Translation of rare disease research into orphan drug development: disease matters

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More than 25 years of orphan drug regulations have yielded several new treatments for patients with rare diseases. Here, we show that successful translation of rare disease research into an orphan drug discovery and development programme is dependent on the disease class, its prevalence and the disease-specific scientific output. Our findings indicate that current orphan drug legislation alone is not sufficient to stimulate orphan drug development for diseases with a very low prevalence. Consequently, additional incentives should focus on stimulating the specific needs of rare disease research at disease class level.

Introduction

It has been estimated that between 5000 and 8000 rare diseases exist, many of which are of genetic origin, affect children at a very early age and are life threatening and/or chronically debilitating [1,2]. Rare diseases exist in all disease classes and range from exceptionally rare diseases that occur in only a few individuals worldwide to more prevalent, but still considered rare, disorders such as cystic fibrosis and narcolepsy – cataplexy. Criteria for a rare disease differ slightly by region. In the USA, a rare disease is defined as a disease that affects less than 200,000 inhabitants, equivalent to approximately 6.5 patients per 10,000 inhabitants [3]. In the European Union (EU), however, a rare disease needs to be life threatening or chronically debilitating, besides having a prevalence of less than 5 patients per 10,000 inhabitants [3]. In the past 25 years, it has been recognized by various authorities that because of the rarity of these diseases, the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat a rare condition would not be recovered by the expected sales of the medicinal product under normal market conditions [4–6]. Therefore, specific legislation to stimulate the discovery and development of drugs for rare diseases – the so-called 'orphan drugs' – has been introduced: in the USA in 1983 [4], in Japan in 1993 [5] and in the EU in 2000 [6]. Sponsors of a potential product for a rare disease can apply at the US Food and Drug Administration (FDA) or the European Medicines Agency (EMEA) for an orphan designation, which results in various benefits that aid the full development of their products. These incentives include reduction of regulatory fees, extra regulatory guidance and a marketing exclusivity period of seven years (USA) or ten years (EU) after approval of the product [3,4,6]. As of March 2009, in the USA, nearly 2000 orphan designations have been assigned, and more than 300 products have been approved for marketing [7]. The EU has approved more than 50 orphan medicinal products and assigned more than 600 orphan designations [8,9]. It is widely acknowledged that these numbers demonstrate how both regulations have been successful in stimulating orphan drug discovery and development by the pharmaceutical industry, particularly in small- and medium-sized enterprises (SMEs), resulting in an important improvement in the situation of specific groups of patients in the USA and the EU [5,7,10,11].

Although these regulations have been instrumental, they are not the only driving force behind the discovery and development of therapies for patients suffering from rare disorders. In two earlier studies, we focussed on success factors in orphan drug discovery and development. First, we showed that the experience of a company in developing orphan drugs is an important predictor for the authorization of orphan drugs [12]. Second, we revealed a strong relationship between orphan drug development and pharmaceutical

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innovation performance (composed of level of R&D expenditure, number of pharmaceutical patents and number of SMEs) in Europe [13]. Here, we specifically focus on the translation of rare disease research into orphan drug development. Only fundamental and clinical research into a rare disorder (such as aetiology, diagnosis and genetics [14]) can reveal the necessary drug targets, which, in turn, can be translated into the discovery of potentially interesting drug leads and subsequent drug development [15]. Development of an orphan drug is thus the actual translation of the findings from fundamental and clinical rare disease research, much of it publicly funded. In both the USA and the EU, certain disease classes – in particular oncology – are associated with a high number of orphan designations and approvals, compared with disease classes with less orphan designations [5,10,11]. This skewed distribution of orphan drug development over the disease classes indicates that certain disease-specific factors exist that favour the translation of rare disease research into orphan drug development. Apart from disease class, we focussed on rare disease research output because the understanding of a (rare) disease forms the necessary foundation for any successful (orphan) drug discovery and development programme. Disease prevalence, an important reason for the implementation of the current orphan drug legislation, was included as a third disease-specific factor.

