

Importance of Research on Rare Diseases and Orphan Drugs

Introduction

There are significant moral, scientific, economic and policy imperatives for conducting research into rare diseases.

A rare disease as defined in the EU Orphan Medicinal Products Regulation (2000) is a disease with an instance of less than five in 10,000 of the population (1).

POINT 1: The Impact of Rare Disease Research on Population Health

Patients affected by rare diseases are at a disadvantage because the cost of developing new treatments is not offset by the financial rewards from sales under normal market conditions. Therefore there are significant unmet medical needs resulting in increased morbidity and mortality for these patients and a tremendous burden on the individual, the community and on the state (2). The specific features associated with rare diseases (low individual patient numbers, diversity, geographical location) require that research is developed and financed at a national and European level in order to optimise funding, infrastructures and technological platforms (3).

When considered individually by disease, the number of patients afflicted by a rare disease appears low. However, there are over 7,000 rare diseases and it is estimated that up to 3.5% of the population will be affected. For Ireland that represents a cumulative total population of approximately 140,000 patients (4).

Research has shown that many major diseases can be subdivided into individual diseases, some of which are classified as rare. This is often the case with cancer and heart disease.

Society supports innovation in healthcare to benefit patients, including rare disease patients. Innovation must continue to be reimbursed and of course show value, which must be measurable and demonstrable. However showing value requires sufficient time to gather data. By limiting funding for rare disease research in Ireland we are bucking not only a national but European and Global impetus in this area (5).

POINT 2: Scientific/Clinical Value

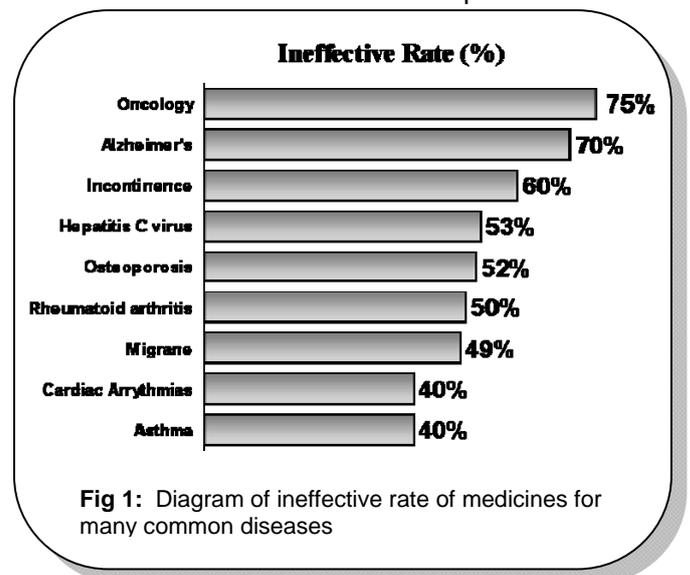
Personalised Medicine, Advanced Therapies and Fundamental and Innovative Clinical Research on Rare Diseases

Currently research into common diseases has a greater chance of finding breakthroughs once sub-classified into individual diseases. Often these are classified as rare e.g. inherited prostate cancer, insulin dependent diabetes etc. This is because there can be considerable variation from patient to patient with respect to effective response to current medicines (illustrated in figure 1).

Almost 50% of cancers are Rare Diseases, when appropriately classified (6). Genetic subdivision of patient populations further enhances the possibility of targeting drugs based not just on clinical and pathological diagnosis, but on genetic diagnosis. This has potential to save vast sums of money by administering drugs only to those who will benefit. The groundbreaking discoveries made for extremely uncommon malignancies such as chronic myelogenous leukaemia (CML), seminoma, gastrointestinal stromal tumour (GIST) are examples of this (7). Research focused on an abnormal gene and its protein product allows for the rational design of a drug to treat conditions. Research into Gleevec has spawned a whole field of research into drugs such as Tyrosine Kinase Inhibitors (8).

More recently genetics has uncovered that in treating hypertension, it may be possible to sub classify patients into those who metabolise the drug Warfarin faster than others, helping to tailor doses for patients rather than present trial and error method (9).

