italy
Future perspectives of therapeutic approaches for epidermolysis bullosa and ichthyoses

18.20 Dr **Paolo Moretti**, Departments of Neurology and Molecular and Human Genetics, Baylor College of Medicine, Houston, USA
The potential of folate/betaine in modifying Rett syndrome phenotype

18.50 Prof **Jan Andersson**, Dept of Infectious Diseases, Karolinska Institutet, Stockholm, Sweden
Horizontal gene transfer for immune reconstitution

20.00 **Banquet Dinner at the Vasa Museum**
(Bus leaves from Grand Hôtel 19.30-19.45)

Wednesday February 16

Morning Theme:
FROM DISEASE TO THERAPY (Session III)

08.30-10.30 **Pharmaceutical Companies' Views**
Chairman: Dr **Håkan Åström**, former Senior Vice President in Pharmacia Corporation, Board Member of Karolinska Institutet

08.30 **Keynote Lecture**: Dr **Bo Jesper Hansen**, CEO, Swedish Orphan International AB, Sweden
A Journey of Hope

09.00 Dr **Erik Tambuyzer**, Genzyme Europe, Chair EuropaBio Healthcare Council
The experience with orphan drugs in the EU from the industry point of view

09.25 Dr **Andrea Rappagliosi**, Vice President, Corporate Health Policy & Government Relations, Serono International SA, Switzerland; European Federation of Pharmaceutical Industries and Associations
The Contribution of the Biotech Industry to the Development of Treatments for Rare Diseases

09.50 Dr **Catarina Edfjäll**, Director, Global Regulatory Liaison, Drug Regulatory Affairs, Actelion Pharmaceuticals, Switzerland
From idea to an orphan drug: A small pharmaceutical company's experiences

10.15-10.40 Refreshments and Networking

10.40-12.00 **FROM DISEASE TO THERAPY** (Session IV)

Facilitating Clinical Studies on Rare Diseases
Chairman: **Claes Wilhelmsson**, Former Director, Research & Development, AstraZeneca

10.40 Dr **Jeffrey Krischer**, Data and Technology Coordinating Center (DTCC), NIH, USA
Data collection and analyses from multiple research sites

11.00 Dr **Giovanna Spinella**, Office of Rare Diseases, NIH, Bethesda, MD, USA
Enhancing rare diseases research efforts: fostering the development of collaborative research teams

11.20 Dr **Roberta Pagon**, Gene Tests, University of Washington, Seattle, USA
How to locate centers performing clinical and research genetic testing: the United States experience

11.40 Dr **Brendan Buckley**, The Cork Clinic, Cork, Ireland
Orphan drugs clinical trials in reality

12.00-13.30 **LUNCH**

Afternoon Theme:
INTERACTION ACADEMIA - INDUSTRY - SOCIETY
Perspectives on Cooperative Possibilities, Funding and Future Prospects

13.30-13.50 **Cooperation between Academia and the Pharmaceutical Industry**
Chairman: **Claes Wilhelmsson**, Former Director, Research & Development, AstraZeneca

13.30 **Keynote lecture**: Mrs **Georgette Lalis**, Director, Consumer Goods, Enterprise Directorate-General, European Commission, Brussels, Belgium
Supporting active collaboration between academia, industry and the society

13.50-14.50 **Role of Patient Support Groups in Rare Diseases and Orphan Products**
Chairman: Mr **Anders Olauson**, EURORDIS, European Patient Forum, Centre Agrenska

13.50 Ms **Diane E. Dorman**, Vice President of Public Policy, National Organisation for Rare Disorders (NORD), USA
Potential to support research and increase awareness on rare diseases research by the National Organization for Rare Disorders

14.10 Ms **Sharon F. Terry**, President, Genetic Alliance, USA
Potential of Genetic Disease Interest groups in supporting research on rare diseases

14.30 Mr **Yann Le Cam**, CE, European Organisation for Rare Disorders (EURORDIS), Paris and Vice-Chairman of the Committee for Orphan Medicinal Products (COMP)
Potential to support research and increase awareness on rare diseases research by the European Organisation for Rare Disorders

14.50-15.30 Refreshment Break and Networking

15.30-16.30 **WHERE DO WE GO FROM NOW, AND HOW**
Chairman: Dr **Maria Wästfelt**, Centre for Medical Innovations, Karolinska Institutet

15.30 Prof **Hans Wigzell**, Former President, Karolinska Institutet, Sweden
How to bring Academia and the Pharmaceutical Industry together, in Rare Diseases and Orphan Drugs

15.50 Dr **Alain Vanvossel,** Head of Unit, Major Diseases Research for Health, Research Directorate-General, European Commission, Brussels, Belgium
Future EU support of Rare Diseases and Orphan Drugs

16.10 Dr **Stephen C. Groft**, Director, Office of Rare Diseases, NIH, USA
Future ways of NIH in supporting progress on Rare Diseases and Orphan Drugs

16.30-17.30 **Conclusions & Closing Ceremony**

Prof **Jan-Inge Henter**, Chairman of the Organizing Committee
Concluding remarks: From here and onwards.

Abstracts

Rare Diseases Research Experiences in the United States of America

Stephen C. Groft

Office of Rare Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, MD USA

The Rare Diseases Act of 2002 (USA Public Law 107-280) provided a legislative mandate to establish the Office of Rare Diseases (ORD) within the Office of the Director of the National Institutes of Health (NIH). Provisions of this legislation require the ORD to stimulate and coordinate research on rare diseases and to support research to respond to the needs of patients who have a rare disease. ORD and the NIH research Institutes and Centers provide support for the existing Rare Diseases Clinical Research Network consisting of 10 research consortia and a Data and Technology Coordinating Center.

The ORD and the National Human Genome Research Center provide support for an intramural Research Program with a focus on patients with undiagnosed rare conditions, programs to stimulate clinical research on rare diseases including the training of clinical and biochemical geneticists as well as researchers interested in rare diseases, and the development of genetic tests for the research community.

The Office also provides resources to sponsor with the research Institutes and Centers a scientific conferences program to stimulate rare diseases research where little exists, where research progress may have stalled, or in response to scientific opportunities. In 2004, over 85 scientific conferences were held. The ORD also supports the activities of patient advocacy groups by supporting the annual meetings of the Genetic Alliance and the National Organization for Rare Disorders. Regional workshops have been conducted to assist patient advocacy groups to become partners with the NIH and gain a better understanding of NIH research programs, resources and opportunities.

An information center focusing on genetic and rare disorders has responded to over 10,000 inquiries in less than four years of disseminating information to the public, health care providers, and the research communities. The ORD Web site continues to be a major source of readily available information with links to other NIH and non-NIH supported databases that provide information about rare diseases and conditions, the published literature, clinical trials, genetic testing, patient advocacy groups, genetics, and research resources.

Future activities of the ORD will focus on the data management and globalization of rare disease research efforts, information development and dissemination to increase public awareness of rare diseases and conditions, recruitment of patients for research studies, the harmonization of study data from multiple research sites, genetic testing, expanding the role and acceptance of patient advocacy groups as research partners, and biospecimens collection, storage, and distribution to the research community.