The aim of this study was to analyze the influence of these three major disease-specific factors on the chance for a rare disease to obtain at least one product with an orphan designation. Considering the low number of rare diseases for which a therapy is being developed, increased knowledge of the underlying translational process will provide better input for novel approaches to improve orphan drug development. Whereas a lack of sponsor interest will call for additional (economic) incentives, a hampered translation of rare disease research findings into orphan drug development might require novel incentives that lie beyond the scope of current incentives that aim to enhance orphan drug discovery and development.

Rare diseases

Publications on rare diseases

This study included all rare diseases that have been reported in the Orphanet report series on prevalence of rare diseases (May 2008 issue), a systematic survey of the literature that is being performed to provide an estimate of the prevalence of rare diseases in Europe [16]. The report series contains prevalence figures of more than 1500 rare diseases, making it the largest publicly available dataset with rare disease prevalence figures currently available. The dataset was extended with 102 rare diseases for which an orphan

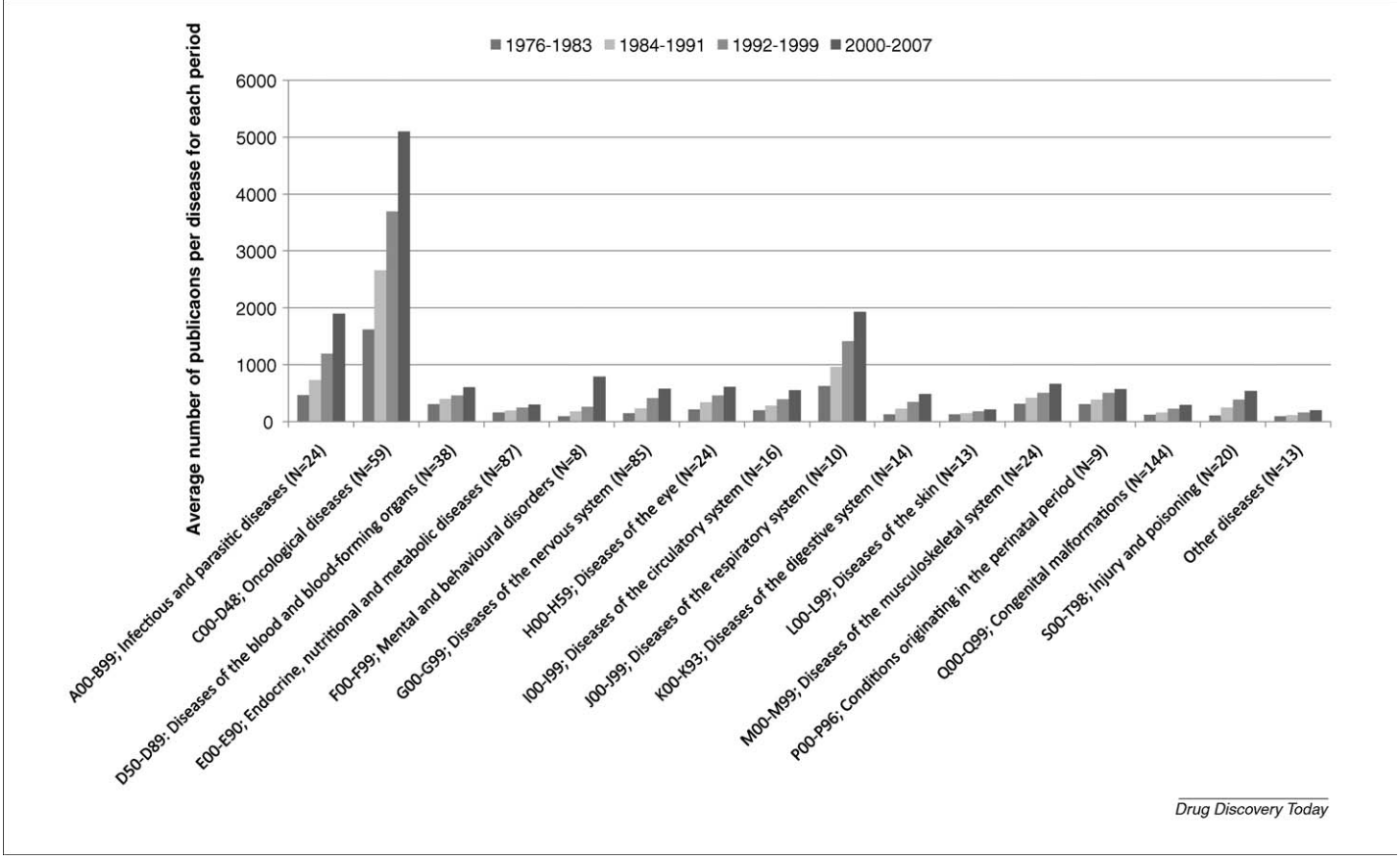

FIGURE 1

Average number of publications per disease, by disease class and time period. The number of publications of each rare disease included in the study was determined with a search in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/). For each disease, a PubMed search string was composed consisting of the disease name and synonyms of the disease mentioned in the Orphanet database (http://www.orpha.net). Possibilities for wrongful inclusion of a publication caused by a disease with the name of an author (e.g. Wilson disease) or a geographic region (e.g. Japanese encephalitis, West syndrome) were addressed by including Boolean NOT statements and PubMed search field tags for these terms, in a way comparable to that of Mendis and Mclean [53]. All searches were limited to English language articles and original research or case reports only. Reviews, comments and letters were excluded.

designation was assigned but that were not mentioned in the Orphanet report series. Exceptionally rare diseases with a prevalence below 0.1/100,000 were excluded from the study because orphan drug development in this group was found to be nearly absent (see http://www.emea.europa.eu/htms/human/orphans/opinions.htm; accessed March 2009). Finally, diseases included in the study were classified according to disease class, based on the International Classification of Diseases (ICD), edition 10 (http://www.who.int/classifications/apps/icd/icd10online/; accessed February 2009).