The value of fundamental research is amplified when linked to clinical outcomes in a translational research environment. Basic and translational research can be carried out in parallel to clinical trials in order to add the value of utilising patient samples and records by additional local research into more fundamental aspects of the disease. This is highlighted in the molecular sub categorisation of patients recruited and ultimately looking for correlations with treatment outcomes. These clinical trials take advantage of translational research networks and clinical trials centres to turn basic research findings into clinical therapies. This can result in significant potential for intellectual property and economic benefit for the research organisation, the clinical centre and ultimately the economy.



Thalidomide - Evaluated for Multiple Myeloma

Creatine - Evaluated for Amyotrophic Lateral Sclerosis

Oxandrolone - Evaluated for HIV lipodystrophy

Carmustine Implants - Evaluated for Glioma

Arsenic Trioxide - Evaluated for Promyelocytic Leukaemia

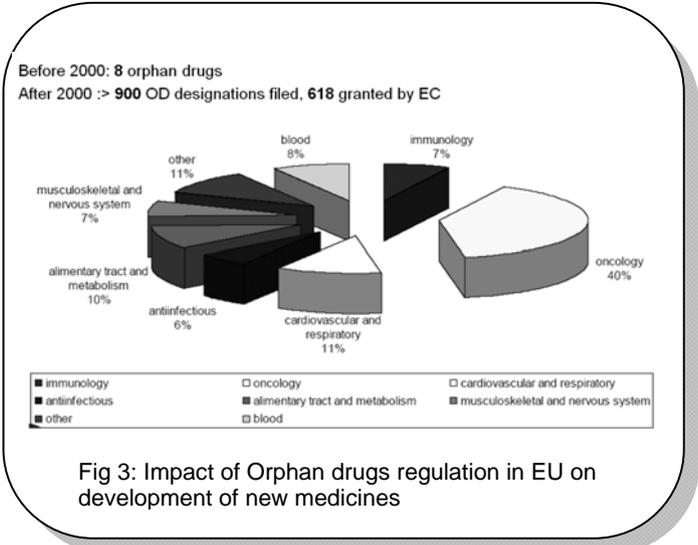
Fig 2: Sample of drugs which have been re-purposed for new conditions due to Orphan Drugs Legislation and Rare Disease Research

The potential for re-evaluating existing drugs for conditions like Rare Diseases is significant; Figure 2 lists examples of this. These would not have been financially viable without the advantages offered under the orphan drugs legislation.

The re-purposing of a drug cannot happen in a vacuum without fundamental research on the natural history and biology of many rare diseases or on the cause of the disease to identify suitable drug targets. The key word in this area is translational and the useful knowledge results in a dynamic bidirectional scaling of the value chain of research, from the laboratory to the bedside and back.

POINT 3: The Economic Impact of Rare Disease Research

A blossoming of the US biotech industry followed the passing of the orphan drugs legislation in 1983. This resulted in the establishment of more than 50% of the world's leading biotech companies including Amgen (Forbes listed worlds largest biotech company, 2008 revenue \$15 billion; products Epogen, for anaemia, and Neupogen- immune modulator) Genzyme (Cerezyme for Gaucher disease, Fabryzyme for Fabry disease, \$4.6 billion) and Genentech (10). In the US from 1983 to 2004, 256 orphan drugs received market authorisation. This was directly attributed to the stimulation of the Orphan Drugs Act (11).



The implementation of the European Orphan Drug legislation in 2000 resulted in a dramatic (30%) increase in new Biotech companies. A significant number of start-ups have been created with many existing companies beginning research on rare diseases. According to the same study, jobs related to orphan medicinal products increased at a quicker pace than general industry trends. All companies surveyed increased their total number of employees in the European Community between 2000 and 2004 (an average increase of 43%). R&D expenditure on rare diseases grew faster than general medicinal R&D investment. The companies surveyed increased R&D investment in orphan medicinal products more than two-fold on average between 2000 and 2004 (12).

