suggests that there must be some pathogens that affect both plants and animals. Indeed, one such example is the bacterium *Pseudomonas aeruginosa*, which attacks both *Homo sapiens* and *Arabidopsis*.

Perhaps more significant are the common conditions that arise when the immune system malfunctions. There are many known autoimmune diseases in humans, but plants also suffer from them. In lesion mimics, the hypersensitive response that triggers cell death is initiated in the absence of a pathogen. In extreme cases, the whole plant dies from multiple lesions, although this is not a major problem for horticulture or agriculture. The exact mechanisms involved are still unknown, but there is common ground for plant and animal immunologists to study the pathways involved in autoimmune disease, especially where PCD is concerned.

Much work still remains to elucidate the immune response in detail, particularly the steps after the pathogen is detected. Nevertheless, cooperation between plant and animal researchers has already yielded important insights into these mechanisms. It is becoming increasingly clear that these two communities, who for so long communicated so little, can pool their resources to investigate immunity.

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Adopting an orphan

Incentives to develop drugs for rare disorders raise hopes and controversy

The spectrum of ailments that haunt mankind is depressingly vast. Major chronic and infectious diseases, such as malaria, AIDS, cardiovascular diseases and cancer, claim millions of lives every year, and exact a heavy toll in both the developed and the developing world. These big killers, however, do not have a monopoly on pain, suffering and death—diseases that affect comparatively few people can have the same result. According to the World Health Organization, some 5,000 such rare disorders exist. Other estimates push the number up to 8,000, depending on the specific classification criteria used. In Europe, a rare disease is defined as one that affects one person in 2,000, whereas in the USA and Japan, the definition of a rare disease is one that afflicts fewer than 200,000 and 50,000 patients, respectively.

Due to their relatively low prevalence, rare diseases as a whole have traditionally been neglected by large parts of the scientific, medical and political communities

Regardless of the precise definition, rare diseases are a serious problem for human and public health. Although each case involves a relatively small number of individuals—from just ten to hundreds of thousands—together, rare diseases affect a major subsection of the population in developed countries, including 25 million US residents and about 6%–8% of the population of the European Union (EU), equivalent to 24–36 million people. But it was not until the early 1980s that various countries, the first being the USA, introduced legislation and incentives to make the development of drugs for rare diseases more attractive for pharmaceutical companies. These have been a major success, and have led to the approval of hundreds of new drugs, but they have not been without criticism. Whereas some critics decry the often

extremely high costs of these drugs, patient advocacy groups push for a wider awareness of rare diseases and for better training of physicians.

About 80% of identified rare diseases have a genetic origin, and the remainder are caused by infections, allergic and autoimmune disorders or poisonings, or have unknown causes (National Organization for Rare Diseases, 2003). In some instances, symptoms manifest at birth or early in childhood, as happens in several lysosomal storage disorders, some neurological disorders such as Rett syndrome, or in osteogenesis imperfecta and related collagen and bone diseases. Many rare diseases, however, appear only in adults. Unfortunately, despite variable aetiology, rare diseases share similar traits: they are usually chronically debilitating, degenerative and often life-threatening.

Due to their relatively low prevalence, rare diseases as a whole have traditionally been neglected by large parts of the scientific, medical and political communities. With the exception of a few conditions that occur more frequently on a global or regional scale, such as cystic fibrosis and thalassaemia, knowledge and awareness of the vast majority of rare diseases is still scant or totally absent, and the medical and social consequences for victims and their families are often devastating. Delay in diagnoses, lack of relevant information and difficulty in finding specialized physicians are common problems, and many patients go completely undiagnosed. Most importantly, even when recognized, thousands of rare diseases cannot be treated, simply because no medicines, therapies or protocols for good clinical practice exist. This is not due to scientific or medical difficulties in tackling rare diseases, but rather lies in their inherent lack of attraction for pharmaceutical companies, which are more interested in developing drugs for common disorders that affect millions than in treating a handful of patients. Thus, the drugs needed to treat these 'orphan' diseases "are