The disease dataset consequently consisted of 588 rare diseases, distributed over 3 prevalence classes, with 161 diseases in the 0.1–0.9 per 100,000 prevalence group, 248 in the 1–9 per 100,000 group and 179 in the 10–50 per 100,000 group. More than 60% ($N = 375$) of the diseases included in the study belong to the disease classes (ICD; *N*) of oncological (C00–D48; 59); endocrine, nutritional and metabolic (E00–E90; 87); nervous system (G00–G99; 85); or congenital (Q00–Q99; 144) diseases. For each disease, we have determined the number of publications in four time periods: 1976–1983, 1984–1991, 1992–1999 and 2000–2007. Fig. 1 provides an overview of the average number of publications per disease for the disease classes that comprise at least 1% of the total number of diseases, for the consecutive time periods. The average number of publications per disease increased over time for all 588 diseases in the study, from 330 publications in the period 1976–1983 to 1319 publications in the period 2000–2007, indicating a consistent increase in scientific output from 1976 to 2007. The highest average number of publications per disease by far was found for the disease class of oncological diseases. At first glance, this increase in rare disease research is encouraging. However, comparison with the general increase of number of publications on overall biomedical research from 1976 to 2007 reveals that the observed increase is not statistically different from the general trend (data not shown). Moreover, the findings are inconclusive regarding whether implementation of specific orphan drug legislation in 1983 (USA) and 2000 (EU) has stimulated rare disease research worldwide.

Orphan drug discovery and development

A sponsor of a potential orphan drug has to submit to the regulatory authorities scientific evidence that confirms the rationale for the use of its medicinal product in the proposed orphan indication [6,7]. Consequently, an orphan designation can be regarded as a proxy indicator for the successful translation of rare disease research into an orphan drug discovery and development programme. In addition, an orphan designation indicates the interest of a sponsor in initiating an orphan drug development programme. For each rare disease included in the study, the number of orphan designations and the distribution of the designations over three time periods (1983–1991, 1992–1999 and 2000–2007) were determined by crosschecking these diseases against the FDA list of orphan designations and approvals (http://www.fda.gov/orphan/designat/list.htm; accessed February 2009) and the European Register of designated orphan medicinal products (http://www.ec.europa.eu/enterprise/pharmaceuticals/register/orphreg.htm; accessed February 2009).

