Theragnostics for Neuroblastoma:

Making Molecular Radiotherapy Work Better

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**ABSTRACT**

Despite improvements in neuroblastoma treatment, survival figures lag behind those of many other childhood malignancies. New treatments, and better use of existing treatments, are essential to reduce mortality. Neuroblastoma expresses several molecular targets for radionuclide imaging and therapy, of which the most widely exploited is the norepinephrine transporter. [123I]meta iodobenzylguanidine (mIBG) imaging and [131I]mIBG treatment, which target this physiological pathway, have been in clinical practice for 40 years. While therapy outcomes have been favourable, [131I]mIBG use has not yet been optimized. Somatostatin receptors and the disialoganglioside (GD2) are alternative targets, but their use remains experimental. The charity Friends of Rosie Children’s Cancer Research Fund organized a workshop bringing together a broad range of scientists including radiochemists, radiobiologists, radiation physicists, clinical researchers including pediatric oncologists and nuclear medicine physicians, and patient advocates from the United Kingdom (UK), United States of America (USA) and continental Europe to share their experiences with molecular imaging and radiotherapy of neuroblastoma, and discuss potential ways of improving treatment outcomes and access. These include development of alternative vectors targeting somatostatin receptors and GD2, isotopes such as alpha particle and Auger electron emitters with different radiation characteristics, and combinations with external beam radiotherapy, immunotherapy and deoxyribonucleic acid (DNA) damage repair inhibitors. Barriers to progress discussed included unpredictable radioisotope supply, production of novel radiopharmaceuticals, lack of data regarding which are the best combination therapies, and insufficient clinical facilities. The aim was to stimulate the development and assessment of more effective treatments.

**KEYWORDS**

Molecular radiotherapy

Neuroblastoma

Radionuclide therapy

Radiopharmaceutical therapy

Theragnostics

**INTRODUCTION**

Approximately half of the children with neuroblastoma have high-risk disease (*1*). Despite therapeutic advances, survival is poor (*2*). Neuroblastoma is characterized by biochemical pathways and cell membrane molecules not found in most normal tissues (*3*), providing opportunities for nuclear medicine imaging and molecular radiotherapy (MRT).

 [123I]meta iodobenzylguanidine (mIBG) is the gold standard for imaging neuroblastoma, and semi-quantitative scoring systems are of prognostic value (*4*). Labelled with a beta emitting isotope, [131I]mIBG MRT is used to treat neuroblastoma (*5*). Despite 40 years of clinical experience, [131I]mIBG therapy is not yet regarded as a standard first-line treatment. Various strategies have been explored to try and improve outcomes. Use of vectors aimed at other molecular targets, or radionuclides emitting radiation with different characteristics, may also be advantageous (*6*). Progress in imaging technology combined with innovative radiotracers may allow for improved disease assessment (*7, 8*).

**METHODS**

The charity Friends of Rosie Children’s Cancer Research Fund (*9*) convened a symposium in Manchester, UK, in September 2024. Twenty one invited speakers included pediatric oncologists (5), cellular, radiation and molecular biologists (4), nuclear medicine physicians (3), radiochemists (3), radiation (clinical) oncologists (2), a pediatric surgeon, a nuclear medicine physicist, a therapeutic radiographer and a parent of a child with neuroblastoma who had received MRT for neuroblastoma (Speaker list in supplementary material). In addition, there was an invited audience of 20 people including clinicians, scientists and parents mirroring the mix of speakers. In addition to questions and debate after each presentation, informal networking continued in the breaks, with the aim of new research proposals and collaborations being created.

**RESULTS**

**Imaging and therapy targeting the norepinephrine transporter**

The physiological pathway which has been most exploited is the norepinephrine transporter, expressed in over 90% of neuroblastoma patients, which can be targeted using mIBG.

[123I]mIBG planar scintigraphy and single photon emission computed tomography (SPECT) computed tomography (CT) is the standard imaging technique for neuroblastoma, including selection of patients for [131I]mIBG therapy (*10*). This two-day procedure is a 45 minute scan requiring general anesthesia (GA) in younger patients performed 24 hours after radiopharmaceutical injection. Thyroid blockade is co-administered to reduce uptake of free iodide by the thyroid gland (*11*). Positron emission tomography (PET)-CT with [18F]fluorodeoxyglucose is recommended when the tumor is [123I]mIBG negative (*12*). However, it is a metabolic tracer not conducive to theragnostics.

PET-CT with [18F]meta fluorobenzylguanidine ([18F]mFBG) is a single-day procedure with scanning an hour after injection, resolution is much greater identifying more lesions, and thyroid blockade is not required (*13*). Due to the short half-life of 18F (110 minutes), national production of the tracer [18F]mFBG may be required because of the potential time taken for international supply lines.

