
Supplementary information

Trends in rare disease drug development

In the format provided by the authors

Data sources and characteristics

Data on drugs for rare diseases in development globally and in China were identified by searching for the drugs' characteristics of "rare disease indications" and "in pipeline status" in the [Pharmaprojects database from Citeline](#), which covers companies in over 130 countries and drug development in over 160 countries. The data snapshot date was 31 December 2022. The data were from multiple sources, including the ClinicalTrials.gov clinical trial registry, Chinese NMPA's Registration and Information Disclosure Platform for Drug Clinical Studies, the Chinese Clinical Trial Register (ChiCTR), scientific conferences, company press releases, published reports, investor presentations and other sources.

Rare disease drugs under development were screened from the Pharmaprojects database. For the global data, drugs for rare diseases under development in all countries were included. The established definitions of rare diseases in the European Union (EU) and the USA were adopted, as diseases with a prevalence of less than 1 in 2,000 people in the EU, or affecting fewer than 200,000 people in the USA, respectively. 5,462 drugs with 556 indications were initially selected from the Citeline database. After excluding 245 agents (4%) with 69 prophylactic indications and 2 discontinued agents (1%), 5,215 drugs (95%) with 487 indications were included in the final analysis dataset (Supplementary Table 1). A separate analysis of drugs with prophylactic indications is presented below.

Data on drugs for rare diseases in development in China were first collected by searching for the drugs' characteristics of "rare disease indications", "in pipeline status" and "in China" in the [Pharmaprojects database from Citeline](#). The indications were then screened further. Drugs for 207 rare diseases from the first and second catalogue of rare disease selected by experts in China were included^{1,2}. Other drugs were further screened based on available epidemiological data for rare diseases. We took the regional Chinese expert consensus in 2021 and the official definition of rare disease in Taiwan as references, using the relatively authoritative epidemiology-based definition of rare disease "incidence or prevalence rate less than 1/10,000 or total cases less than 140,000" as the selection criteria for data in China³. Cancer incidence data in China were referred to in the epidemiology data released from the Chinese National Cancer Center in 2022⁴ and GLOBOCAN 2020⁵. Epidemiology data for other diseases in China were obtained from publicly available authoritative platforms in China, such as China Medical Information Platform and literature. Drugs for diseases with unknown epidemiology data were excluded. If the drug was designed to treat a subtype of the disease and the subtype met our definition of a rare disease, the drug was included even if the disease was not identified as a rare disease; for example, drugs for stomach cancer were excluded, but drugs for the HER2⁺ subtype of stomach cancer were included. 1,134 drugs with 198 indications were initially selected from the Citeline database. 261 drugs (23%) with 63 indications were excluded based on the definition of rare disease or the absence of available epidemiologic data, as were 33 agents (3%) with 6 prophylactic indications. This led

to the identification of a total of 840 qualified rare disease drugs with 123 indications for analysis (Supplementary Table 2).

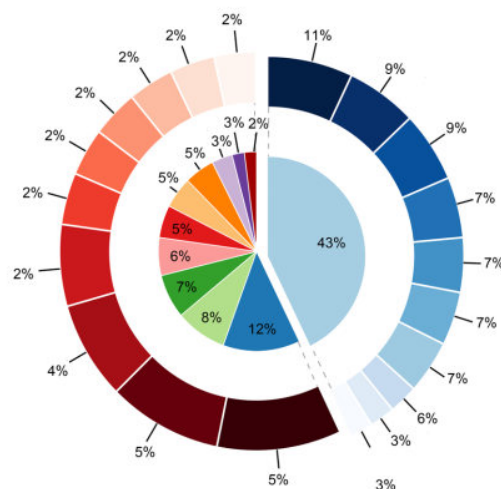
Analysis of rare disease drugs in development globally and in China

For the annual numbers of rare disease drugs in preclinical and clinical development shown in Figure 1, a starting date was defined for each drug according to the earliest event date in the databases searched. All drugs were classified into six stages of development based on the highest status reached: preclinical, phase I, phase II, phase III, pre-registration and N/A (lacking adequate information).

