

## Hopes for intractable and rare diseases research

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February 28, 2013 marks the sixth international "Rare Disease Day". On and around this day, hundreds of patient organizations from more than 60 countries and regions worldwide plan to host awareness campaigns in line with this year's theme, "Rare Disorders without Borders". Public awareness of intractable and rare diseases has heightened in recent decades. Much progress has also been made worldwide, such as specific legislation to encourage discovery and development of orphan drugs in the United States (US), the European Union (EU), and some parts of Asia. However, there are still many gaps in knowledge with regard to therapeutic tools and strategies. Intractable and rare diseases cause patients substantial physical suffering, psychological despair, and economic hardships due to bleak therapeutic outcomes and the lack of practical support in everyday life. The features of intractable and rare diseases and the increasing number of types of identified diseases make these diseases an important public health issue and a challenge to medical care worldwide. The following are specific aspects of research on intractable and rare diseases that need to be promptly promoted.

*An International Classification of Diseases (ICD) code to promote the definition and classification of intractable and rare diseases*

Intractable diseases, or "nanbyo" (literally "hard-to-treat diseases" in Japanese), mainly refer to rare diseases that have resulted mostly from unidentifiable causes and/or a lack of clearly established or curative treatments. According to the World Health Organization (WHO), rare diseases are rare and often debilitating or even life-threatening diseases or conditions with a prevalence of 0.65-1‰. The conventional view is that rare diseases as a whole affect around 10% of individuals worldwide, but the definition and categorization of rare diseases differ slightly by region. In the US, rare diseases are defined as diseases that affect fewer than 200,000

Americans (prevalence of < 0.75‰), while stipulated prevalence rates in other regions are < 0.5‰ in the EU, fewer than 2,000 patients (prevalence of < 0.11‰) in Australia, fewer than 50,000 patients (prevalence of < 0.4‰) in Japan, fewer than 20,000 patients (prevalence of < 0.4‰) in South Korea, or a prevalence of < 0.1‰ in Taiwan. The current outlook for identification of a specific rare disease and estimation of the true burden of rare diseases is bleak given the lack of proper classification and coding of rare diseases. Currently, there is no special coding system for rare diseases. The current ICD code that is used in most countries is not suitable for rare diseases. The absence of a universally recognized coding system is an obstacle for reliable registration of patients in national or international databases, preventing assessment of the economic and social effects of rare diseases. Fortunately, the good news is that the European Rare Disease Task Force of the Health and Consumers Protection Directorate General of the European Commission has set up a working group to collaborate with the WHO on the ICD-10, and the group is considering all other existing classifications to provide the rare disease community with a uniform system. A revised ICD code is urgently needed to both promote the definition and classification of intractable and rare diseases and to obtain accurate epidemiological data on these diseases at the national and international levels.

*Specific legislation to encourage discovery and development of orphan drugs*

Currently, orphan drugs – the medicinal products intended for the diagnosis, prevention, or treatment of rare diseases – are a major facet of how rare diseases are dealt with. In the past few decades, many countries have realized that orphan drugs will not lead to substantial sales under normal market conditions because of the high costs and risks of drug development, insufficient knowledge of the pathophysiological mechanisms of rare diseases that the drugs diagnose or treat, and difficulties in conducting clinical trials with small patient populations and a small potential market. Therefore, specific legislation to encourage the discovery and development of orphan drugs was enacted in many

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countries and regions, including the US in 1983, Japan in 1993, Australia in 1997, the EU in 1999, Taiwan in 2000, and South Korea in 2003. Incentives include financial subsidies, market exclusivity, tax credits, fee waivers, fast track approval, and protocol assistance, resulting in substantial improvements in the treatment of patients with a range of rare diseases. While China is actively preparing to regulate and encourage the development of orphan drugs, it still lags far behind the US, the EU, Japan, and other countries and regions with orphan drug legislation. Evidence has shown that all of the incentives have successfully encouraged the development of new pharmaceutical products to treat rare diseases. Prior to 2010, 352 orphan drugs were approved in the US, helping an estimated 12 million Americans, compared to only 10 such drugs in the decade preceding the Orphan Drug Act (1983). Similarly, 720 drugs had received orphan drug designation from the European Medicines Agency (EMA) and 63 designated orphan medicinal products have been authorized for marketing in the EU. Furthermore, data have shown that an average of 15 new orphan drugs are approved annually in the US and 10-12 new orphan drugs are approved annually in the EU. Thus, China and other countries without orphan drug legislation need to promptly establish domestic legislative regulations and incentives to encourage discovery and development of orphan drugs.

*Government-funded special biomedical research programs to enhance basic and applied research on intractable and rare diseases*

Biomedical research on intractable and rare diseases has provided insights into the pathologies of these diseases and revealed their underlying mechanisms. Such work may ultimately reveal possible avenues to therapeutics. Moreover, once biomedical research identifies suitable drug candidates and becomes more translational, it will garner industry attention, potentially leading to safe and effective orphan drugs. In Western countries, many research centers or projects have been established to support special biomedical research programs on rare diseases and development of orphan drugs, such as the Office of Rare Diseases Research (ORDR) established in the US in 1993 within the National Institutes of Health (NIH) and the Rare Disease Task Force (RDTF) established in EU in 2004 within the European Commission Public Health Directorate. In Asian countries, biomedical research on intractable and rare diseases has made great advances in Japan due to the systematic Specified Disease Treatment Research Program established in 1972 with the support of the Ministry of Health, Labor, and Welfare. As a result, special research programs and research grants from

government sources to study 130 diseases increased to 10 billion Japanese yen in 2010. Recently, 214 diseases were designated for a second round of special research programs. In China, support for special biomedical programs on intractable and rare disease research comes mainly from the National Natural Science Foundation of China (NSFC). Data showed that 366 projects (involving 32 rare diseases) were funded by the NSFC from 1999 to 2007 with total funding of 89.358 million RMB and annual funding of about 10 million RMB, accounting for just 1/10th of similar funding in the US. Special biomedical research programs that enhance basic and applied research on intractable and rare diseases would benefit patients through better diagnosis and more treatment choices. Government-funded special biomedical research programs need to be promptly implemented in China and other countries to promote research on intractable and rare diseases.

*Patients' advocacy organizations and disease registry networks to provide vast information on intractable and rare diseases*

In recent years, progress has been made in the dissemination of knowledge and information by established patients' advocacy organizations, such as the National Organization for Rare Disorders (NORD) in the US and the European Organization for Rare Diseases (EURORDIS) in Europe, but the delay in diagnosis and treatment is still a huge challenge to cope with. A survey of 18,000 individuals found that 25% of patients waited for 5-30 years before being correctly diagnosed and 40% of patients were diagnosed incorrectly before they were correctly diagnosed. Furthermore, clinical studies on orphan drugs also face challenges due to the small size of the trial population and the fact that patients are often geographically dispersed. Disease registry networks need to be established to promote epidemiological and basic research and improve the clinical outcome for patients with intractable and rare diseases. In Western countries, some web-based resources, such as the Rare Diseases Clinical Research Network (RDCRN) in the US and the Orphanet in Europe, have been established in order to facilitate collaboration on clinical outcomes and to share accumulated experience so that patients with intractable and rare diseases are not delayed access to orphan drugs. More patients' advocacy organizations and disease registry networks need to be promptly established to facilitate interaction among patients, clinicians, researchers, the pharmaceutical industry, and governmental bodies with the ultimate goal of promoting intractable and rare disease research worldwide.

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