Disease-specific factors associated with orphan drug development

To verify the role of disease-specific factors in the translation of rare disease research into an orphan drug discovery and development programme, the association between rare disease prevalence, class and scientific output and the likelihood of a rare disease obtaining at least one product with an orphan designation in the

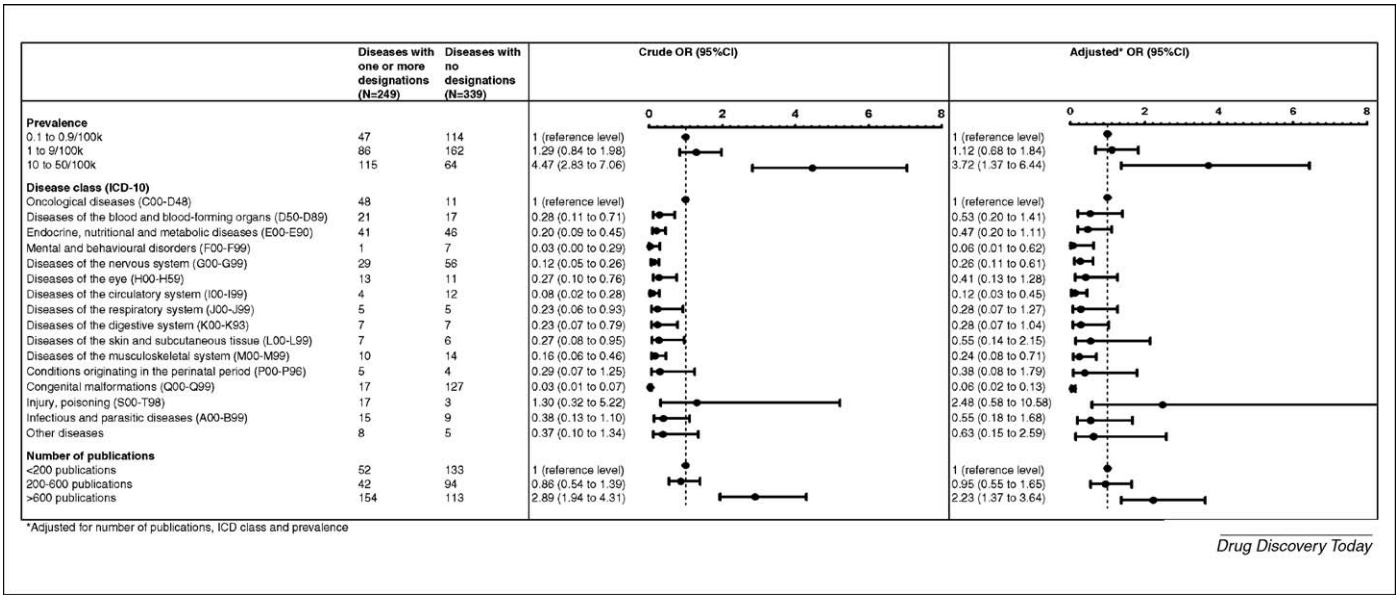

FIGURE 2

Characteristics of rare diseases ($N = 588$) potentially associated with obtaining at least one orphan designation in the US (1983–2007) or the EU (2000–2007). Characteristics of orphan drugs with and without at least one orphan designation were compared with univariate logistic regression analysis using SPSS Version 16 for Mac (SPSS, Chicago, IL). Odd ratios (ORs) and 95% confidence intervals (95%CI) were calculated for each of the categories in the three characteristics. The outcome was defined as obtaining at least one orphan designation in the US (1983–2007) or the EU (2000–2007). To test whether any of the characteristics were mutually related, a multivariate model was used in which the characteristics with statistically significant crude ORs were compared using a backwards stepwise selection method in which the removal testing was based on the probability of the likelihood-ratio statistic based on the maximum partial likelihood estimates.

USA or the EU was determined. Odds ratios (ORs) and 95% confidence intervals (95%CI) were calculated for each of these disease-specific characteristics in a logistic regression model (Fig. 2).

