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LETTER TO THE EDITOR Open Access

A decade of incremental advances in radiopharmaceuticals: a promising future ahead

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To the Editor,

Radiopharmaceuticals, also known as nuclear pharmaceuticals, are specialized drugs labeled with radioisotopes for diagnostic or therapeutic purposes. Therapeutic radiopharmaceuticals fall into three categories: specific nuclides like ^{131}I that selectively accumulate in target tissues, endo-interventional agents (e.g., ^{90}Y and ^{32}P microspheres) directly delivered to tumors, and radionuclide drug conjugates (RDCs), which are precision-targeted drugs composed of a radioisotope, chelator, linker, and biotargeting agent [1, 2]. With the successful introduction of Lutathera and Pluvicto, RDCs have demonstrated exceptional therapeutic efficacy, positioning them as powerful tools in addressing unmet clinical needs. In order to capture the current research status of RDCs, we analyzed clinical trial activity spanning the past decade.

Clinical trial landscape of RDCs

To evaluate global trends, we analyzed RDC-related clinical trials using the Informa Database (https://pharma.id.informa.com/). As of August 2024, a total of 361 trials have been identified during the decade (Supplementary Fig. S1.). However, only 52.9% of these trials are actively in the pipeline, and of the 75 completed trials, 66% are in early development phases (I/II) (Supplementary Fig. S2.). Notably, the majority of ongoing trials remain in Phase I or II, with only 10.2% reaching Phase III (Fig. 1A). β-emitting radionuclides were predominant in terms of radiation type, but drug development for α radiation is gradually emerging. For the biotargeting part of RDCs, small molecule targeting is most prevalent in the β-rays and antibody in the α-rays (Fig. 1B). Lutetium 177-labeled drugs are all the rage, and interest in targeted α therapies, represented by actinium 225-labeled drugs, is rising rapidly (Fig. 1C). RDCs focus primarily on oncology, targeting prostate cancer and neuroendocrine tumors. Research into other cancers, including lung, non-Hodgkin's lymphoma, and central nervous system (CNS) tumors, is also progressing (Fig. 1D). The two most common targets in RDC development are somatostatin receptors (SSTR) and prostate-specific membrane antigen (PSMA), which are selectively expressed in neuroendocrine and prostate cancers, respectively, thereby

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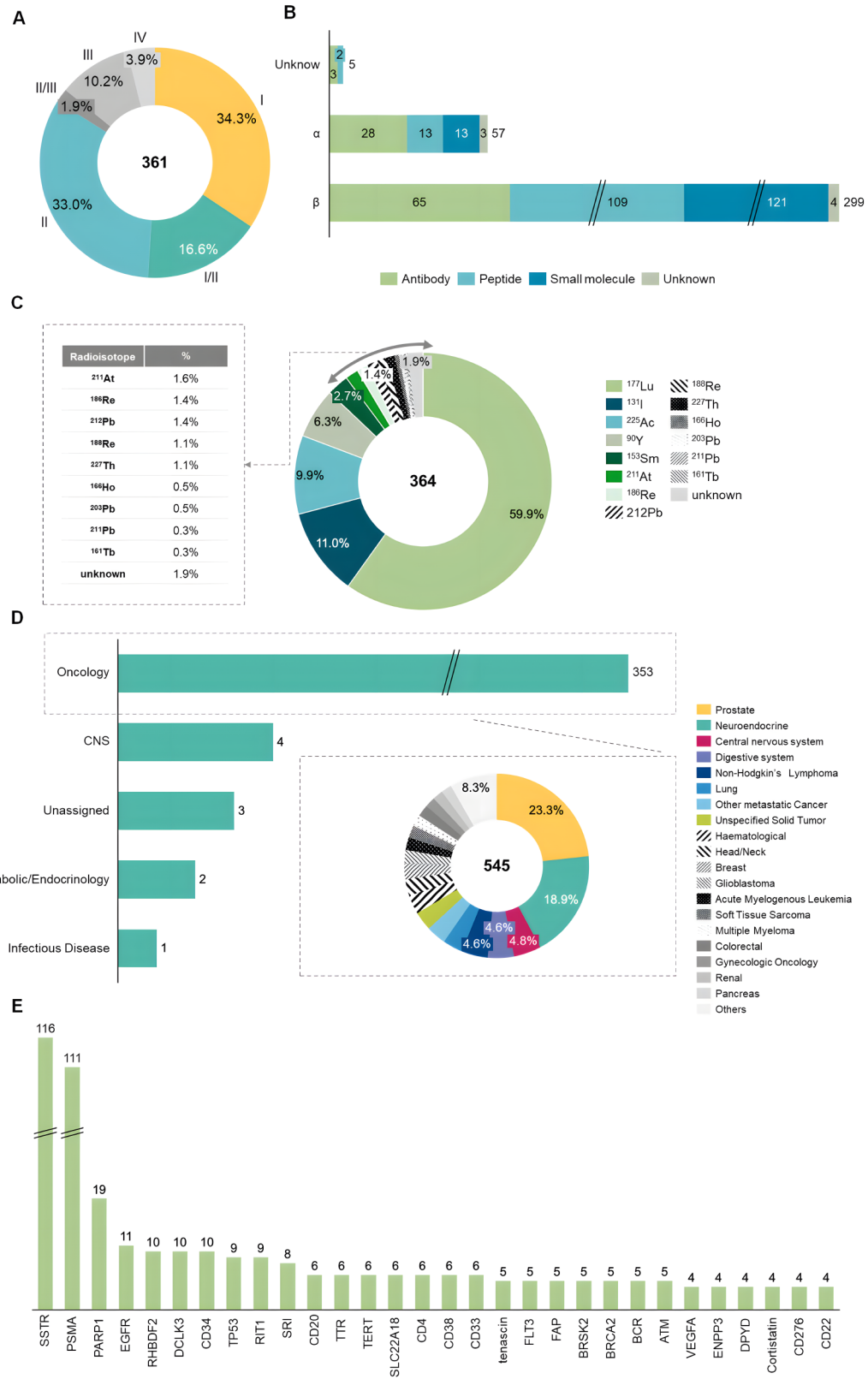