Essential medicines for rare diseases

Hans V. Hogerzeil

Medicines Policy and Standards
WHO, Geneva, Switzerland

Orphan diseases can be divided into rare diseases and neglected diseases. Rare diseases are life-threatening or severely debilitating; they are too rare to create a profitable market for drug development. Examples are cystic fibrosis and haemophilia. Neglected diseases are diseases which are rare in rich countries but may be common in developing countries; there are many patients but they are generally too poor to ensure a profitable market. Examples are malaria, tuberculosis, paediatric HIV/AIDS, sleeping sickness, leishmaniasis, Chagas' disease and Buruli ulcer. In other words, some rare diseases in rich countries are common in developing countries.

Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available at all times, in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility.

Can medicines for rare diseases ever be considered as essential medicines? In developing countries, medicines for truly rare diseases should generally not be listed as essential, because they do not constitute a public health priority. However, if the treatment is relatively cost-effective (e.g. less than $300 per life-year saved) the medicine could be supplied through special clinics, outside the national list of essential medicines. If the treatment is cost-effective at a higher cost the medicine should not be listed, and also not be supplied or reimbursed in the public sector; but it should be available in the private sector.

The WHO Model List of Essential Medicines has a strong focus on public health relevance and value for money, to help countries make responsible reimbursement decisions. It only includes medicines for "rare" diseases if these are common in certain areas of the world; these are often neglected diseases rather than rare diseases.

The Role of the EMEA in Orphan Drug Development

Thomas Lönngren

EMEA, London, UK

Orphan legislation, eagerly awaited by the hundreds of thousands of patients suffering from rare diseases, has been successfully implemented in the EU. As we approach the fifth anniversary of orphan legislation, one can conclude that the orphan initiative to date has been very successful.

The Committee for Orphan Medicinal Products was established in April 2000 and meets at the EMEA on a monthly basis to review the higher than anticipated number of designation applications being submitted. Sponsors developing potential 'orphan' medicinal products are encouraged to seek advice from the EMEA on how to apply for designation. Designation provides access to a number of valuable incentives such as, protocol assistance, fee reductions and market exclusivity, to assist sponsors in the development and ultimately provide medicinal products to patients with rare diseases in the shortest possible time-frame.

In January 2005, the Committee for Orphan Medicinal Products adopted its 265th positive opinion recommending orphan designation, 245 medicinal products have been officially designated as orphan by the European Commission and nineteen orphan medicinal products have received marketing approval in the EU. As a consequence, up to 830,000 patients suffering from these orphan diseases in the Community stand to benefit from availability of these new treatments

The importance of protocol assistance in guiding sponsors towards a successful application for marketing authorisation and ultimately providing patients with more rapid access to orphan medicinal products is underlined. Since orphan legislation was implemented, the EMEA has seen a progressive increase in the number of protocol assistance requests being submitted by sponsor each year. In January 2005, a total of 71 protocol assistance and follow-up requests had been received by the Agency.

The EMEA is responsible for managing a special contribution, which is allocated by the European Parliament and the Council of Ministers on an annual basis, for the purpose of granting fee exemptions (in part or total) for orphan medicinal products. For 2005, 3 700 000 has been granted, which will permit the Agency to continue with the same fee reduction policy applied in 2002-2004, i.e 100% fee waiver for requests for protocol assistance and a 50% reduction for all other fees.

The true impact of the orphan initiatives on public health is being revealed progressively as the number of orphan products reaching the market, and thus available to patients, increases.

EU Public Health Programme and action on rare diseases

John F Ryan

European Commission, Luxembourg

Legal background

– As regards public health, the Treaty calls on the Community to act in prevention of major public health scourges, and to co-ordinate its activity in this area.

– The Treaty also includes provisions on regulation of products (pharmaceuticals) and on research.

Action Programme 1999-2002

• The first specific action programme to co-ordinate Member State activity on rare diseases was adopted in 1999. (Decision 1295/99/EC)

• The decision text states that Community measures may contribute unique added value to the treatment of problems the scale of which in individual countries is too small to allow necessary analysis or effective intervention.

• As a guide, the Decision took low prevalence to be less than 5 per 10,000 in the Community.

• Because of their rarity, people affected by individual rare diseases lack information about them and do not benefit from health resources and services which they need.

• The programme aimed to improve information and understanding of rare diseases

• It aimed to foster a wider dissemination of information particularly to patients and carers

• It aimed to take a coherent approach with other EU initiatives on orphan drugs and medical research

• A first objective was to promote the development of a European information network on rare diseases. The information was to comprise a description of the disease, prevention measures, treatments, research programmes, and a list of sources for further information.

• A second objective was to contribute to training and refresher courses for professionals in order to improve early detection, recognition, intervention and prevention.

• A third objective was to promote trans-national co-operation and networking between groups of persons directly or indirectly affected by the same rare conditions, or volunteers and professionals involved.

• A fourth objective was to support at EU level the monitoring of rare diseases in the Member States and early warning systems for clusters, and promote the networking and training of experts concerned with the handling of rare diseases and with rapid response to clusters.

Projects supported 1999-2002

• This programme ended in December 2002, having supported 24 projects in total for an amount of 6.5M (only 60% of the budget allocated to the programme)

Projects supported in 2000

• EUROMUSCLENET - MUSCLE DISEASES - PROTOTYPE OF RARE AND DISABLING DISORDERS: CREATION OF A EUROPEAN

INFORMATION NETWORK SPK (SCHLOSSPARK-KLINIK KG) (GERMANY)

• EDDNAL - EUROPEAN DIRECTORY OF DNA LABORATORIES IPG (INSTITUT DE PATHOLOGIE ET DE GENETIQUE) (BELGIUM)

• ORPHANET 1 : A EUROPEAN DATABASE ON RARE DISEASES AND ORPHAN DRUGS (PHASE 1) INSERM (INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MÉDICALE) (FRANCE)

• INFORMATION NETWORK FOR IMMUNODEFICIENCIES UNIVERSITY OF TAMPERE (FINLAND)

• TEAM 1 - TRANSFER OF EXPERTISE ON RARE METABOLIC DISEASES IN ADULTS (PHASE1)DEPARTMENT OF INTERNAL MEDICINE - UMC (UNIVERSITY MEDICAL CENTER) UTRECHT (THE NETHERLANDS)

• EAGS - CREATING A EUROPEAN ALLIANCE OF PATIENT AND PARENT GROUPS FOR GENETIC SERVICES AND INNOVATION IN MEDICINEGENETIC INTEREST GROUP (UNITED KINGDOM)

• ORPHAN MEDICINAL PRODUCTS TO THE SERVICE OF PATIENTS AFFECTED BY RARE DISORDERS (PARD 1)EURORDIS (EUROPEAN ORGANISATION FOR RARE DISORDERS) (FRANCE)

• EUROCAT 1 : SURVEILLANCE OF CONGENITAL ANOMALIES IN EUROPE (PHASE 1)UNIVERSITY OF ULSTER (UNITED KINGDOM)

• NEPHIRD 1 - NETWORK OF PUBLIC HEALTH INSTITUTIONS ON RARE DISEASES (PHASE 1)CENTRO NAZIONALE MALATTIE RARE - ISTITUTO SUPERIORE DI SANITA (ITALY)

Projects supported in 2001

• EUROCAT 2 : SURVEILLANCE OF CONGENITAL ANOMALIES IN EUROPE (PHASE 2) UNIVERSITY OF ULSTER (UNITED KINGDOM)

