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Europe's research into rare diseases (1)

A Half Century of Progress

Over the last half century, there has been a growing awareness of the existence of huge numbers of rare human diseases and the need to find cures for illnesses that concern relatively small numbers of patients. In the first of a two-part series, Jeremy Garwood looks at the latest European investments in R&D for rare diseases and orphan drugs.

On 28th February 2013, the European Commission announced €144 million of funding for 26 research projects covering an array of rare diseases, including cardiovascular, metabolic and immunological disorders. These projects bring together over 300 participants from academic institutions, industry and patients' groups in 29 countries (*www.euractiv.com*).

But that isn't all. Overall, during the last six years, the European Commission's funding for rare disease-related research projects has amounted to some €500 million, covering around 100 projects. These projects form part of the International Rare Diseases Research Consortium (IRDiR Consortium) which was launched in April 2011 by the European Commission and the USA's National Institute of Health (NIH) to foster international collaboration in the rare diseases field (*www.irdirc.org*).

Tools and therapies

The IRDiR Consortium has set itself two main objectives to be achieved by the year 2020. Firstly, it aims to develop diagnostic tests for most rare diseases. As of 2012, there were diagnostic tools available for 1,883 of the more than 6,000 known rare diseases. Secondly, it has set a target for developing new therapies for these diseases. The target of delivering 200 new therapies is more modest, but is nevertheless ambitious. However, they seem to have got off to a good start with 56 new therapies authorised between 2010 and 2012.

The ultimate scale of this health challenge, i.e. curing thousands of obscure diseases, is huge, but considerable progress has come from a growing public awareness of the issues involved.

No more than 1 in 2,000 …

Rare diseases are, by definition, not very common. Officially, to be recognised as a rare disease, the number of sufferers must be below a certain proportion of the population. In the European Union, this is defined as no more than 1 in 2,000 individuals, while in the USA, it is no more than about 1 in 1,250. The number of disorders that fit this definition is large – the Orphanet registry lists over 6,000 distinct rare diseases (see the box on rare diseases on page 40). Estimates of the total number who suffer from rare diseases, many of whom are children, are of the order of about 30 million people in Europe (6% of the EU population) and 25 million in North America. For around 80% of rare diseases, the origin is genetic while others are the result of infections, allergies and environmental causes. They are usually chronically debilitating or life-threatening. The Global Genes Project estimates that there are 350 million people worldwide affected by a rare disease (*http://globalgenes.org*).

…but 350 million affected?

However, the true prevalence of rare diseases is unknown, since there is no source of data at the population level. Based on published data by disease, Orphanet (the European rare disease database) finds that the distribution of rare disease prevalence tends towards very low numbers. Only 105 diseases have a prevalence ranging from 1 to 5 in 10,000, while 233 have a prevalence ranging between 1 in 10,000 and 1 in 100,000. Another 1,000 rare diseases probably have a prevalence of around one per million. The remaining 5,000 diseases affect only a few patients worldwide, usually due to a single mutation in family members.

Once neglected; awareness now growing

Forty years ago, when faced with a choice, most researchers would have concentrated their efforts on common diseases; rare diseases were neglected.

One common explanation was that drug development costs had become too high for pharmaceutical companies. As a result, they would only support R&D of products with a big mar- ▸▸

Photo: Eurordis

Advertisement for "Rare Disease Day", an annual global charity event to raise awareness of rare diseases and improve access to medical treatment.

ket, i.e. targeted for the treatment of common diseases with the potential for large volumes of sales. The pharmaceutical industry was not interested in the development of treatments for rare diseases with small numbers of patients. The term 'orphan drug' was coined to highlight this reluctance to adopt 'orphan diseases'.

Nevertheless, there has been a growing recognition that rare diseases are an important public health issue and that governments should improve their outcomes. Public awareness of rare diseases has increased due to the work of patients' support groups and charities. Set up in 1983, the National Organisation of Rare Disorders (NORD) in the USA was instrumental in the approval of the Orphan Drug Act. NORD now consists of more than 2,000 organisations (*www.rarediseases.org*).

In Europe, the European Organization for Rare Diseases (EURORDIS) was created in 1997 based on the model of NORD. It is an alliance of patients' associations dedicated to improving the quality of life of people living with rare diseases and has been a driving force in advocating for the adoption of European regulations for Orphan Drugs (*www.eurordis.org*).

Government incentives for the Development of Orphan Drugs

A major turning point for research into rare diseases came in the USA with the passing of the Orphan Drug Act in 1983. This act provided tax relief for companies investing in clinical research for orphan drugs, and it provided seven years of exclusivity for a product approved for an orphan disease, even though the product might be otherwise in common use (see text box on orphan drug development incentives, page 43).