Table 1 | Comparison of the policies on orphan drugs worldwide

	USA	EU	Japan	Australia
Legal framework	Orphan Drug Act (1983); Orphan Drug Regulation (1993)	Regulation (CE) No. 141/2000 (2000)	Orphan Drug Regulation (1993)	Orphan Drug Policy (1997)
Administrations involved	FDA / OOPD	EMA / COMP	Ministry of Health, Labour and Welfare/ Organization for Pharmaceutical Safety and Research	Therapeutic Goods Administration
Prevalence criterion of the disease for orphan status (per 10,000)	7.5	5	4	1.1
Market exclusivity (years)	7	10	10	5 (similar to other drugs)
Funding	Grants for clinical research (pharma and academia eligible)	Framework Programmes for Research plus national measures	Grants for clinical and non-clinical research (pharma only eligible)	No
Tax credits	50% for clinical costs	Managed by member states	6% of both clinical and non-clinical costs	No
Protocol assistance	Yes	Yes	Yes	Yes
Accelerated review	Yes	Yes	Yes	Yes
Reconsideration of orphan status	No	Yes (every 6 years)	Yes	Yes (every 12 months)
Number of designated orphan drugs	1,449*	269*	167**	92***
Number of orphan drug marketing authorizations	269*	20*	95**	43***

Sources: STOA, 1999; Stolk *et al.* 2005; Orphanet, www.orpha.net; EU Community Register of Orphan Medicinal Products, pharmacos.eudra.org/F2; US Office of Orphan Products Development, www.fda.gov/orphan; Japanese Organization for Pharmaceutical Safety and Research, www.kiko.pmda.go.jp; Australian Therapeutic Goods Administration, www.tga.gov.au. *, as of April 2005; **, as of February 2004; ***, as of December 2004.

like children who have no parents and... require special efforts to develop," commented US Representative Henry Waxman (D-CA), who has sponsored many health- and drug-related bills before Congress.

...even when recognized, thousands of rare diseases cannot be treated, simply because no medicines, therapies or protocols for good clinical practice exist

This regrettable situation remained largely unchanged for many years, and it was only in the past few decades that orphan diseases gained recognition as a serious public health problem, thanks to the activism of patients' associations and professional groups. In the early 1980s, it finally became clear that society cannot

tolerate patients suffering without a remedy just because their disease is rare, and that the development of orphan drugs by pharmaceutical and biotechnology companies requires special encouragement. The USA was the first to react and, in 1983, Congress passed the Orphan Drug Act (ODA) to provide significant incentives for sponsors to develop drugs and biologicals, including vaccines and *in vivo* diagnostics, to tackle rare diseases. These benefits extend from development to market, and include expedited review by the US Food and Drug Administration (FDA) and thus shorter approval time, tax credits, seven years of market exclusivity and waivers of certain fees. In addition, the FDA's Office of Orphan Products Development (OOPD) administers research grants to both private and public parties to support clinical trials of orphan drugs. To qualify for incentives, candidate

medicines must first receive 'orphan designation' from the OOPD, and then go through the normal evaluation process for safety and efficacy (Haffner *et al.*, 2002). Since the ODA came into effect, its impact on the development of orphan drugs has been tremendous. During the 1970s and early 1980s, fewer than ten new drugs for rare disorders were developed. By contrast, from 1983 to April 2005, a total of 269 orphan drugs received market approval in the USA and 1,449 orphan designations were accepted (www.fda.gov/orphan). Together, these 269 new drugs now provide help for more than 11 million people in the USA alone.

The ODA initiative was so successful that it inspired similar legislation in Japan (1993) and Australia (1997). In 1999, the European Orphan Medicinal Products Regulation was adopted to implement a common policy on orphan drugs in the EU. Although largely based on the US legislation, the establishment of the EU framework was preceded by a study from the Scientific Technology Options Assessment (STOA) Unit of the European Parliament, which comparatively analysed the existing orphan drug policies in other countries worldwide, with a special focus on incentives and assistance to stimulate the research and development of appropriate treatments for rare diseases. A Committee of Orphan Medicinal Products (COMP) was created within the European Medicines Evaluation Agency (EMA) to examine applications for orphan designation. To justify orphan status, the EU regulation requires a disease prevalence of 5 in 10,000 individuals, which lies between the US and Japanese criteria (7.5 and 4, respectively; see Table 1). As an alternative to prevalence, orphan designation can also be granted on economic grounds if the drug meets public health needs but would not generate sufficient financial returns. The set of incentives for orphan medicine development was formulated by mixing various extra-EU legislations and includes 10 years' market exclusivity, waiving of registration fees, technical assistance for elaboration of the application file and accelerated marketing procedures (Table 1). Other provisions, such as tax breaks and grants for clinical research costs, were largely delegated to the member states.

