From the analyst's couch

https://doi.org/10.1038/d41573-023-00177-8

Trends in rare disease drug development

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Advances in the understanding of the biology underlying rare diseases, as well as progress with therapeutic platforms such as nucleic-acid agents, have enabled increased research and development (R&D) on drugs for rare diseases. Governmental incentives and regulatory initiatives have played a key role too, such as the Orphan Drug Act of 1983 in the USA.

In the past decade, China has also introduced policies to promote R&D on rare disease drugs. The document *Opinions on Encouraging Drug Innovation to Give Priority to Review and Approval* issued by the National Medical Products Administration (NMPA) in 2017 specified 18 categories of priority review and approval, including rare disease drugs, which accelerated approvals of rare disease drugs and other agents for urgent clinical needs. This policy was strengthened by *Drug Administration Law of the People's Republic of China* in 2019 and *Provisions of Drug Registration* in 2020. Recently, *Guidance for Clinical Research and Development of Rare Disease Drugs*, issued by the NMPA in 2022, provided detailed suggestions on trial design for rare disease drugs.

To investigate the impact of these changes in China in comparison with R&D globally, we analysed the pipeline of therapeutic agents for rare diseases in preclinical and clinical development in China and globally in the past ten years and the status at the end of 2022 (see Supplementary information for details of the data and analysis).

The rare disease R&D landscape

Overall trends. From 2012 to 2022, the number of rare disease agents in preclinical and clinical development increased globally and in China (Fig. 1a). At the end of 2022, there were a total of 840 agents being developed for rare diseases in China, among which 412 (49%) were at the preclinical stage. For all agents with approved investigational new drug (IND) applications, 206 (25%) agents have reached phase I, 152 agents (18%) have reached phase II, 56 (7%) agents have reached phase III and 14 agents (2%) were at the pre-registration stage (Fig. 1b). In comparison, there were 5,215 agents for rare diseases in development globally at the end of 2022, with a similar distribution across each phase of development (Fig. 1b).

The number of rare disease drugs in the pipeline in China has increased substantially in the past five years, with an average annual growth rate of 34%, compared with 24% for the global pipeline. The timing of this growth is consistent with the introduction of the medical and health care systems reforms in China from 2017 onwards.

Therapeutic areas. Analysis of all rare disease drugs revealed that oncology was the most active therapeutic area globally and in China, accounting for 43% of the global pipeline and 71% of the pipeline in China (Fig. 2). Although very few rare tumours were included in the first and second official lists of China's 207 rare diseases, this category encompassed a large group of indications with low incidence but poor prognosis.

Taking a deeper look at individual indications in the oncology area, the top six indications in China were similar but not identical to those in the global pipeline (Fig. 2). Non-Hodgkin lymphoma, pancreatic cancer, myeloma, acute myelogenous leukaemia and ovarian cancer were present in both top-six lists, while stomach cancers in the global top-six list were not considered rare tumours in China, in line with the differences in incidences of these diseases. Additional indications are shown in Supplementary Fig. 1.

Beyond oncology, the next largest therapeutic areas globally were neurological (12%), respiratory (8%), alimentary/metabolic (7%) and immunological diseases (6%) (Fig. 2). The focus in China was different. Notably, only 4% of all agents in development in China were for neurological diseases and only 2% were for alimentary/metabolic diseases, and there might be extensive unmet medical needs in these areas. In recent years, the establishment of clinical cohorts with neurological and metabolic rare diseases, supported by the National Rare Diseases Registry System of China, has been collecting more information to promote drug development in these areas.

In addition, in contrast to the similarity in the top-six rare cancer indications globally and in China, the top six non-oncology indications were quite different (Fig. 2). Only idiopathic pulmonary fibrosis and amyotrophic lateral sclerosis were shared in the two top-six

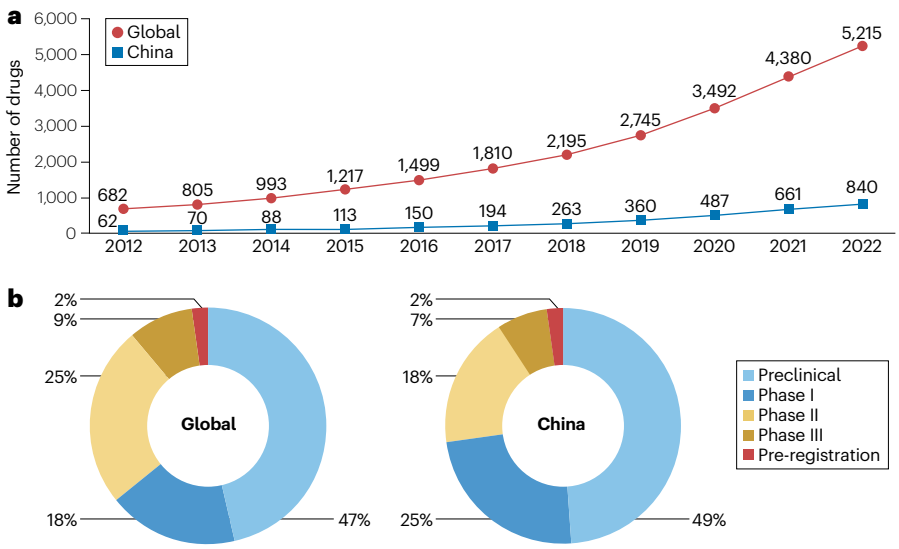

Fig. 1 | Trends in rare disease drug development. a, Annual numbers of rare disease agents in preclinical and clinical development globally and in China from 2012 to 2022. **b**, Breakdown of all rare disease agents globally and in China by stage of development, as of 31 December 2022. See Supplementary information for details of the data and analysis.