Fig. 1 The clinical landscape of RDCs. (**A**) Clinical phase of RDCs. (**B**) The rays and biotargeting types of RDCs. (**C**) Types and percentage of nuclides in RDCs. (**D**) Types of diseases targeted by RDCs. (**E**) Distribution of the main targets of RDCs

minimizing effects on normal tissues and improving efficacy (Fig. 1E). In global participation, the United States leads with 157 clinical trials, followed by China, France, and Australia. These countries benefit from robust nuclear infrastructure, which supports radiopharmaceutical research and development (Supplementary Tab. S1).

Promising candidates and clinical milestoness

Of the 361 clinical trials reviewed, only 26 trials have achieved completion with successful primary outcomes, while 18 are either in Phase III or planning to begin. Among these, PNT-2002's SPLASH trial reached its Phase III primary endpoint, although overall survival data remain under analysis. ^{131}I-Omburtamab, targeting neuroblastoma, was submitted for EMA and FDA approval. Currently, further studies are exploring its potential in ventricular tubular meningioma and medulloblastoma. Additionally, the U.S. FDA has granted Orphan Drug and Fast Track designations to ^{186}Re-obisbemeda for glioblastoma and leptomeningeal metastases, underscoring its promise in these challenging cancers. Other promising RDCs are shown in supplementary Tab. S2.

Discussion

Despite advances, few RDCs have achieved market approval, highlighting the complexity of translating these agents into clinical use. For an RDC to be effective, it must achieve high specificity for tumor tissue, minimizing radiation exposure to healthy cells. Ideal RDC characteristics include (1) a target highly expressed at the tumor site, (2) a biotargeting agent with strong affinity, allowing for optimal internalization and pharmacokinetics, (3) an appropriately balanced molecular weight for efficient diffusion in solid tumors and appropriate metabolic pathways; (4) selection of radionuclides should consider emission type (α, β, γ), matched to the disease and treatment goals, and the half-life, which must align with the pharmacokinetics of the targeting moiety [3, 4]. For CNS lesions, RDCs should ideally cross the blood-brain barrier to maximize therapeutic precision [5].

Conclusion

Although technical challenges remain, the expanding field of radiopharmaceuticals holds promise for a new era of precision cancer therapy. With continued scientific and technical refinements, RDCs are expected to advance toward commercial availability, benefiting a broader patient population. Moreover, the recent trend of major pharmaceutical acquisitions in this sector signals increased investment, potentially accelerating radiopharmaceutical innovations in the coming years.

Supplementary Information

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Supplementary material 1

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Author contributions
Liangxue Zhou contributed to the study design and manuscript review, Yu Xiong and Xiaowen Han conducted data analysis and prepared the initial draft, and Hui Jian and Lizhi Li performed data analysis.

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Data availability
All data for this study are publicly available.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
All authors disclosed no relevant relationships.

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