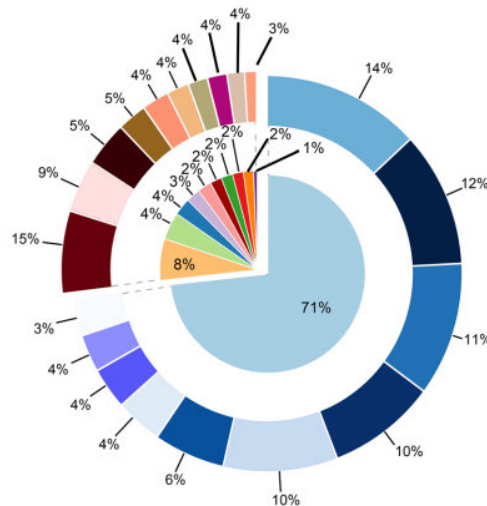
For the analysis of therapeutic areas shown in Figure 2 and Supplementary Figure 1, all drugs were first categorized into two major categories — oncology and non-oncology — and these two categories were separately analysed to obtain the number of drugs for each indication. Non-oncology drugs were further categorized as neurological, respiratory, alimentary/metabolic, immunological, musculoskeletal, blood and clotting, sensory, anti-infective, cardiovascular and others. Indications with the top ten most drugs were displayed, along with percentage of all oncology or non-oncology drugs.

For the analysis of drug types shown in Supplementary Figure 2, all drugs were first classified into biological and chemical drugs. Chemical drugs included synthetic and semisynthetic compounds. Natural drugs or unclassified drugs were manually annotated. Biological drugs were further classified into protein, peptide, cellular, nucleic acid, bacterial and others.

Global



China



All

- Anticancer
- Neurological
- Respiratory
- Alimentary/Metabolic
- Immunological
- Others
- Blood and Clotting
- Musculoskeletal
- Sensory
- Anti-infective
- Antiparasitic
- Cardiovascular

Non-cancer

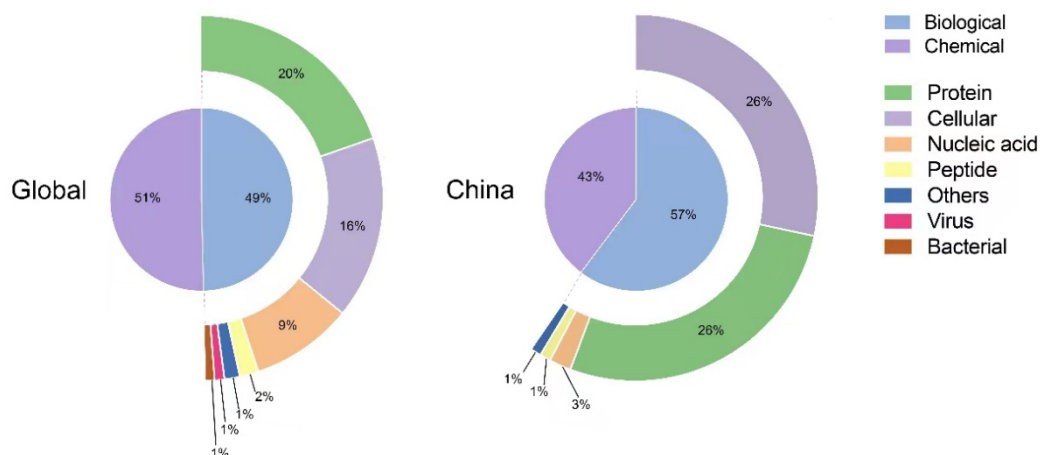
- Amyotrophic lateral sclerosis
- Pulmonary fibrosis
- Acute respiratory distress syndrome
- Duchenne muscular dystrophy
- Cystic fibrosis
- Huntington's disease
- Pulmonary hypertension
- Cytokine release syndrome
- Frontotemporal dementia
- Graft versus host disease
- Haemophilia A/B
- Thrombocytopenic purpura
- Neuromyelitis optica
- Juvenile idiopathic arthritis
- Paroxysmal nocturnal hemoglobinuria
- Thalassaemia
- Myofibrosis