In the European Union, the principle of orphan drugs has been acknowledged since 1991, but the EU's own orphan medicinal products legislation did not come into effect until 2000 (Regulation (EC) No 141/2000). The definition of rare diseases is broader than in the US, in that it also covers some tropical diseases. In 2007, the US Federal Drug Authority (FDA) and the EU's European Medicines Agency (EMA) extended their cooperation by agreeing to use a common application process for potential orphan drugs.

The key rationale behind the Orphan Drug Regulation is that it addresses the need to offer incentives for the development and marketing of drugs to treat, prevent, or diagnose rare conditions, because, "without such incentives, it is unlikely that products would be developed for rare diseases as the cost of developing and marketing products for these disorders would not be recovered by sales" (Orphanet/RD Platform 'Report on rare disease research, its determinants in Europe and the way forward' May 2011).

The EMA's Committee for Orphan Medicinal Products notes that in the first ten years since the EU passed its regulation, it has granted more than 850 orphan drug designations, with >60 receiving marketing authorization. ('European regulation on orphan medicinal products: 10 years of experience and future perspectives' *Nature Reviews Drug Discovery* 2011 10:341-9).

Another 259 designations were accorded in 2011-12, and the EMA expects >150 in 2013.

A major source of revenue

But this is not the same as market authorisation to sell them. In 2012, there were only 70 orphan drugs on the European market, plus another 75 drugs with an indication for rare diseases. In total, these substances have a designation for more than 550 rare diseases.

Meanwhile, the orphan drug market has become a major source of revenue for the biotechnology and pharmaceutical industries. Global orphan drug sales increased at a rate of 10% a year between 2005 and 2011, to reach $86 billion (*Bloomberg*

Rare diseases

Some 30 Million Patients in Europe

In the EU, orphan diseases affect less than 1 in 2,000 people. Around 80% are genetic in origin. Many of them appear early in life. They are frequently life-threatening with >30% mortality before adulthood, and can be chronically debilitating with a significant impact on quality of life.

It is estimated that some 30 million people in Europe have a rare disease. Orphanet is a European database for orphan diseases and ongoing research. There are around 7,000 rare diseases on its 2012 list (www.orpha.net). It also provides a list of these diseases by decreasing prevalence. At the upper limit (around 50 cases per 100,000 of the European population) are diseases like cleft palate, obesity due to melanocortin-4 receptor deficiency, congenital bilateral absence of vas deferens, and isolated spina bifida. Many cancers are also rare diseases, e.g. Renal cell carcinoma (35.8/100,000), Gastric cancer (29/100,000) and Adrenocortical carcinoma (1/100,000). There are also infectious diseases, such as tuberculosis (20/100,000) and botulism (0.05/100,000). Most genetic diseases are so rare that there may be relatively few published cases (ever) – e.g. carnitine palmitoyl transferase II deficiency: >300 published cases; glycogen storage disease due to LAMP-2 deficiency: 84 cases; MIDAS syndrome: <50 cases; sudden infant death - dysgenesis of the testes: 21 cases; fingerprint body myopathy: <20 cases; 'German syndrome': 5 cases; growth delay due to insulin-like growth factor I deficiency: 4 cases; 'sparse hair - short stature - skin anomalies': 4 cases; or 'split hand - urinary anomalies - spina bifida': 3 cases. -JG-

News 7/04/13). Some orphan drugs have 'blockbuster' status. For example, Amgen's Erythropoietin (trade name Epogen) had sales of €1.8 billion in 2003. And Sanofi made €2.8 billion in 2011 from sales of a handful of orphan drugs it acquired when buying Genzyme. In 2010, the world's most expensive drug was Soliris, an orphan drug from Alexion Pharmaceuticals that cost €315,000 per patient per year for the treatment of paroxysymal nocturnal hemoglobinuria, bringing in total annual sales of €415 million.

Orphan drugs such as Epo, yielding sales of 1.8 billion euros in 2011 alone, can be very lucrative.

Actions of the European Commission

The EC restated its position in 2008:, 'Rare diseases: Europe's challenge' (Com(2008)679),

"Although each rare disease only affects a relatively small number of patients and families, taken as a whole they represent a serious health burden for the EU. Moreover, the need to bring together expertise and make efficient use of the limited available resources means that rare diseases is an area where European cooperation can add particular value to the actions of the Member States.