Prevalence

It was found that a disease with a prevalence between 10 and 50 per 100,000 had a more than threefold higher chance of obtaining at least one product with a designation (adjusted OR = 3.72; 95%CI = 1.37–6.44) than a disease with a prevalence of 0.1–0.9 per 100,000 (Fig. 2). The likelihood for a disease with a prevalence between 1 and 9 per 100,000 did not differ from that of a disease with a prevalence between 0.1 and 0.9 per 100,000. As mentioned in the Orphanet report series on the prevalence of rare diseases [16], it is difficult to assess the exact prevalence rate of each rare disease from the available data sources. It is likely that there is an overestimation for most rare diseases because the few published prevalence surveys are usually done in regions of higher prevalence and are usually based on hospital data. Therefore, the estimates included in the Orphanet report series are an indication of the assumed prevalence but might not be accurate [16]. We believe that the impact of the estimated prevalence rates on our findings is limited because our analyses were done at disease class or prevalence group level and not at the individual disease level. We conclude from the results that the likelihood for the initiation of an orphan drug development programme is associated with the prevalence of a rare disease, although these findings might be partly influenced by the association between scientific output and the prevalence of a rare disease. An explanation for the observed association between prevalence and the likelihood that an orphan drug is taken in development is a lack of commercial interest by potential sponsors. According to various sources, drug development is risky and costly [17–19]. Moreover, conducting a clinical trial for a rare disease results in many practical limitations, such as finding sufficient patients and statistical challenges [20]. These factors, combined with an intrinsic small market, make a favourable decision to develop a drug for less prevalent rare diseases unlikely [21,22], despite the incentives provided by current orphan drug legislation [3,23,24].

Disease class

Fig. 2 shows that oncological diseases were associated with the highest chance to obtain at least one product with an orphan designation, in particular when compared to mental and behavioural disorders (adjusted OR = 0.06; 95%CI = 0.01–0.62), diseases of the nervous system (adjusted OR = 0.26; 95%CI = 0.11–0.61), diseases of the circulatory system (adjusted OR = 0.12; 95%CI = 0.03–0.45), diseases of the musculoskeletal system (adjusted OR = 0.24; 95%CI = 0.08–0.71) and congenital malformations (adjusted OR = 0.06; 95%CI = 0.02–0.13). Congenital malformations were associated with a significantly lower chance to obtain at least one product with an orphan designation in comparison with all other disease classes (data not shown).

These findings are in line with findings by US and EU regulatory authorities that oncological diseases – and, to a lesser extent, endocrine, nutritional and metabolic diseases – comprise the highest number of orphan designations and approvals [7,10,11]. Clearly, the translation of rare disease research into orphan drug development requires certain characteristics that oncological diseases and endocrine, nutritional and metabolic diseases possess and congenital malformations lack. Successful translation of disease research into drug development consists of sufficient understanding of disease to discover the necessary drug targets and drug leads, which in turn can generate sufficient interest from sponsors to initiate a drug development programme [13,15,25–28]. Within oncology, an important boost was given to the translation of research by the 1971 National Cancer Act. This act provided the National Cancer Institute with not only the necessary funding and the mandate to support basic research but also the application of the results of the research to reduce cancer incidence, morbidity and mortality [29]. Since then, considerable public and private expenditures on oncology research, both in the USA and the EU, and a high-level transnational research infrastructure have evolved [30,31]. Consequently, knowledge and understanding of oncology have advanced rapidly and have turned oncology into an attractive niche indication for the pharmaceutical sector [32,33].

The observed differences between disease classes might also be explained by differences in the feasibility of identifying a suitable target and drug lead [27]. Within oncology, increased emphasis is given to targeted drug discovery [34]. A notable success in this area has been the development of imatinib, the first tyrosine kinase antagonist, which was introduced as an orphan drug for the treatment of chronic myelogenous leukaemia [35]. Most of these inhibitors were not approved for general cancer disease because of their broad action spectrum and non-specific actions (high evolutionary conservation of different kinases). However, when tested on rare cancer diseases, several of these kinase antagonists, originally developed for general cancer diseases, showed beneficial effects and were approved despite their non-specificity [36,37]. Similar important advances in the areas of biochemistry, enzymology and cell biology boosted the understanding of many rare endocrine, nutritional and metabolic diseases [38,39]. For these diseases, a missing or dysfunctional enzyme or substrate was discovered as the underlying cause [40,41] and has resulted in the development of a number of therapies that involve administration of the missing or dysfunctional enzyme or substrate [42]. For congenital malformations, however, the underlying cause might be an inherited (genetic) condition, toxic exposure of the foetus or birth injury, but in many cases, the cause is still unknown. Even if the cause is known, a therapy might not be feasible owing to the permanent nature of the defect, which involves the arrest, delay or misdirection of the development of a structure in embryonic life. Nonetheless, our results indicate that congenital malformations might benefit considerably from an increase in scientific research.