• SCN - EUROPEAN NETWORK ON THE EPIDEMIOLOGY, PATHOPHYSIOLOGY AND TREATMENT OF SEVERE CHRONIC NEUTROPENIA MEDIZINISCHE HOCHSCHULE HANNOVER (GERMANY)

• A EUROPEAN INFORMATION NETWORK ON PAEDIATRIC RHEUMATIC DISEASES PRINTO (PAEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION) (ITALY)

• RARE PULMONARY DISEASES - ESTABLISHMENT OF DIAGNOSTIC CRITERIA AND REFERENCE/TRAINING CENTERSINSTITUTE OF PATHOLOGY, UNIVERSITY OF GRAZ (AUSTRIA)

• NEW COMMUNICATION TECHNOLOGIES (WEB SITE) TO THE SERVICE OF THE RARE DISORDERS NETWORK AND SHARING OF GOOD PRACTICES IN DIFFERENT HELP SERVICES TO PATIENTS, ALREADY EXISTING IN EUROPE (HOT LINE) (PARD 2) EURORDIS (EUROPEAN ORGANISATION FOR RARE DISORDERS) (FRANCE)

• A EUROPEAN EDUCATIONAL PROGRAMME ON RARE DISEASES ISTITUTO DI RICERCHE FARMACOLOGICHE 'MARIO NEGRI' (ITALY)

• CAUSE - CHARGE ASSOCIATION AND USHER SYNDROME IN EUROPE SENSE INTERNATIONAL (UNITED KINGDOM)

• ORPHANET 2 (PHASE 2) INSERM (INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MÉDICALE) (FRANCE)

Projects supported in 2002

• ORPHANET 3 (PHASE 3) INSERM (INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE) (FRANCE)

• ENERCA - EUROPEAN NETWORK FOR RARE CONGENITAL ANAEMIAS UNIDAD DE ERITROPATOLOGIA -HOSPITAL CLINIC I PROVINCIAL DE BARCELONA (SPAIN)

• RARE FORMS OF DEMENTIA ALZHEIMER EUROPE (LUXEMBOURG)

• ESTABLISHING EUROPEAN NEUROFIBROMATOSIS LAY GROUP NETWORK. HEALTH PROMOTION, IMPROVING HEALTH INFORMATION AND KNOWLEDGE FOR NEUROFIBROMATOSIS (NF) IN EUROPE NF EUROPE (EUROPEAN FEDERATION FOR NEUROFIBROMATOSIS ASSOCIATIONS) (BELGIUM)

• PAN-EUROPEAN NETWORK FOR PATIENTS INFORMATION ON RARE DISEASES AND ORPHAN DRUGS (PARD 3) EURORDIS (EUROPEAN ORGANISATION FOR RARE DISORDERS) (FRANCE)

• NEPHIRD 2 - A EUROPEAN NETWORK FOR EPIDEMIOLOGICAL AND PUBLIC HEALTH DATA COLLECTION ON RARE DISEASES (PHASE 2) CENTRO NAZIONALE MALATTIE RARE - ISTITUTO SUPERIORE DI SANITA (ITALY)

• TEAM 2 - ONGOING TRANSFER OF EXPERTISE ON PREVENTION, DIAGNOSIS AND TREATMENT OF COMMON COMPLICATIONS IN ADULTS WITH RARE METABOLIC DISEASES (PHASE 2) DEPARTMENT OF INTERNAL MEDICINE - UMC (UNIVERSITY MEDICAL CENTER) UTRECHT (THE NETHERLANDS)

Projects supported in 2003-2004

• No rare disease projects were selected for funding in 2003

• 3 projects were selected in 2004:

• ENERCA II Network of Rare and Congenital Anaemias (Fundació de l'Hospital Clínic i Provincial De Barcelona)

• RDTF Scientific Secretariat of Rare Disease Task Force (INSERM France)

• PARACELSUS: Policy action and information on rare diseases in Europe (Eurordis, France)

Evaluation of EU Action Programmes

• The Commission has asked for an external evaluation of the pre-2003 action programmes on public health.

Evaluation Recommendations

• As regards Rare Diseases the evaluation recommendations are:

– Better define the general objective

– To match the ambitions with financial resources

– To encourage the Commission to further invest in rare diseases particularly because of enlargement

– To examine the question of care and treatment

– Continue paying particular attention to prevalence ratios and incidence figures

Between now and 2008

• The Commission has established a task force on rare diseases to help with co-ordinating its action in this area.

• It will support a major conference in June 2005 under the Luxembourg presidency of the EU to review projects supported to date and express the political interest in continued focus on rare diseases. A political declaration is planned.

• The EU Public Health Programme will continue to support projects on rare diseases in its annual calls for proposals

Application for marketing authorisation of orphan drugs - the European experience

Per Nilsson

Medical Products Agency, Uppsala, Sweden

Since the implementation of the EU Orphan Medicinal Products Directive, the EMEA's Committee for Orphan Medicinal Products (COMP) has reviewed >400 applications for orphan status designation, resulting in >200 European Commission designations to date.

During 2000-2004, EMEA received 46 applications for marketing authorisation of new products with orphan designation, which have been reviewed or are under review by the EMEA Committee for Human Medicinal Products (CHMP). A small number of applications have been submitted for review by European National Competent Authorities.

The experience of the work within CHMP with the orphan medicinal products will be reviewed in this presentation.

The Orphan Drug Act, the Rare Diseases Act, and their Implications today in Finding Cures

Marlene E. Haffner

FDA Office of Orphan Products Development Rear Admiral, U.S. Public Health Service.

Over the past 22 years, the U.S. Orphan Drug Act (ODA) has proven to be tremendously successful. More than 265 drugs and biological products to treat rare diseases have been brought to market since 1983. In the aggregate, these approved orphan products treat more than 13 million patients in the U.S. Advances in gene therapy have likewise evolved steadily since the early 1980s, and are further enhancing the possibilities of treatment for rare diseases – many of which are genetic in origin. Such progress now requires a redefining of the term "medically plausible subset," for purposes of designating orphan products.

In the draft version of planned regulation changes with respect to subsets, FDA proposes first to replace the term "medically plausible subset" with the term "orphan subpopulation of a disease or condition," and goes on to clarify this regulatory construct.

The cost of drug development related to the small number of patients requiring therapy remains a major problem. More dollars must be made available for research - both basic and applied. The Orphan Products Grant Program, administered by the Office of Orphan Products Development (OOPD), funds up to $350,000 in costs annually to sponsors investigating rare disease therapy. For FY 2005, the program will award a total of $14.4 million to researchers helping to improve the progress of rare disease therapies moving from research bench to patient bedside. Investigations funded by the program have contributed to the FDA approval of 39 products to treat rare diseases. Attention must likewise be devoted to making the availability of ODA incentives more widely known among both academia and the pharmaceutical industry. The 2002 Rare Diseases Act (H.R. 4013) provided statutory authorization for the NIH Office of Rare Diseases (ORD), and increased the ORD budget; much combined effort is needed now to attain our mutual goals.

The journey from idea to practice : personal experiences and goals for the future

Alain Fischer

INSERM U 429 & Unité d'Immunologie et Hématologie, Paris, France

The cure of rare diseases is a formidable challenge. Thousands of diseases spread over in all fields of medicine require meticulous studies including description of the natural history of the disease, delineation of its physiopathology and therapeutic approaches.