The introduction of orphan products regulation and incentives in the EU created

So far, some 270 drugs have been granted EU orphan designation, and 20 have reached the market

a positive environment for drug companies and revitalized research and industrial activities in this otherwise neglected sector. So far, some 270 drugs have been granted EU orphan designation, and 20 have reached the market (Table 2; <http://pharmacos.eudra.org/F2>). Most applications are for products to treat cancer-related conditions, followed by metabolic disorders and diseases of the musculoskeletal and nervous systems (Meyers & Lipucci Di Paola, 2003). The first drugs to receive EU orphan marketing authorization in 2001 were two products to treat Fabry disease—a lipid storage disorder caused by a deficiency of the lysosomal enzyme α -galactosidase A—and Glivec®, developed by Novartis (Basel, Switzerland), for the treatment of chronic myeloid leukaemia. The latest addition to the European orphan drug market is Orfadin® (nitisinone), developed by the Stockholm-based company Swedish Orphan International, to treat hereditary tyrosinaemia type 1—a congenital and fatal liver disease for which no treatment was previously available. Tyrosinaemia type 1 is caused by a genetic enzyme deficiency that results in an abnormal catabolism of tyrosine, with the accumulation of toxic metabolites and irreversible damage to the liver and kidneys in early childhood. There are around 200 children in Europe with this genetic defect, who face an 80% risk of dying unless treated. Orfadin, in conjunction with a special diet, gives them a 90% chance of survival.

Since orphan drug regulations were passed in various countries, patients, clinicians, policy makers and industry have unanimously acknowledged their huge impact on the development of new drugs (Bosanquet *et al*, 2003; Stolk *et al*, 2005). However, stakeholders continue to discuss some key problems, which is almost inevitable given the complexity of the matter. A recurring theme is the high price of many orphan drugs, which can reach several hundred thousand US dollars per year for some enzyme-replacement therapies. Many think that this has a lot to do with market exclusivity, which gives companies a monopoly over treating a specific rare disease. However,

Table 2 | Orphan medicinal products with marketing authorization in the EU

Product	Designated orphan indication	Sponsor	Tradename
α -Galactosidase A	Treatment of Fabry disease	TKT Europe AB	Replagal™
α -Galactosidase A	Treatment of Fabry disease	Genzyme Europe BV	Fabrazyme®
1,5-(Butylimino)-1,5-dideoxy, D-glucitol	Treatment of Gaucher disease	Oxford GlycoSciences (UK) Ltd	Zavesca®
N-carbamyl-L-glutamic acid	Treatment of N-acetylglutamate synthetase (NAGS) deficiency	Orphan Europe	Carbaglu®
Arsenic trioxide	Treatment of acute promyelocytic leukaemia	Cell Therapeutics (UK) Ltd	Trisenox™
Anagrelide hydrochloride	Treatment of essential thrombocythaemia	Shire Pharmaceutical Development Ltd	Xagrid™
Busulfan (intravenous use)	Conditioning treatment before haematopoietic progenitor cell transplantation	Pierre Fabre Médicament	Busilvex®
Nitisinone	Treatment of tyrosinaemia type I	Swedish Orphan International AB	Orfadin®
Iloprost	Treatment of different forms of pulmonary hypertension	Schering AG	Ventavis®
Bosentan	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	Actelion Registration Ltd	Tracleer®
Ibuprofen	Treatment of patent ductus arteriosus	Orphan Europe	Pedea®
Imatinib mesylate	Treatment of chronic myeloid leukaemia	Novartis Europharm Ltd	Glivec®
Laronidase	Treatment of mucopolysaccharidosis type I	Genzyme BV	Aldurazyme®
Pegvisomant	Treatment of acromegaly	Pfizer Ltd	Somavert®
Ziconotide (intraspinal use)	Treatment of chronic pain requiring intraspinal analgesia	Elan Pharma International Ltd	Prialt®
Zinc acetate dihydrate	Treatment of Wilson's disease	Orphan Europe S.a.r.l.	Wilzin®
Cladribine (subcutaneous use)	Treatment of indolent non-Hodgkin's lymphoma	Lipomed GmbH	Litak®
Celecoxib	Treatment of familial adenomatous polyposis	Pharmacia-Pfizer EEIG	Onsenal®
Porfimer sodium (for use with photodynamic therapy)	Treatment of high-grade dysplasia in Barrett's oesophagus	Axcan Pharma International BV	PhotoBarr®
Mitotane	Treatment of adrenal cortical carcinoma	Laboratoire HRA Pharma	Lysodren®