The positron emitter 124I is an alternative to 123I ,and [124I]mIBG can be visualized on PET-CT. The longer half-life (4.2 days) allows sequential scanning over days, and measurement of retention in tissues over time enables prediction of tumor and normal organ radiation doses which would follow [131I]mIBG therapy (*14*).

The introduction of long axis field of view (total body) PET-CT technology with exquisite sensitivity and spatiotemporal resolution expands the technological constraints on the three-way trade-off between image quality, scan duration and radiation dose reduction. This may reduce scan time so that GA may be unnecessary (*15*).

There have been several clinical trials of [131I]mIBG therapy over four decades; mostly early phase studies in refractory or relapsed high-risk neuroblastoma. The main exception is the Children’s Oncology Group (COG) phase III randomized trial ANBL1531 (NCT03126916): a comparison of the addition of [131I]mIBG therapy to standard induction therapy. Recruitment is complete, results are not yet available. Recent clinical trials of MRT are detailed in Table 1.

A review of [131I]mIBG therapy reported response rates varying from 0% to 75% (mean 32%). This was due to very different case mix, highly variable administration schedules, and no use of standardized response criteria (*5*). Another review concluded that [131I]mIBG therapy can be an effective treatment to reduce tumor burden in about one third of patients (*16*).

Administration of [131I]mIBG therapy to children faces various logistic challenges. These include irregularities in radiopharmaceutical supply, the need for specialized inpatient facilities in a pediatric environment, provision for accommodation and training in radiation protection for adult carers, regular staff training, a prolonged admission for radiation protection, radioactive waste storage and disposal, and the requirement for multiple time point scanning, often under GA, for dosimetry. In addition, medical complications require more complicated management when the patient is highly radioactive. Nausea and vomiting are usually prevented with prophylactic antiemetics. Myelosuppression is common, requiring regular blood tests while the child is radioactive necessitating special handling in the laboratory, and may indicate the need for blood and platelet transfusions. For whole body radiation doses exceeding 2 Gy, hematopoietic stem cell transfusion is usually required.

**Administered activity, whole body and tumor dosimetry**

There are different administration schedules in use for MRT. For instance, a fixed administered activity may be used, regardless of the size of the patient. In some studies, the administered activity is adjusted by weight.

However, the amount of radioactivity administered, even if weight-adjusted, does not result in a uniform radiation dose to the whole body (*17*). This is because of differing kinetics between patients, due to a heterogeneous burden of disease, and varying avidity of and retention by neuroblastoma cells for the radiopharmaceutical, which may change even within the same course of treatment (*18*). It may be helpful to standardise whole body dose, as this is a proxy for toxicity (*19*). This can be achieved by initially administering a weight-based activity, measuring the resulting whole body radiation dose received, and administering a second activity calculated to raise the total whole-body dose from the two administrations combined to a desired level (*20*). This method has been used in several clinical trials including MINIVAN (NCT02914405) with a prescribed whole-body dose of 2 Gy to avoid the need for stem cell support, and MIITOP (NCT00960739) and VERITAS (NCT03165292) with a prescribed whole-body dose of 4 Gy (*21*). It is not known if this split administration strategy achieves more favourable outcomes. Even when the whole-body dose is standardized, the tumor dose may vary by an order of magnitude (*22*). This matters, as response relates to tumor dose received (*23*). Accurate tumor dosimetry is therefore highly desirable, despite the additional practical difficulties inherent in younger children such as the need for serial imaging under GA.

**Alternative targets for molecular imaging and radiotherapy in neuroblastoma**

Alternative molecular targets in neuroblastoma can be imaged (Figure 1). The somatostatin receptor, particularly subtype 2 (SSTR2) is frequently expressed (*24*). [68Ga]Ga-DOTATATE or DOTATOC PET CT is used to show and quantify the distribution of somatostatin receptors on neuroblastoma (*25*). Interestingly, sometimes disparate distributions from [123I]mIBG scans are apparent, indicating the phenotypic heterogeneity of different neuroblastoma deposits (*26*).

Demonstration of somatostatin receptor avidity on [68Ga]Ga-DOTATATE PET scans allows treatment with the radiolabelled somatostatin analogue [177Lu]Lu-DOTATATE (*27*). An initial clinical trial showed limited antitumor activity, though several newer trials evaluating [177Lu]Lu-DOTATATE for neuroblastoma are in progress: LuDO-N (NCT04903899) and NEUROBLU-2 (NCT03966651). At present, [177Lu]Lu-DOTATATE MRT for neuroblastoma is experimental, and should only be used in clinical trials.