These tasks require a) sites of clinical and laboratory expertise, b) strong correction to basic research and c) interaction with motivated pharmaceutical companies. Not an easy way indeed! In our experience, we tried to address some of these issues in the field of Primary ImmunoDeficiencies (PID).

We have the chance to concentrate at Necker University Hospital in Paris a national reference center for PID including clinical and diagnostic laboratory facilities, a research unit and a cell and gene therapy facility.

In my presentation, I will take the example of Severe Combined ImmunoDeficiencies (SCID) (incidence 1 case in 1 x 10^5 live births) to present our views about research on rare diseases from disease phenotype description in the 70's, molecular identification in the 90's, to therapy with advances from the 70's to 2005 and remaining challenges.

Based on this experience, I will make a few proposals regarding how to organize academic research on rare diseases (reference centers, need for platforms at an transnational level) and interaction with pharmaceutical companies.

Early oral cysteamine therapy for nephropathic cystinosis, and the investigation of nitisinone in the treament of alkaptonuria

William Gahl

National Human Genome Research Institute, Bethesda, USA

Cysteamine treatment represents a therapeutic success story for the lysosomal storage disorder, cystinosis, which results from defective transport of cystine out of lysosomes. Cysteamine enters lysosomes, reacts with cystine, and forms the free thiol cysteine and the mixed disulfide cysteine-cysteamine, both of which can freely exit the cystinotic lysosome.

Depletion of 80-95% of cellular cystine can be achieved. Long-term oral cysteamine therapy is associated with prevention or slowing of renal glomerular deterioration, improved growth, preservation of thyroid function, depletion of muscle cystine and, recently, maintenance of swallowing function.

Cysteamine (Cystagon^R, Mylan Pharmaceuticals) was approved by the U.S. Food and Drug Administration August 15, 1994 for pre-transplant cystinosis patients as a result of a successful union of academia and industry; it remains the treatment of choice for cystinosis throughout the world.

Cysteamine eyedrops, which dissolve the corneal crystals of cystinosis patients, have proven efficacy and safety and are about to enter the U.S. regulatory system under the sponsorship of Sigma-Tau Pharmaceuticals, Inc.; they are currently used only under an Investigational New Drug exemption.

Nitisinone, which inhibits the second reaction in the tyrosine catabolic pathway, is approved for the fatal liver disease, tyrosinemia type I. However, nitisinone (Orfadin^R, Swedish Orphan International AB), prevents the formation of homogentisic acid, which accumulates in alkaptonuria and causes joint and cardiac valve destruction. Clinical trials are planned to determine if low-dose

nitisinone will prevent or retard limitation of motion in the hip joints of alkaptonuria patients; an IND will be obtained for these studies.

Genotype-phenotype correlation in inflammatory bowel disease, and the way to therapy

Jean-Pierre Hugot

Hopital Robert Debré, Paris, France

Crohn Disease (CD) affects about 1/1500 people in Western countries. This life long disease usually occurs in young adults. It is characterised by a recurrent or chronic inflammation of the digestive tract. Its treatment requires imunosupressors and anti-inflammatory drugs including amino-salicylates and steroids. More recently, biological therapies, mainly based on antibodies directed against pro-inflammatory chimiokines, have been developed. However to date CD treatment remains mainly symptomatic.

Research of new therapeutic agents was limited by the absence of identified aetiological factors for the disease. CD is a complex genetic disorder resulting of the complex interplay between several genetic and environmental risk factors. As a result, the genetic and epidemiological dissection of the disease will likely show in future a large heterogeneity at the risk factor level which may be only in part suspected at the phenoypic level today. From the therapeutic point of view, it means that from one patient to another one, different aetiological treatments will be required.

Recent progresses based on positional cloning methods allowed to identify several CD susceptibility genes. Little is known about the very recently described genes coding for the Dlg5 and Octn1 and 2 proteins. Our knowledge is less limited for the first reported CD susceptibility gene : CARD15/NOD2. CARD15/NOD2 is mutated in about 50% of CD patients and 20% of healthy controls. The most common mutations are characterised by a loss of response to the muramyl dipeptide which is found on the bacterial walls. However, the exact mechanism by which the mutations may cause the disease is still subject to debate. Very recently, it has been proposed that Card15/Nod2 is unable to inhibit a pro-inflammatory pathway driven by the Toll Like Receptors (TLRs). Despite of this lack of knowledge about the disease mechanisms, we are currently screening of a libary of small chemical reagents in order to find components interacting with the Card15/Nod2 pathway.

From the preventive point of view, CD treatment will require to increase our knowledge on environmental factors. CARD15/NOD2 discovery allows to focus on bacteria present in the gut. By consequence, it is expected that a better knowledge on host-bacteria interaction will allows to identify key bacterias and to develop preventive actions.

Tyrosinemia: From defect to therapy

Elisabeth Holme

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Tyrosinemia type I (OMIM 276700) is a rare recessively inherited disorder caused by deficiency of fumarylacetoacetase, the last enzyme of the tyrosine degradation pathway (Mitchell et al, 2001). Tyrosine degradation occurs mainly in liver and kidney tubules, in which tissue toxic metabolites (fumarylacetoacetate, succinylacetoacetate and succinylacetone) accumulate. Tyrosinemia type I is characterized by progressive liver disease with poor prognosis (van Spronsen et al, 1994). Severe renal tubular dysfunction with hypophosphatemic rickets and a porphyria-like syndrome caused by inhibition of prorphobilinogen synthase by succinylacetone, are also common findings in patients with the disease. In children, who not succumb in liver failure, there is a high risk for childhood hepatocellular carcinoma (HCC) development and survival beyond adolescence is extremely rare.

Tyrosinemia type I was recognized as a disease entity during the 1960th, but the primary cause of the disease was unknown until 1977 when succinylacetoacetate and succinylacetone was identified in the patient's urine (Lindblad et al, 1977).

Traditionally the patients have been treated with a diet restricted in phenylanine and tyrosine. Dietary and supportive therapy may be life saving in acute cases, but does not prevent a progressive course of the disease and liver transplantation was the only cure.

During the late 1980th it was found at ICI Central Toxicology Laboratory that a group of herbicidal chemicals were potent inhibitors of tyrosine degradation by inhibiting 4-hydroxyphenylpyruvate dioxygenase, the second enzyme of the pathway (Lock EA, 1998). Rats exposed to the chemicals developed corneal lesions, a known effect of high tyrosine levels. Our group was contacted, since we had access to the human enzyme and were experts on tyrosinemia in humans.

We realized that such a chemical could be an effective drug for treatment of tyrosinemia type I, by preventing production of the toxic metabolites and the plasma tyrosine increasing effect of the drug, was considered to be manageable by a continuation of the dietary treatment. In 1991 a critically ill infant was given the drug NTBC (2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohenanedione, nitisinone). The response to the treatment was dramatic and the pilot study was expanded to include 5 patients (Lindstedt et al, 1992).