Cancer

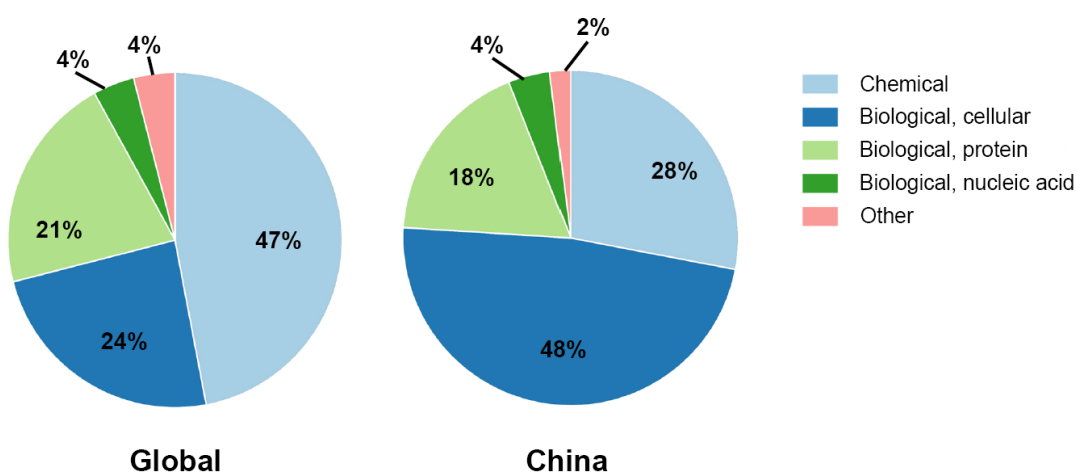
- Pancreatic cancer
- Acute myeloid leukemia
- Ovarian cancer
- Multiple myeloma
- Liver cancer
- Non-Hodgkin's lymphoma
- Stomach cancer
- B cell lymphoma
- Renal cancer
- Myelodysplastic syndrome
- Chronic lymphocytic leukemia
- Cholangiocarcinoma

Supplementary Figure 1 | **Detailed information on therapeutic areas and indications of rare disease agents in development globally and in China, including preclinical and clinical pipelines.** This figure provides more granularity on the data that are presented in Figure 2. For cancer and noncancer areas, the top 10 indications with the most pipelines is presented in the outer rings and the 'others' is not presented here.

a



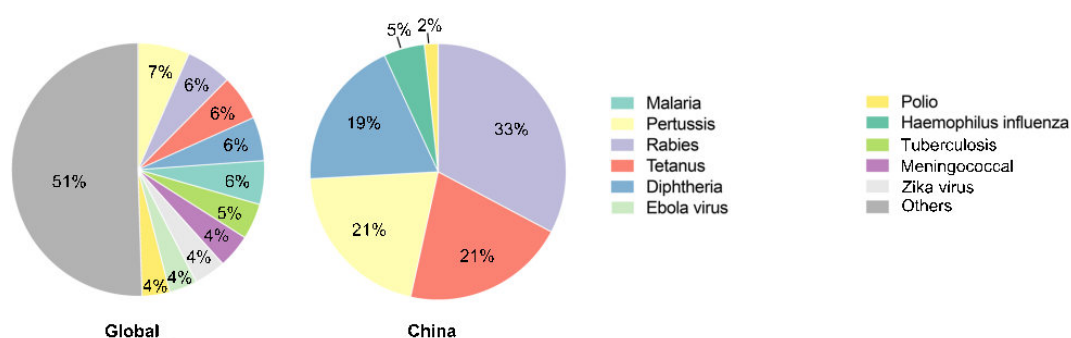
b



Supplementary Figure 2 | **Drug types of rare disease agents. a**, Drug types overall globally and in China. The biological group was further classified into 7 main groups: cellular, protein, nucleic acid, peptide, virus, bacterial and others . **b**, Drug types for rare disease agents with academic institutions as one of the sponsors, globally and in China.

Prophylactic agents

As noted above, prophylactic agents were removed from the main analysis due to their large target populations, and analysed separately (245 agents globally and 33 agents in China). The indication distribution of prophylactic agents was different globally and in China (Supplementary Figure 3). The number of indications was much larger globally, and prophylactic agent development in China focused on a limited number of areas.



Supplementary Figure 3 | **Indication distribution of prophylactic agents for rare diseases.** All indications with more than 1% are listed here. Prophylactic agents were not included in the total indication distribution analysis, due to their large target population. Although the prevalence rates of these indications were very low, the potential market was quite large, and they were not the target of China's supportive policies for rare disease drug development.

References

1. National Health Commission of the People's Republic of China. Notice on the first official list of rare diseases. June 8, 2018 (in Chinese).
2. National Health Commission of the People's Republic of China. Notice on the second official list of rare diseases. September 18, 2023 (in Chinese).
3. Joint Meeting of the Chairpersons of Rare Disease Societies. A report on the definition of rare diseases in China. Shanghai (2021). (in Chinese)
4. Rongshou, Z, et al. Cancer incidence and mortality in China, 2016. *J. Natl Cancer Center* 1-9 (2022).
5. Sung H, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **71**, 209-249 (2021).