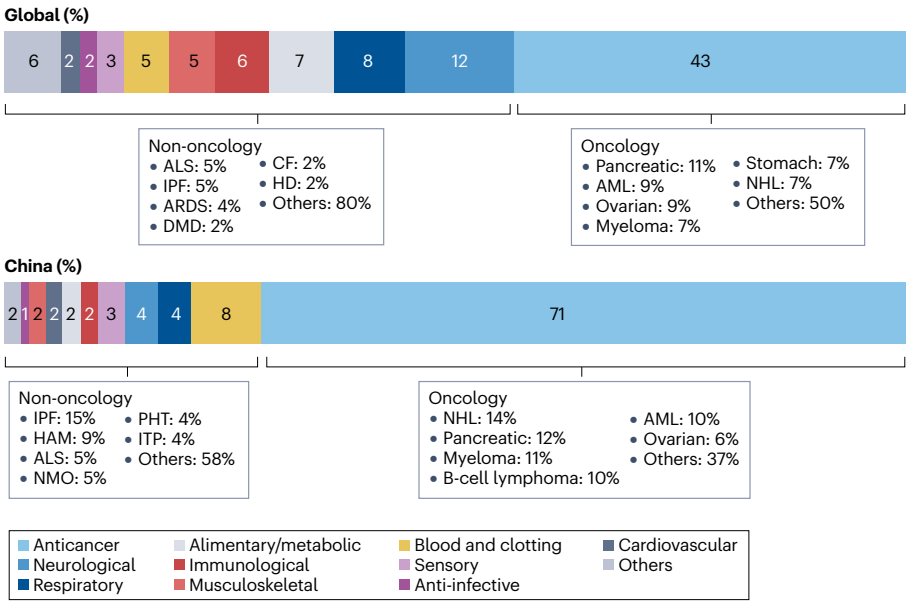

Fig. 2 | Therapeutic areas of rare disease agents in development globally and in China. The figure shows the percentages of rare disease agents in preclinical and clinical development by therapeutic area as of 31 December 2022. Oncology is the largest therapeutic area both globally and in China. The top six indications in terms of the number of agents for oncology and non-oncology therapeutic areas are highlighted in boxes, with the percentages for each indication shown. More detailed information on therapeutic areas and indications is provided in Supplementary Fig. 1. Prophylactic agents were not included in this analysis due to their large target population. More information on prophylactic agents for rare diseases is provided in Supplementary Fig. 3. AML, acute myelogenous leukaemia; ALS, amyotrophic lateral sclerosis; ARDS, acute respiratory distress syndrome; CF, cystic fibrosis; DMD, Duchenne muscular dystrophy; HAM, haemophilia; HD, Huntington disease. IPF, idiopathic pulmonary fibrosis; ITP, idiopathic thrombocytopenic purpura; NHL, non-Hodgkin lymphoma; NMO, neuromyelitis optica; PHT, pulmonary hypertension. See Supplementary information for details of the data and analysis.

lists, partly owing to the different incidences of non-oncology rare diseases.

For some active non-oncology indications, such as haemophilia, there are several approved drugs available from multinational corporations in China, and the drugs with these indications in development in China were mainly sponsored by domestic companies.

Drug and sponsor types. Globally, biological agents made up almost half (49%) of the overall pipelines of rare disease agents, with protein (20%), cellular (16%) and nucleic-acid (9%) agents as the top three groups (Supplementary Fig. 2a).

In China, biological agents accounted for 57% of the pipeline, with the two largest groups — cellular (26%) and protein (26%) agents — making up nearly all of the pipelines, and nucleic-acid agents being the next largest group but making up only 3% (Supplementary Fig. 2a). Given the continued progress with nucleic-acid platforms globally and their high relevance to rare diseases, therapies based on such platforms could be a promising opportunity for growth in the pipeline of rare disease agents in China.

Academic institutions were involved in sponsoring the development of 15% of agents globally and 25% of agents in China. Chemical agents represented 47% of the global group of such agents, followed by cellular and protein agents, with 24% and 21%, respectively (Supplementary Fig. 2b). By contrast, in China, cellular agents were the largest group of agents with academic institutions as one of the sponsors (48%), followed by chemical agents (28%) and protein agents (18%) (Supplementary Fig. 2). As next-generation technologies such as cell therapies have gained an important role in R&D for rare diseases, and academic institutions in China working on such therapies have built relationships with industry sponsors to partner at early stages in their development, these could also be an area of rapid growth for the rare disease drug pipeline in China.

Outlook

China's supportive policies for rare disease drug development have promoted medical innovation in this field, reflected by the rapidly increasing numbers of agents in the rare disease pipeline in China over the past five years (Fig. 1). Comparison with the global pipeline highlights different focuses in therapeutic areas, drug types and the translational research of academic institutions. These observations could inform further policymaking and investment to meet unmet medical needs, strengthen weaknesses, avoid clustering of multiple agents in the same field, and promote cooperation between academic institutions in China and industry sponsors. With the continued help of governmental incentives and regulatory reforms in this field in China, sustained growth in rare disease drug development is anticipated in the future.

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Acknowledgements

The authors gratefully acknowledge X. Wang and S. Ji from the Center for Drug Evaluation, National Medical Products Administration in China, as well as Z. Yan, Y. Li, C. Ge and J. An from the Tsinghua Clinical Research Institute, Tsinghua University, for their contribution to the work.

Competing interests

S. Zhou is an employee of Citeline. The other authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/d41573-023-00177-8