After the publication there were requests from around the world for the drug. A protocol for a long-term study was prepared with the intention to evaluate if NTBC treatment could be a lasting alternative to liver transplantation. The protocol requested regular laboratory follow-up of critical parameters performed in our laboratory and reports on routine laboratory and clinical findings to our

database. Until 1996 we provided the drug and all patients receiving the drug were included in the study. In 1996 Swedish Orphan AB, which had the license to commercialize the drug took over the responsibility to provide the drug. Although no longer mandatory most users of the drug continued to join our study. Around 400 patients have now been included in the study and 320 of these have an on-going NTBC treatment. NTBC treatment is most effective in patients with an early start of NTBC. In patients picked up by neonatal screening and with an immediate start of NTBC treatment there has been no deaths and no development of HCC. In patients with acute tyrosinemia and NTBC start before 6 moths the survival rate is 92% and there has only been 1 case (0.6%) of liver malignancy. The older the patients are at the start of treatment the higher the risk for liver malignancy. In patients, many of whom had been on dietary treatment for various length of time at the start of treatment with NTBC between 2 and 7 years of age, HCC has occurred in 20% of the cases. However, most of these cases have been detected early enough for successful liver transplantation.

The general condition of the patients is good, there has been no development of kidney disease and porphyria-like crisis has only occurred due to interruption of therapy. Adverse events are few and has in no case required interruption of therapy (Holme and Lindstedt, 1998, Holme and Lindstedt, 2000).

Successful therapy and clinical studies in hemophagocytic lymphohistiocytosis: Academia and patient organizations in collaboration

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Background: Familial hemophagocytic lymphohistiocytosis (FHL) is a rare autosomal recessive disease, invariably fatal when untreated with a median survival of only 1-2 months after diagnosis. It is clinically characterized by fever, large liver and spleen, and low blood counts (cytopenia), and some patients also develop neurological impairment as a result of inflammatory activity in the brain. The symptoms are caused by inflammatory mediators (cytokines) and in 1999 it was shown that FHL is associated with defective triggering of programmed cell death (apoptosis), resulting in the widespread accumulation of inflammatory cells (T cells and macrophages). Subsequently, two genes causing the disease have been revealed (perforin and Munc13-4). Still 10-15 years ago many children still died of their disease, and sometimes they were not even appropriately diagnosed. There was, therefore, a need for improved diagnosis and improved therapy in FHL.

Methods: The Histiocyte Society, founded in 1985, includes physicians and scientists. Its work is in part supported by parent organizations. In 1991 the Histiocyte Society developed diagnostic guidelines for FHL, and in 1994 it initiated the first prospective international collaborative therapeutic study (HLH-94), aiming at improved survival. The treatment protocol combined regimens previously reported to be beneficial, including chemotherapy and immunotherapy, followed by bone marrow transplantation. The clinical study was supported by parent organizations that also support basic research in this and other histiocytic diseases.

Results: 236 eligible patients aged less than 15 years from more than 20 countries initiated the treatment protocol HLH-94 between July 1, 1994 and July 31, 2003. The estimated 3-year probability of survival overall is now over 50%. Since many countries collaborate in the study, statistical analyses on how to improve therapy further are facilitated. A second international study (HLH-2004) was recently launched, based on data from HLH-94.

Conclusions with regard to Rare Diseases: Although FHL is a rare disease, large series of patients and meaningful statistical studies are provided through wide international collaboration in studies supported by parent organizations. Survival of affected children has been greatly improved worldwide. This is an example of successful collaboration between clinical scientists and dedicated parent organizations, indicating the potential value of patient groups in supporting clinical studies as well as basic research in rare diseases.

The Rare Lung Diseases Consortium: Disorders, Defects and Development of Novel Therapies

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Great strides in rare lung disease research have elevated diseases such as lymphangioleiomyomatosis (LAM) and pulmonary alveolar proteinosis (PAP) from obscurity to clarity in less than a decade and serve as exemplars of the power of integrating basic science, clinical medicine and translational research. However, transforming an improved understanding of pathogenesis into accurate diagnostics and effective therapies requires a greater number of patients than can be recruited to any one clinical research center because the patient populations are small and widely distributed, geographically.

The Rare Lung Diseases Consortium (RLDC), a component of the National Institutes of Health funded Rare Diseases Clinical Research Network (RDCRN), was established to address these inherent difficulties. The RLDC is currently comprised of 10 clinical research centers distributed throughout the United States, with sites in Japan and Australia.

Its mission is to improve the delivery of medical care to individuals with rare lung diseases by: (1) increasing awareness among the general population, individuals with chronic lung diseases and the medical community, (2) use of rigorous, standardized diagnostic approaches to improve the accuracy of identifying specific rare lung diseases among individuals with chronic lung disorders, (3) use of detailed longitudinal assessment to improve our understanding of the clinical manifestations and natural history, and (4) enhancing the diagnostic and clinical management skills of pulmonary health care workers. The diseases currently under study within the RLDC include alpha-1 antitrypsin deficiency, LAM, PAP and hereditary interstitial lung diseases.

In addition to providing specific information regarding these diseases on a public Website (http://www.raredise asesnetwork.org) that is maintained by the RDCRN's Data and Coordinating Center, the RLDC anticipates initiation of the Sirolimus Multicenter International Lymphangiomyomatosis Efficacy and Safety Trial (SMILES Trial), a phase III, randomized, double-blind, placebo-controlled study. The RLDC central laboratory is currently providing specialized diagnostic testing to identify individuals with PAP on a global basis. A third, longitudinal, study in alpha-1 antitrypsin deficient individuals will evaluate the use of high resolution chest CT scanning for the early diagnosis of emphysema, which these individuals are prone to develop.

Other aspects of the RLDC program include training in rare lung disease clinical research, conduct of a pilot and demonstration project program, and development of web-based information on rare lung diseases to basic and clinical investigators, clinicians, individuals affected or possibly affected by a rare lung disease, and the general public. An important component of the RLDC is involvement of patient advocacy groups such as the Alpha-1 Foundation, LAM Foundation, Pulmonary Fibrosis Foundation, and its newly established groups, the pILD family network Foundation and the PAP Foundation.

Future therapeutic approaches for epidermolysis bullosa and ichthyoses

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Over the past two decades, the identification of the genes associated with most monogenic skin disorders has provided the basis for the design of novel therapeutic approaches, mainly of gene therapy, for these rare but severe and even lethal diseases. The majority of gene therapy strategies have been based on ex vivo models which fulfill the most important requirements for effective genetic correction of inherited diseases, i.e. high efficiency of gene transfer and long-term, sustained transgene expression in the target cell population.

A number of studies have been focused on genetic correction of two major groups of genodermatoses: inherited epidermolysis bullosa (EB), blistering disorders of skin and mucosae due to defective epithelial-mesenchymal adhesion, and ichthyoses, scaly skin diseases characterized by altered epidermal keratinization.

To date, phenotypic reversion has been achieved in vitro and in vivo in animal models for different recessive forms of EB and ichthyosis. Stable gene correction of structural skin protein defects at molecular and functional levels has been obtained by transduction of skin cells using retroviral and lentiviral vectors, and also non-viral gene transfer models. In most cases the target cell population has been represented by epidermal keratinocytes. These cells, in fact, contain stem cells and can be cultured in vitro to generate genetically engineered epidermal sheets which can in turn be grafted onto patients.

These promising results have led to the approval and initiation of the first clinical trial using genetically engineered keratinocytes in a non-lethal EB form. However, hurdles to transfer to the clinical practice the gene therapy for genodermatoses are still numerous and range from vector biosafety and host immune response issues to need for evidence of trangene expression persistence to therapeutic levels.