Disease-specific scientific output

For the association between the number of publications and a disease obtaining at least one product with a designation, the disease dataset was divided into three equal subgroups, based on the number of publications in the group of diseases without an orphan designation (Fig. 2). A disease for which more than 600 publications have been published had a twofold higher likelihood for obtaining at least one product with an orphan designation (adjusted OR = 2.23; 95%CI = 1.37–3.64) than a disease with less than 200 publications. The chance for a disease with from 200 to

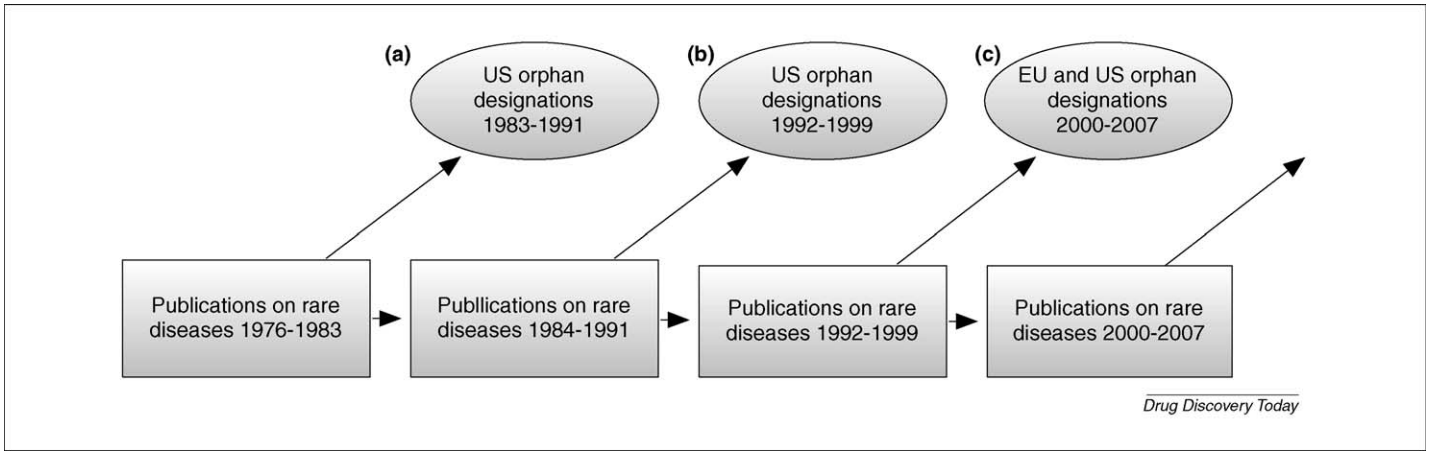

FIGURE 3

Publications on rare diseases and orphan designations. Depiction of the study design in which the association between the number of PubMed publications in one eight-year period and the likelihood of obtaining at least one product with an orphan designation in the next period was determined for the disease classes of oncological diseases; endocrine, nutritional and metabolic diseases; and congenital malformations. The results of these analyses are shown in Tables 1–3, respectively.