And further on,

"For most severe rare diseases that would potentially be treatable, there is simply no current specific treatment. The development of therapies faces three hurdles: the lack of understanding of underlying pathophysiological mechanisms, the lack of support of early phases of clinical development and the lack of opportunity/cost perception from the pharmaceutical industry."

The EC has been actively supporting research projects on rare diseases through its Framework Programmes for Research, Technological Development and Demonstration Activities. Under the Fifth Framework Programme for Research (FP5: 1998-2002), 47 rare disease-related projects were funded for €64 million in total.

The Sixth Framework Programme (FP6: 2002-2006) saw a significant funding increase: around €230 million for a total of 59 rare disease projects. It brought, "incomparable European added-value in the field of rare diseases", through the support of multidisciplinary collaborative projects, particularly in the research areas of neuromuscular diseases and myopathies, skin and kidney disorders, autoimmune and metabolic diseases, rare cancers, mental and neurological disorders, and respiratory diseases.

Well funded EC's framework programmes

In the Seventh Framework Programme (FP7: 2007-13), a total of €500 million has been given to around 100 projects. The supported projects correspond to one of two criteria: either they should aim to shed light on the course and/or mechanisms of rare diseases, or they must test diagnostic, preventive and/or therapeutic approaches, in order to, "alleviate the negative impact of the disease on quality of life of the patients and their families, as appropriate, depending on the level of knowledge concerning the specific (group of) disease(s) under study."

The FP7 research funds were distributed in three chunks. For the period 2007-2010, 50 research projects received €237 million. Of these, 17 projects were specifically aimed at supporting research on the natural history and pathophysiology of rare ▶▶

diseases (for a total of €71 million), and 8 projects covered the preclinical and clinical development of orphan drugs (for a total of €36 million).

Independent organisations also supportive

An additional €127 million was also allocated to rare disease-relevant projects, funded under other sections of the Health Theme where the keyword "rare disease" did not appear in their titles. For example:, "High throughput molecular diagnostics in individual patients for genetic diseases with heterogeneous clinical presentation," and, "Gene therapy tools targeting the central nervous system," or, "Structuring clinical research on rare cancers in adults."

In the latest round of funding, 26 projects received €144 million from the EC. However, there are also many organisations, including non-governmental patient groups and medical charities, who have been independently supporting research on rare diseases for many years. The IRDiR Consortium has so far brought together 30 organisations ready to invest, over a five-year period, more than €7.6 million into research which contributes to its R&D objectives for 2020. These include France's association against myopathies (AFM), Italy's Telethon Foundation, the UK's National Institute for Health Research, and the US National Cancer Institute.

However, there remain certain specific research problems associated with rare diseases. These are essentially due to the limited number of patients and scarcity of relevant knowledge and expertise. There have been several European projects dedicated to the collection and sharing of data about rare diseases, including RD Platform and RD-Connect. Much of this rare disease information is diffused through the Orphanet website, which also provides an overview of orphan drugs and ongoing projects funded by charities, national governments, and the EC (see text box on the European rare diseases research landscape in 2012, page 40).

Examples of EU-funded projects

Launched in January 2013, **RD-Connect** is a six year EC funded project (€12 million) to develop an integrated research platform in which complete clinical profiles are combined with -omics data and sample availability for rare disease research (*http://rd-connect.eu*).

Its objectives include the development of common standards for databases, biobanks and patient registries, the provision of a suite of clinical bioinformatics tools, including data mining and knowledge discovery tools for the analysis and integration of molecular and clinical data to discover new disease genes, pathways and therapeutic targets, and to develop an integrated platform to host the processed data from Neuromics, EURenOmics and future IRDiRC projects. It includes researchers from the European Bioinformatics Institute, the universities of Heidelberg, Newcastle, Uppsala, Paris 7, etc., and companies like Genzyme (now part of Sanofi, France), GlaxoSmithKline (UK), and Orphan Europe (Italy).

Jeremy Nicholson, the Chief Scientist of Metabometrix, is involved in the EURenOmics project, to identify novel genetic causes of rare renal diseases.

EURenOmics (€12 million of EC funds) is a project which aims to identify novel genetic and epigenetic causes and modifiers of rare renal disease and their molecular pathways. It also plans to develop diagnostic testing, discover biomarkers of disease activity, and develop *in vitro* and *in vivo* disease models to apply high-throughput drug candidate screening (www.eurenomics.eu). The consortium includes the universities of Bristol, Nijmegen, Leuven, Oulu and Zurich, and firms like Genomatix (Germany), Metabometrix Ltd. (UK), Multiplicom Inc. (Belgium), Philochem AG (Switzerland), and Philogen S.p.A (Italy).