Source: EU Community Register of Orphan Medicinal Products, <http://pharmacos.eudra.org/F2>

according to Emerging Biopharmaceutical Enterprises (EBE; Brussels, Belgium), and EuropaBio, the European Association for Bioindustries (Brussels, Belgium), the “costs for [developing] orphan medicinal products...relate to a product that is destined for a small group of people, meaning that all these costs need to be recuperated from a small market with a small number of patients” (EBE/EuropaBio, 2005). It is this, and not market exclusivity, that explains high prices, according to drug developers.

A related concern is the fact that certain drugs that were originally approved in the USA as orphan drugs later became top sellers, either because the once rare condition they were intended to treat increased in frequency, such as AZT to block HIV replication, or because they proved effective

A recurring theme is the high price of many orphan drugs, which can reach several hundred thousand US dollars per year...

against more common disorders, such as epoetin- α , which was originally approved to treat anaemia and is now used to stimulate the production of red blood cells in surgery patients and patients undergoing cancer chemotherapy (Maeder, 2003). In these cases, the alliance created between industry and society to treat rare diseases has been distorted, critics maintain, and corrections should be made to orphan drug legislation to restore its original spirit. In the USA, biotech lobby groups have so far succeeded in blocking such changes, but the EU situation is different. Article 8 of the regulation states that "this (market exclusivity) period may however be reduced to six years if, at the end of the fifth year, it is established...that the product is sufficiently profitable not to justify maintenance of market exclusivity." The European Community (EC) has yet to decide, however, just how 'sufficiently profitable' a drug must be to fall under Article 8; it is guided through this delicate passage by a recent independent survey on orphan drug pricing in the EU, conducted by Alcimed, a consultancy company based in Paris, France (Alcimed, 2004). This leaves a bitter taste for companies, for which the ten years' market exclusivity is by far the most important stimulus to develop orphan drugs. Their stance is that orphan drugs that were designated as such on the basis of prevalence—virtually all of those now on the EC's list—should not have their market exclusivity reduced on the basis of financial criteria. "Article 8," they propose, "should be eliminated as it

potentially damages the psychological climate to support the development by industry of rare disease therapies," and, after all, "for the good of European patients, it would be preferable, as a 'carrot', to allow some companies to make significant profits with a few successful products, which, in turn, could act as a strong incentive and, thus, a booster for more companies to invest in many more treatments" (EBE/EuropaBio, 2005).

To meet the public health threat of untreatable diseases, society needs to do much more than just offer financial incentives to industry...

As the pharmaceutical industry argues against tightening EU orphan drug regulation and asks for more supporting measures, particularly calling on individual member states to grant additional incentives, patients' organizations are also speaking out. To meet the public health threat of untreatable diseases, society needs to do much more than just offer financial incentives to industry, they claim. "We need better information on the prevalence of rare diseases in the different countries and on who is doing research on these. We need more research on the pathogenesis and on potential approaches for treatment," said Jean-Jacques Cassiman, Secretary of the European Platform for Patients' Organizations, Science and Industry (EPPOSI), a patient-led partnership between patients, industry and academic science. "We need more financial incentives for collaborations within academia, between

academia and industry, and within industry, to do this research and to take the risk of working on potential therapeutics." Other patients' groups, such as the European Organization for Rare Diseases (Eurordis) and the European Genetic Alliance Network (EGAN), also stress the need for better diagnosis, training of health professionals, early treatment and equal access to orphan drugs throughout Europe. This would also involve eliminating regional and national differences in distribution, taxation and reimbursement policies, a combination of factors that explains the differences of up to 70% for the annual cost per patient of a given orphan medicine between various EU countries.

So far, no one can honestly deny that the legislative and economic incentives have created a positive climate for developing drugs and treatments for rare diseases in Europe and elsewhere. Nevertheless, what is needed now is an optimized framework to better balance the needs and expectations of patients, pharmaceutical companies and healthcare systems.

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