Protein-based therapy represents a recently proposed simpler alternative approach for treatment of specific forms of EB. However, the elicitation of an immune response by the exogenous protein is one of the major concerns linked to this treatment modality. Finally, diseases characterized by enzymatic defects, such as some ichthyosis forms, appear amenable to enzyme replacement therapy.

The potential of folate/betaine in modifying the Rett syndrome phenotype

Paolo Moretti

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Objective: To study the modification of disease severity by dietary methyl donors in a mouse model of Rett syndrome.

Background: Knock-in mice expressing a truncated allele of MeCP2 ($Mecp2^{308/Y}$) recapitulate many of the neurologic manifestations of Rett syndrome (RTT) and provide an excellent model for studying the biological basis of RTT and testing treatment interventions. Current data support the hypothesis that loss of MeCP2 function alters methylation-dependent gene expression. Methyl donors such as folate and betaine are available as nutritional supplements and have been shown to modify DNA methylation levels in vivo and in vitro and affect the expression of endogenous genes. We hypothesized that dietary methyl donors modify the neurologic deficits of $Mecp2^{308/Y}$ mice by modulating the level of DNA methylation of MeCP2-regulated genes.

Design/Methods: We performed a controlled randomized trial in which wild-type and mutant animals were exposed prenatally and postnatally to diets containing low or high concentrations of methyl donors. The behavioral and morphologic phenotype of all animals was studied from weaning until death.

Results: $Mecp2^{308/Y}$ mice exposed pre- and postnatally to a low methyl donor diet showed significant modification of key phenotypes including improved neurologic function and increased life span. The health and behavior of wild-type mice were not influenced by these dietary manipulations.

Conclusions: These data indicate that reduction of dietary methyl donor content improves the neurologic deficits and general health of $Mecp2^{308/Y}$ mice. The results raise important questions about the influence of nutrition on the epigenetic regulation of neuronal gene expression. Work is underway to determine whether dietary methyl donors affect DNA methylation and gene expression in $Mecp2^{308/Y}$ mice and to establish whether other Mecp2 alleles are susceptible to similar dietary effects.

Horizontal gene transfer for immune reconstitution

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In most individuals with HIV infection, HIV-specific CD4 T-cell proliferation is undetectable soon after primary infection, with the exception of some patients with good prognosis. Moreover, although infected individuals have a high frequency of HIV-specific CD8 T cells these cells appear to be dysmature. The molecular basis for such impaired T cell responses is most likely multifactorial.

Our current goal is to develop a therapeutic HIV-1 vaccine based on horizontal transfer of autologous HIV-1 DNA by using apoptotic bodies. Horizontal transfer of HIV-1 DNA contained in CD4 T cell derived apoptotic bodies achieves this. The principle comprise induction of apoptosis in CD4 T cells carrying integrated HIV-DNA that are added to in vitro differentiated DC. Such cultured DC rapidly ingests HIV-1 containing apoptotic bodies, which result in DC transfer of HIV-1 DNA.

Furthermore, we have demonstrated that it is possible to transfer HIV-1 DNA by inducing apoptosis in a cell line carrying an integrated copy of a replication in-competent 8E5/LAV reverse transcriptase negative HIV-1 strain. In addition, HIV-1 DNA can be detected in high frequencies (up to 50%) of recipient cells for at least 8 weeks and the recipient cells were shown to express HIV proteins (p24 and gp120). We have proved that DC that has ingested HIV-1 DNA containing apoptotic bodies is capable of inducing HIV-antigen specific T cell proliferation and IFN- production.

We have performed in vivo immunizations with apoptotic bodies derived from syngeneic splenocytes infected with HIV-1/MuLV pseudovirus capable of replicating in mice and demonstrated induction of both HIV-1 specific T- and B-cell responses in mice. Finally, mice immunized with apoptotic bodies derived from HIV-1/MuLV infected splenocytes, without addition of adjuvant, were completely protected against challenge with replication competent HIV-1/MuLV while control groups remained susceptible and became infected. Immunization with apoptotic bodies containing HIV-1/MuLV did not induce any viral replication in the recipients.

These experiments demonstrate that apoptotic bodies derived from HIV-1 infected cells can be used as a safe immunogen without need for additional adjutants. We now plan to explore these findings and advance into human pilot trials

1. National Institutes of Health, Rare Diseases Clinical Research Network, RFA: FF-03-008, February 27, 2003.

A Journey of Hope

Bo Jesper Hansen

Swedish Orphan International AB, Stockholm, Sweden

Swedish Orphan International is a privately owned pharmaceutical company which develops, makes available, markets and distributes pharmaceutical products which may be designated or approved as orphan drugs or pharmaceuticals fulfilling an unmet medical need. Swedish Orphan International is regarded as a pioneer and industrial forerunner within the orphan drug industry, where Swedish Orphan International has played an important role in pioneering the creation of a new sector within the pharmaceutical market.

Swedish Orphan International was founded in 1988 as we had identified a market opportunity based on the enactment of the US Orphan Drug Act (the “ODA”) by the Food and Drug Administration (“FDA”) in 1983. The ODA provided significant financial incentives for pharmaceutical companies to develop therapeutic products for rare disorders. Already in the first few years following the enactment of the ODA, the number of products designated and approved increased rapidly. However, few of these products reached markets outside the US in any structured way and the knowledge about the ODA outside the US was almost non-existing.

Swedish Orphan International was founded with the aim to in-license and develop orphan drugs in order to market and distribute these internationally. Since the inception in 1988 Swedish Orphan International’s commitment and vision for the company’s concept have created a new sector within the pharmaceutical market but also established the company as a successful frontrunner in this opportunistic market.

Since 1993 Swedish Orphan International has used the profits generated by its in-licensed products for the in-house focused development of proprietary products i.e. Orfadin® for the treatment of the very rare, severe and life-threatening metabolic disorder, Hereditary Tyrosinemia Type 1. Orfadin®, the Company’s first in-house developed proprietary product, was launched in 2002, in the USA. Swedish Orphan International has a broad, balanced and innovative product portfolio within the following therapy areas: hematology, infectious diseases, metabolic disorders, poison control, oncology, respiratory diseases, urology/nephrology, cardiology, pain control and diseases affecting the immuno-compromised patients.

Mission

Swedish Orphan International’s mission is to provide patients, healthcare personnel and the pharmaceutical industry with an independent global network, specializing in the development, marketing and distribution of orphan products for the treatment of rare disorders, and products and services to satisfy unmet medical needs where current treatment is either unavailable or unsatisfactory.

The experience with orphan drugs in the EU from the industry point of view

Erik Tambuyzer

Genzyme Europe, Chair EuropaBio Healthcare Council, Brussels, Belgium

The European Union is catching up in the field of rare diseases, having made research on them a public health priority and by the introduction of the EU orphan medicinal products Regulation. Orphan drug regulations, primarily in the US (since 1983) and in Europe (since 2000), have encouraged industry to respond to the need of the patients suffering from rare, serious and often life-threatening diseases by offering economic incentives. Some 80 % of the rare diseases have a genetic origin and therefore, many of the medicines to treat them, called orphan medicines, are based on biotechnology. They are often developed by small biotech enterprises, and are at the basis of many biotech companies, but less by large pharma companies. Orphan drug regulations in both the US and Europe have been a success for patients waiting for therapies recognizing however that the experience in Europe is still young. Europe now needs to bolster its approach, taking the enlargement into account on the one hand, but also the need to go beyond the Regulation on the other.