POINT 4: Global and European Policy in Rare Disease Research

The European Union Economic and Social Committee has recommended making national strategies on rare diseases an integral part of national public health policy. This recommendation was adopted by the European Council of Ministers on June 9, 2009. Member states are being

urged to identify ongoing research and research resources in order to establish state of the art facilities and to assess the research landscape in the area of rare diseases (13).

Rare Disease as a public health priority was a primary focus of the French presidency of the European Commission (July '08 - Jan '09). This remains so for the current Czech presidency and the incoming Swedish presidency (July '09 - Jan '10) (14). All of these developments are further supported by the establishment of The Office of Director for Rare Diseases at the European Commission.

In late May 2009 the US NIH announced the launch of a \$24 million Therapeutics for Rare and Neglected Diseases Programme (TRND). This is the first integrated drug development pipeline within the NIH designed to produce new treatments for rare and neglected diseases. It is specifically intended to stimulate research collaborations with academic scientists working on rare illnesses (15).

European and global trends in human health and research policy support national policies on rare diseases which in turn call for the sustainability and development of research in this area. As a country with a small population we will require international support in our efforts and will need to show our support and understanding of the area by investing in research and contributing to the global effort.

Dr. Patrick Corley – Assistant Director of Research, Fighting Blindness
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If research into rare diseases and orphan drugs was restricted, then research into the following conditions would be severely compromised

Cancer (45)	Infection (59)	Neurological (10)	Immunology (29)	Endocrinology (9)	Metabolism (43)	CNS (14)
Prostate Cancer (familial)	AIDS Wasting	Alzheimer's Disease	Graft versus Host Disease	Addison's Disease	Celiac Disease	Autism
Children's Cancers	Tuberculosis	Parkinson's Disease	Irritable Bowel Syndrome	Cushing's Syndrome	Cystic Fibrosis	Asperger's Syndrome
Kidney Cancer	Meningitis	Epilepsy	Myasthenia Gravis	Graves' Disease	Diabetes	Manic Depression
All Brain Tumours	Hepatitis B	Motor Neuron Disease	Pemphigus			OCD
Hodgkin's Disease	Hepatitis C	Huntington's Disease	Rheumatic Fever			Anorexia Nervosa
Multiple Myeloma	Aspergillosis	Tourette Syndrome	Lupus			
Chronic Myleogenous Leukaemia	Creutzfeldt Jakob Disease					
Malignant Melanoma	Cytomegalovirus Infection					
Pancreatic Cancer	Fetal Varicella Zoster	**Table abridged from data on Orpha.net EU Portal for Rare Diseases				
Non Small cell lung Cancer	Legionnaires' Disease	Figures in brackets is number of diseases subcategories in each disease area i.e. Cancer (45) = 45 different types of cancers				
Ovarian Cancer	Leptospirosis					
	Pertussis					

References:

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- 4 IPPOSI/IMB meeting “Medicines for Rare Diseases – an Opportunity for Patients, Science and Industry”, Dublin, 9 November 2007 – citing Orpha.net figures
- 5 Genzyme Value of Innovation – Value of Innovation Presentation
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- 8 Müller BA. “Imatinib and its successors--how modern chemistry has changed drug development. “[Curr Pharm Des.](#) 2009;15(2):120-33
- 9 Takeuchi F, et. al.”A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. [PLoS Genet.](#) 2009 Mar; 5(3):e1000433. Epub 2009 Mar 20.
- 10 Sales and revenue figures from individual company annual reports.
- 11 Reaves ND. “A model of effective health policy: the 1983 Orphan Drug Act.” [J Health Soc Policy.](#) 2003;17(4):61-71.
- 12 Commission Working Staff document Brussels 20.6.2006 SEC (2006) 832 on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained
- 13 Council Recommendation in the field of Rare diseases 9.06.09 2947TH Employment Society Policy Health & Consumer Affairs.
- 14 EURODIS - website rare diseases on the French agenda of French Presidency of EU
- 15 US NIH Office of Rare Diseases (ORDR) website