600 publications to obtain at least one product with an orphan designation did not differ from that of a disease with less than 200 publications. A secondary analysis by disease class further elucidated the influence of the number of publications within a disease class on the likelihood of a disease obtaining at least one product with an orphan designation. In this analysis, each disease class dataset was divided in two equal subgroups, based on the number of publications in the group of diseases without an orphan designation. Because the average number of publications per disease varied between disease classes, a many different number publications were used as a cut-off point for each disease class. An oncological rare disease with a high number of publications per disease (more than 1200) was found to be five times more likely to obtain at least one product with an orphan designation (OR = 5.20; 95%CI = 1.29–20.89) than an oncological disease with less than 1200 publications. In addition, endocrine, nutritional and metabolic diseases with a high number of publications (more than 200) were four times more likely to obtain at least one product with a designation (OR = 4.08; 95%CI = 1.50–11.08) than a disease with less than 200 publications in the same disease class. For diseases in other disease classes, we did not observe a statistically significant association between a high number of publications and obtaining at least one orphan designation. However, for the congenital malformations, a clearly increased (although not statistically significant) chance for obtaining at least one designation was found for a disease with more than 360 publications (OR = 2.60; 95%CI = 0.88–7.73). The effect became more pronounced when a cut-off point of 850 publications, representing the lowest number of publications of the upper quartile of the diseases without an orphan designation, was used (OR = 4.00; 95%CI = 1.45–11.05).

Finally, to exclude the possibility that the observed association was due to post-designation scientific output, the association between several publications in one eight-year period and the chance of obtaining at least one designation in the following eight-year period was analyzed (Fig. 3). Only disease classes for which a positive association was found between number of publications and obtaining at least one designation were included in the analysis. The results depicted in Tables 1–3 show that oncological diseases with a higher number of publications in each of the three periods (1976–1983, 1984–1991 and 1992–1999) had a higher

TABLE 1

Diseases with high and low number of publications between 1976 and 1983 for oncological diseases (*N* = 59), congenital malformations (*N* = 144) and endocrine, nutritional and metabolic diseases (*N* = 87) with and without at least one US orphan designation obtained in the next period (1983–1991)

	Number of diseases with at least one designation between 1983 and 1991 (US)	Number of diseases without designations between 1983 and 1991 (US)	OR (95%CI)
Oncological diseases			
Low number of publications (<200)	2	18	1 (reference level)
High number of publications (>200)	22	17	11.65 (2.37–57.23)
Endocrine, nutritional and metabolic diseases			
Low number of publications (<50)	0	40	1 (reference level)
High number of publications (>50)	9	38	NA
Congenital malformations			
Low number of publications (<50)	1	72	1 (reference level)
High number of publications (>50)	4	67	4.30 (0.47–39.44)

TABLE 2

Diseases with high and low number of publications between 1984 and 1991 for oncological diseases (*N* = 59), congenital malformations (*N* = 144) and endocrine, nutritional and metabolic diseases (*N* = 87), with and without at least one US orphan designation obtained in the next period (1992–1999)

	Number of diseases with at least one designation between 1992 and 1999 (US)	Number of diseases without designations between 1992 and 1999 (US)	OR (95%CI)
Oncological diseases			
Low number of publications (<300)	2	18	1 (reference level)
High number of publications (>300)	23	16	12.94 (2.63–63.71)
Endocrine, nutritional and metabolic diseases			
Low number of publications (<75)	4	38	1 (reference level)
High number of publications (>75)	18	27	6.33 (1.93–20.83)
Congenital malformations			
Low number of publications (<75)	1	73	1 (reference level)
High number of publications (>75)	4	66	4.42 (0.48–40.59)

TABLE 3

Diseases with high and low number of publications between 1992 and 1999 for oncological diseases (*N* = 59), congenital malformations (*N* = 144) and endocrine, nutritional and metabolic diseases (*N* = 87), with and without at least one orphan designation obtained in the US or the EU during the next period (2000–2007)