Because of the rarity and heterogeneity of the treated disease, orphan medicine development necessitates a lot of out-of-the-box thinking, in terms of diagnosis, design of clinical trials and their practical set-up (including recruitment of patients) manufacturing and upscaling, care of the patient as well as distribution. The treated diseases are not only rare, clinically very heterogeneous and often not yet studied, but also underdiagnosed and presenting different clinical symptoms for different patients at different ages. Orphan medicines may also not fit well in regulatory frameworks or health care reimbursement systems, set up for common medicines. In addition, they may have to be offered at high prices because of the small potential market. But there is also a "return on investment" for society: this type of innovation dramatically improves the patient's quality of life and gives them back a chance in life.

As is proven in public surveys in France, society is very supportive for rare disease research and continued investment in this field it is recommended to resolve the many open questions that still require an answer, and also because research in rare diseases brings often additional knowledge about more common diseases. In the industry's opinion, it is now necessary to not only look at the regulatory approval of a medicine, but to put efforts into the development of a coordinated European framework from research to access in this field. This framework should encompass measures regarding research, diagnosis, screening, development of therapies, and clinical trials into one coherent approach, which would also include appropriate ways to make products available under so-called compassionate use circumstances. And very importantly, such framework should result in a sustainable system for equitable and timely access to the orphan medicines for patients.

To build consensus around such framework approach, partnerships involving patients, clinicians, authorities, and industry are the only way forward, and may bring a pragmatic and well supported model for addressing new needs and opportunities. The presentation will cover the above topics and present the industry view for them.

The Contribution of the Biotech Industry to the Development of Treatments for Rare Diseases

Andrea Rappagliosi

SERONO INTERNATIONAL S.A., Corporate Health Policy & Government Relations, Geneva, Switzerland.

An overview in the last 20 years of how the Biotech Industry has contributed to the research and development of new and innovative treatments in order to meet unmet medical needs especially in the field of rare diseases. The contribution of Biotechnology has been key in bringing therapies to people who are left at the margin of the healthcare system.

From Idea to an Orphan Drug: a small pharmaceutical company's experience

Catarina Edfjäll

Actelion Pharmaceuticals Ltd., Switzerland

When the focus of research and discovery is on innovative products for high unmet medical need, the term 'orphan disease' is inevitably encountered. Defined as illnesses which are serious, life threatening or chronically debilitating, they are frequently characterised by limited therapeutic options available to the treating physician. Whilst only a small number of patients may suffer from a particular rare disease, in total, over 30 million Europeans suffer from orphan diseases. For this sizeable population there are currently very few treatment options available, therefore, there is a clear need for the development of new orphan drugs. This need for specialist treatments has been recognised by the European Commission, and catered for through the orphan drug procedure at the EMEA, which was established in 2000.

Bosentan, a marketed orphan drug (Tracleer®), is a dual endothelin receptor antagonist (ERA) with affinity for both ETA and ETB receptors. Originally developed by F. Hoffmann-La Roche in Basel, Switzerland, bosentan was recognised to have potential in the incurable orphan disease pulmonary arterial hypertension (PAH). The company decided that developing bosentan for the treatment of PAH was not compatible with the company infrastructure, the growth potential being small for such a large pharmaceutical company. Recognising the potential for a new class of drug in a disease area with such great medical need, the discovery team after founding Actelion Pharmaceuticals Ltd. in 1997, in-licensed bosentan (Tracleer®).

The successful development and marketing of the orphan drug Tracleer® as the first oral treatment for PAH, has provided a therapy which is associated with improved walking distance and a prolonged time to clinical worsening in this severely debilitating disease. Today close to 20 000 patients world wide have received this orphan drug. The revenue generated from Tracleer® has contributed to Actelions' growth to a company of almost 900 employees worldwide within 7 years. Considerable revenue has been re-invested in the continued development of Tracleer® in other orphan indications, as well as the launch of another orphan drug, Zavesca®, for Gauchers' Disease type I, and its continued development in other orphan indications. The success of Tracleer® has helped Actelion to continue the research and development of many new molecules, which in turn could lead to innovative treatment options for other diseases of high unmet medical need.

The process and required investment for the development of orphan medicinal products are similar to those for conventional medicines. Unquestionably, quality, efficacy and safety must be proven. However, the limited patient population, characteristic of orphan diseases, hinders the possibility of generating sufficient safety data within a reasonable time frame. Consequently, the majority of orphan drugs are approved under exceptional circumstances in the EU. In this situation, companies are requested to agree to and fulfil many post approval commitments, such as large additional studies and/or post marketing surveillance programmes. This represents quite a challenge, both from a logistic, financial and resource point of view for small and medium sized enterprises (SMEs), which may not have a mature infrastructure and established affiliates in every country. Nevertheless, these challenges are not insurmountable, as Actelion's experience clearly shows. However, additional protection that rewards the pioneering work into new classes of drugs, and a pan-European implementation of national incentives, such as tax cuts and grant programmes, are urgently needed to further stimulate research and development of new orphan drugs.

Data Collection and analyses from multiple research sites

Jeffrey Krischer

Data Technology and Coordinating Center, Rare Diseases Clinical Research Network, University of South Florida, Tampa, Florida USA

The Data Technology and Coordinating Center (DTCC) provides informatics and biostatistical support for the NIH funded Rare Diseases Clinical Research Network. The network itself is comprised of ten clinical research consortia focused on different groups of rare diseases, which in turn are comprised of a variable number of clinical sites in the United States and in Europe and Asia. In all, the network consists of more than 311 investigators located in 55 clinical sites in 20 states and 8 countries studying over 41 diseases.

The DTCC coordinates clinical research in this geographically and clinically diverse setting by building web-based tools to facilitate protocol development, subject recruitment, data collection, adverse event reporting and monitoring, and statistical analyses. Internet tools provide widely disseminated public access to affected individuals, their family members and health care providers to communicate information about rare diseases and to help identify available network protocols for potential study accrual. A patient contact registry is an example of a mechanism by which interest individuals can learn of new studies as they become available. The Network communication tools provide secure access worldwide and are easily extendable to new clinical settings. They provide for password protected access, user defined content and different levels of permissions to fit consortia needs. The security framework provides a customized look to the website allowing the presentation only of items for which the individual has permission to see. Protocol management and communication tools implemented in this framework provide for study specific clinical data collection, electronic transfer of laboratory or imaging data, and a variety of mechanisms to monitor study progress and compliance. Results of data analyses for interim study monitoring, adverse event review and study endpoints can rapidly be made available to the protocol research team no matter where they are located. The DTCC also promotes standardized approaches to data collection, employing structured data dictionaries that are common to multiple diseases and protocols that provides for consistently defined data elements across diseases, as appropriate, and from study to study. By design, data collected from longitudinal, natural history studies will be consistent with data from companion interventional trials, thereby enhancing their long term value.

Collectively, these systems facilitate research in rare diseases by transcending geographic boundaries, by providing a comprehensive informatics environment for the conduct of studies in many different clinical settings and by promoting standards that enhance the value of the accumulating data for future research. They provide a scaleable, extensible environment to meet foreseeable future research needs.