Neuromics (another €12 million) will focus on ten rare neurodegenerative and neuromuscular disorders, including ataxia, spastic paraplegia, Huntington's disease, muscular dystrophy and spinal muscular atrophy (*http://rd-neuromics.eu*). It will use next generation whole-exome sequencing to increase the number of known gene loci and will increase patient cohorts through large scale genotyp-

European rare diseases research landscape (2012)

Some 30 Million Patients in Europe

Funded projects, excluding clinical trials:
4 277 ongoing research projects, covering 2,132 diseases

By category:
461 - Gene search
576 - Mutations search
225 - Gene expression profile
322 - Genotype-phenotype correlation
936 - In vitro functional study
425 - Animal model creation / study
691 - Human physiopathology study
136 - Pre-clinical gene therapy
62 - Pre-clinical cell therapy
117 - Pre-clinical drug development / drug delivery
27 - Pre-clinical vaccine development
374 - Observational clinical study
194 - Epidemiological study
270 - Diagnostic tool / protocol development
110 - Biomarker development
20 - Medical device / instrumentation development
73 - Health sociology study
9 - Health economics study
62 - Public health / health services study

Clinical trials:
2,611 ongoing national or international clinical trials for 618 diseases

Percentage of clinical trials by category:
74% drug; 17% protocol; 2% gene therapy; 3% cell therapy; 3% medical device trial; 1% vaccine clinical trial (Source: Orphanet).

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Orphan Drug Development Incentives in the USA and EU

Broad Support from the State

USA: Orphan Drug Act (1983)
- 7 year market exclusivity for orphan drugs (designated as therapies for rare diseases)
- tax credits totalling half of development/clinical trial costs
- specific research and development grants
- 'fast-track' processing of drug development and approval
- protocol assistance, including access to Investigational New Drug Program and pre-approval
- not charged usual FDA application fees

European Union: Orphan Medicinal Products Regulation (2000)
- 10-year market exclusivity for an orphan drug once a marketing authorisation is granted
- Free scientific advice (termed protocol assistance) during the development phase
- Fee reductions and exemptions for European Medicines Agency procedures
- European Union and national grants to foster orphan drug development

By 2010, 850 molecules in development had received orphan designation in Europe. There were another 111 designations in 2011 and 148 in 2012. The EMA has already predicted >150 new designations in 2013.

In 2012, there were 70 orphan drugs on the European market plus another 75 drugs with at least an indication for a rare disease or a group of rare diseases. -JG-

ing by gene panel enrichment and next generation sequencing. It also aims to develop biomarkers for clinical application, identify disease modifiers and develop targeted therapies using the latest generation genetic approaches. Coordinated from the University of Tubingen, Germany, the consortium includes public research at the universities of Cambridge, Milan, Aix-Marseille and Western Australia, as well as businesses like deCODE genetics (Iceland), Profilomic (France), Ariadne Diagnostics (USA) and Agilent Technologies (Sweden).

Meanwhile, the **DevelopAKUre** project directly addresses at the clinical development of an orphan designated drug, Nitisinone, for the treatment of a rare Mendelian disease, Alkaptonuria (AKU). The total cost of this orphan drug development project has been estimated at €11 milion, of which €6 million is provided by the EC (*http://pathlabs.rlbuht.nhs.uk/developakure.pdf*). The goal is to get enough data to apply to the EMA for marketing authorisation of Nitisinone for AKU. The consortium includes researchers from Liverpool University, the AKU Society UK patient group for dissemination and patient recruitment, three companies (from Denmark and the Netherlands) for biomarker analysis and clinical trial coordination, an industry partner (Swedish Orphan) supplying the drug and regulatory support, three universities (UK, Italy, Slovakia) for the analysis of data, and three clinical trial centres (UK, France, Slovakia) to reach required numbers.

What is wrong with Orphan Drug Policies?

There can be no doubt that the research commitment of the EC, NIH, many patient groups and medical charities, has led to progress in the search for a better understanding of rare diseases and how they might be cured. However, there has also been great controversy about the role that orphan drug legislation has played in providing excessive profits for the biotechnology and pharmaceutical industries. The orphan drug designation gives drug makers ten years of market exclusivity in the EU (seven years in the USA) and the chance to set as high a price for their treatments as the 'market' (i.e. patients, their health insurance, and health authorities) can support.

The second part of this series, to be published in the next *Lab Times* ssue, will look at the role that public legislation encouraging R&D on rare diseases and their treatment has played in supporting the growth of the biotechnology industry and changing research policies in a profit-hungry pharmaceutical industry. Jeremy Garwood