	Number of diseases with at least one designation between 2000 and 2007 (US)	Number of diseases without designations between 2000 and 2007 (US)	OR (95%CI)
Oncological diseases			
Low number of publications (<400)	11	7	1 (reference level)
High number of publications (>400)	36	5	4.58 (1.21–17.35)
Endocrine, nutritional and metabolic diseases			
Low number of publications (<100)	15	31	1 (reference level)
High number of publications (>100)	22	19	2.39 (1.00–5.71)
Congenital malformations			
Low number of publications (<100)	3	64	1 (reference level)
High number of publications (>100)	13	64	4.33 (1.18–15.94)

chance of obtaining an orphan designation in the next period. The same applies to endocrine, nutritional and metabolic diseases with a high number of publications. For congenital malformations, a significantly higher chance for a disease with a high number of publications to obtain an orphan designation in the following period was only observed in the last eight-year period (1992–1999). In the following period (2000–2007), orphan designations were granted for 16 congenital malformations, of which 7 were granted by the EMEA, compared with 5 diseases with a designation in each of the 2 preceding periods. Qualitatively similar results were found for these three disease classes when publications of two consecutive eight-year periods (e.g. 1976–1991 or 1984–1999) were compared with obtaining a designation in the next eight-year period (1992–1999 or 2000–2007) (data not shown).

Thus, rare diseases with a high number of scientific publications are more likely to obtain a product with an orphan designation than rare diseases with a low number of publications. Interestingly, for congenital malformations, a significantly higher chance was observed for a disease with a high number of publications between 1992 and 1999 to obtain an orphan designation in the following eight-year period. An explanation for this observation, which is confirmed by several studies, could be that the elucidation of the human genome between 1990 and 2003 might have accelerated the identification of new genes causing certain congenital malformations [43,44]. Although the human genome project has brought about a great increase in the identification of disease-relevant genes and proteins, this has not yet resulted in the expected flood of new compounds, according to Lindsay [45]. Our finding indicates that the human genome project is not just paving the way for the identification of novel drug targets and better cell and animal models [45] but might also promote orphan drug development for congenital malformations.

Concluding remarks

This study has shown that successful translation of rare disease research into an orphan drug discovery and development programme is dependent on the disease class, the disease prevalence and the disease-specific scientific output. Previous studies have already shown the importance of pharmaceutical innovation for orphan drug discovery and development [13], and numerous analyses have amplified that the big challenge in the successful drug discovery and development lies in the translation of biomedical research into discovery and development of a successful product [15,26]. This translation incorporates the two-way process of using

knowledge from basic research for the discovery and development of new methods for the treatment, prevention or diagnosis of diseases [15,46], involving industry and regulators, as well as academia [47]. Although the increase in biomedical research has sometimes been reported not to deliver the expected flood of new medicinal products [18,45], our study has shown that rare disease research really paves the way for new treatments that might provide a benefit to patients with a rare disease. Moreover, the observed close link between rare disease research and orphan drug development seems to substantiate the view of Tralau-Stewart *et al*. that industry needs academia and academia needs industry in future (orphan) drug discovery and development programmes [48]. Finally, these findings provide two important policy implications for further stimulating orphan drug development. First, the current orphan drug legislation is not sufficient to stimulate orphan drug development for diseases with a low prevalence or exceptionally rare diseases and, consequently, new (economic) incentives and other initiatives will be required. Pharmacy preparations, which have proven their added value in exceptionally rare disease management [49,50], public–private partnerships, such as the European Innovative Medicines Initiative (http://www.imi-europe.org; accessed June 2009) or the European Rare Diseases Therapeutic Initiative [51] and patient-initiated crowd-sourcing or open-source research, such as LAMsight (http://www.nytimes.com/2009/08/25/health/25web.html; accessed August 2009), might prove to be valuable developments in accomplishing this. Of course, future discussions on the details of supplementary orphan drug policies will have to include (public) costs. Second, a strong transnational research agenda on rare diseases is required to provide the necessary input for more orphan drug development programmes. This agenda should not merely focus on stimulating rare disorder research in general but should also focus on the specific needs at disease class level, in close interaction with patient organizations and learned societies. In this respect, the disease class of oncological diseases can serve as a valuable role model for other disease classes. The first step in Europe, which is already under way, will be to link national efforts [52] within a common European strategy for rare disease management with the aim of levering national research resources on rare diseases through synergistic cooperation and preparation of joint strategic activities (http://www.e-rare.eu; accessed April 2009). In the USA, the National Institutes of Health are already providing support for specific, preclinical research and product development for rare and neglected diseases (http://www.nih.gov/news/health/may2009/nhgri-20.htm; accessed June 2009).

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