Enhancing Rare Diseases Research Efforts:Fostering the Development of Collaborative Research Teams

Giovanna Spinella

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"Rare disease" is defined in the United States through law (Orphan Drug Act, P.L. 97-414, 1983; Health Promotion and Disease Prevention Amendments, P.L. 98-551) as a condition affecting fewer than 200,000 Americans or a disease with a greater prevalence but for which no reasonable expectation exists that the costs of developing or distributing a drug can be recovered from the sale of the drug in the United States.

In the United States, more than 25 million people are thought to be affected by an estimated 6,000 rare diseases or conditions leading to significant morbidity and mortality. Despite the advances and opportunities for research in rare diseases, there remain difficulties in clinical diagnosis and management. Diagnosis may be straightforward with well-described phenotypes or difficult with poorly defined criteria. There is insufficient characterization of the course of many rare diseases. Treatment can be equally challenging with many questions concerning appropriate and best clinical management.

Rare diseases pose unique challenges to identification and coordination of resources and expertise for small populations dispersed over wide geographic areas. Rare diseases research requires collaboration of scientists from multiple disciplines sharing research resources and patient populations. Rigorous characterization and longitudinal assessment is needed to facilitate discovery of biomarkers of disease risk, disease activity, and response to therapy.

In addition, controversies concerning current treatment strategies could be resolved by systematic assessment. Well described patient populations will be important to bring promising therapies to the clinic.

GeneTests : Finding a Clinical/ Research Laboratory, the US Experience

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GeneTests, (www.genetests.org) was established in 1992 (as "Helix") to help clinicians and researchers identify US laboratories offering molecular genetic testing for inherited disorders. It currently compromises the following:

Laboratory Directory: About 580 international laboratories offering clinical and/or research testing for about 1100 diseases. Approximately 75% of the laboratories are US and approximately 25% are international. Listings are revised as needed and updated yearly.

Gene Reviews: About 280 expert-authored, peer reviewed, highly structured disease descriptions that focus on the use of generic testing in diagnosis, management, and genetic counseling. About 70% of authors and reviewers are from the US and about 30% are international. One new entry is added each week. Entries are revised as needed and updated every two years.

Clinic Directory: A listing of about 1000 US and international genetics clinics that provide genetic evaluation and genetic counseling.

Education Materials: Materials that attempt to make technical information in GeneTests accessible to non-genetics healthcare professionals include an illustrated glossary of over 200 genetic terms, educational materials on the use of genetic testing in patient care, and PowerPoint teaching modules.

Resources: For each disorder in the gene GeneTests database, English language consumer health-oriented resources that are national/international in scope, have a mechanism for scientific/medical input, and are consistent with the GeneTests mission.

External links: Links to PubMed citations, NCBI databases (EntrezGene, OMIM), genomic databases (locus-specific databases, HGMD, GeneCards, the GDB Human Genome Database, and GenAtlas).

Currently about 25,000 to 35,000 GeneTests records are viewed each day.

In addition to the above content, GeneTests has developed a disease naming system top accommodate clinicians who think in terms of phenotypes and laboratorians who test for alterations in genes. The GeneTests naming system accommodates the situations in which: (1) mutations in a single gene produce phenotypes previously thought to be distinct, but which actually compromise a continuum; and (2) a single phenotype is caused by mutations in more than one gene.

Orphan drugs: clinical trials in reality

Brendan Buckley

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Many more medicinal compounds receive designation as orphans than are authorised for use. This is to some extent inevitable, as the preliminary data on which orphan drugs receive designation may fail subsequently to translate in larger studies into the safety and efficacy which are necessary for marketing authorisation.

However, even good orphan drugs may fail to reach market. Among the major barriers to this are difficulties in performing adequate clinical trials, particularly in very rare diseases. In Europe, these include problems of case-finding and coordination in a multi-lingual and multi-cultural continent with a diversity of healthcare systems. Funding of clinical trials is much more difficult than in the USA. Better trial designs to maximize information yield are needed, along with a commitment to long-term follow-up of participants. Training of investigators needs to be rigorous so that error and uncertainty in data collection are minimized. All of these barriers may potentially be overcome, and some solutions will be discussed in this presentation.

Potential to Support Research and Increase Awareness on Rare Diseases Research By the National Organization for Rare Disorders

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The National Organization for Rare Disorders (NORD), a unique federation of voluntary health organizations, is dedicated to helping people with rare "orphan" diseases. For over 20 years, NORD has been committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and service.

Research Grant and Fellowship Programs

In 1989, NORD funded four research grants totaling $142,000. In the 16 years since the inception of the program, nearly $4.5 million dollars has been awarded to fund 110 grants and fellowships. This dynamic and ever growing program provides seed money in small grants to academic scientists studying new treatments or diagnostics for rare diseases. The clinical researchers supported by NORD's research grants provide preliminary data indicating that a treatment (drug, device, or medical food) may be safe and effective when used for a larger number of patients. Researchers can then use the preliminary data to apply for larger multi-year government grants or to attract a commercial sponsor who will manufacture an orphan product and get it approved for marketing by the U.S. Food & Drug Administration (FDA).

The Power of the Many

In the United States, there are nearly 30 million Americans living with one of the 6,000 known rare diseases. The opportunity for the rare disease community to affect federal public policy in order to increase funding for and awareness of rare diseases is powerful and far-reaching. In 2001, NORD was instrumental in the introduced of the Rare Diseases Act (RDA) in the United States Congress. The purpose of the Act was to increase funding for the study of rare diseases at the National Institutes of Health (NIH) and to codify the Office of Rare Diseases. Within 15 months, this legislation was signed into law on November 6, 2002. This amazing feat would never have been possible, however, without the active support of nearly 140 patient and industry organizations, along with thousands of individual patients, family members, researchers, genetic counselors and healthcare providers across the country.

Today, because of their efforts to ensure passage of the RDA, the Office of Rare Diseases now stands as a permanent office at the NIH; $51 million now funds the Rare Diseases Clinical Research Network, consisting of seven Rare Diseases Clinical Research Centers and a Data and Technology Coordinating Center; Congress now recognizes that "understanding the pathogenesis of rare diseases may advance our understanding of more common medical disorders"; and, most importantly, the rare disease community has been empowered to advocate for the millions who live with rare "orphan" diseases. [1]

EU support to Research on Rare Diseases and Orphan Drugs

Alain Vanvossel

European Commission, Research Directorate General, Health Directorate, Major Diseases Unit, Brussels, Belgium

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Recognising the importance to stimulate rare disease research activities at the European level, the European Union provides direct financial support for selected research projects through its Framework Programmes for Research, Technological Development and Demonstration Activities.

Like former Framework Programmes, the aim of the current FP6 – running from 2002 to 2006 – is to develop and exploit European research. The various types of instruments – Integrated Projects, Networks of Excellence, Specific Targeted Research Projects, Coordination Actions and Specific Support Actions used to support rare disease research will be presented.

A wide range of projects are to be funded in both basic and clinical research, in various areas of FP6 (thematic priorities, research for policy support, ERA-Net scheme). This will be illustrated through FP6 starting and running projects. Prospect of Priority 1's fourth call for proposals will also be given.

Medium-term perspectives on European research for rare diseases will be addressed through reflections on the future FP7 elaboration. The first stages of FP7 development will be detailed, such as the envisaged major objectives and areas.

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