Neuroblastoma cells also highly express disialoganglioside GD2, which is a well-established immunotherapy target with monoclonal antibodies including dinutuximab, dinutuximab beta and naxitamab (hu3F8) (*28*). Anti-GD2 antibodies have been radiolabelled for theragnostic applications. Radioimmunotherapy using [131I]-3F8 was initially explored in neuroblastoma patients but with dose limiting myelotoxicity (*29*). More recently, [131I]-dinutuximab was evaluated (*30*). In addition to MRT, clinical PET-magnetic resonance (MR) imaging of GD2 expression of neuroblastoma lesions using [64Cu]Cu-dinutuximab beta has recently been reported (*31, 32*) which may allow stratification of anti-GD2 therapies based on tumor lesion GD2 expression in patients.

Finally, neuroblastomas also commonly express B7 homolog 3 (B7-H3) which is a cell surface immunoregulatory glycoprotein. A radiolabelled antibody 8H9 ([131I]omburtamab) has been evaluated mainly in children with CNS relapsed neuroblastoma (NCT03275402) (*33*).

**Radiation sensitizers**

The co-administration of various drugs alongside MRT has been shown in preclinical studies and sometimes clinical studies to enhance its cytotoxicity. This occurs via increasing the amount of DNA damage, inhibiting repair of DNA damage or re-distributing cells into radiation-sensitive phases of the cell cycle. Examples include the camptothecin-derived topoisomerase I inhibitors topotecan and irinotecan (*34*), which both increase DNA damage and inhibit repair (*35*). There is preclinical evidence of synergy with [131I]mIBG therapy (*36*). Combinations of [131I]mIBG therapy with topotecan or irinotecan have been explored in clinical trials (*21, 37*). Preclinical research has shown that the histone deacetylase inhibitor vorinostat increases expression of functional norepinephrine transporter and decreases expression of DNA damage repair proteins in neuroblastoma (*38, 39*). The MIITOP study of [131I]mIBG therapy with topotecan reported an objective response rate of 13%, but there was no comparator arm (*21*). The NANT 2011-01 trial reported objective response rates of 14% for both the [131I]mIBG alone arm and the [131I]mIBG with vincristine and irinotecan arm, and 32% for the [131I]mIBG with vorinostat arm (*37*).

Poly (ADP-ribose) Polymerase (PARP) inhibitors, such as olaparib and talazoparib, also potentiate cytotoxicity in experimental models (*40, 41*). They may have increased benefit in neuroblastoma patients with homologous recombination repair pathway alterations, for example *ATRX* mutations (*42*), or germline *BARD1* variants (*43*). Others have shown that increased levels of oncogene induced replication stress (e.g. *MYCN* amplification (*44*)) also result in preclinical sensitivity to PARP inhibitors. The use of olaparib with [131I]mIBG therapy and subsequent maintenance talazoparib has been reported (*45*). A clinical trial of [131I]mIBG therapy with talazoparib is in preparation.

For optimal outcomes, DNA repair inhibitors which differentially sensitise tumor cells, compared with normal tissue, to radiation damage, are desirable, otherwise the effect is simply equivalent to dose escalation with no change in the therapeutic index. In addition to PARP inhibitors, Polymerase theta (POLQ) inhibitors are in this category, and offer a novel prospect of synergy with MRT, but have yet to be investigated for neuroblastoma (*46, 47*).

**Combinations with immunotherapy**

There is preclinical evidence of a complex interplay between radiation effects and response to immunotherapy (*48*). Empirical support for the concept of MRT potentiating immunotherapy can be found in the significantly superior outcomes of patients with relapsed neuroblastoma who received [131I]mIBG therapy before allogeneic bone marrow transplantation and dinutuximab beta immunotherapy, compared with those treated with allogeneic transplant and immunotherapy only (*49*). One current trial, MINIVAN (NCT02914405), is evaluating treatment of patients with [131I]mIBG therapy prior to double immunotherapy with dinutuximab beta and the anti-programmed cell death protein 1 (PD-1) monoclonal antibody nivolumab. Another trial (NCT03332667) evaluated [131I]mIBG with dinutuximab with and without vorinostat. Results of both trials are awaited.

**Combining external beam and molecular radiotherapy**

External beam radiotherapy (EBRT) to the primary tumor site is part of the standard treatment for high-risk neuroblastoma. However, as most patients have disseminated disease, there is a rationale for combining EBRT with MRT which simultaneously targets metastatic deposits. An important benefit of this combination is that EBRT and MRT have non-overlapping toxicity profiles. This means that it may not be necessary to compromise on the administered dose of either component. Sequencing of the two treatments is likely to be important. For example, preclinical research suggests that external irradiation of a tumor alters blood vessel permeability, which in turn may enhance tumor uptake of subsequently delivered MRT (*50*). Conversely, however, external radiation may provoke intra-tumoral inflammation, fibrosis or an increase in the hypoxic fraction among surviving cells, leading to impaired tumor uptake or reduced radiotoxicity of subsequently administered MRT. While there is currently a dearth of research into the optimisation of EBRT and MRT combinations in neuroblastoma, preclinical research in other tumor types has shown that maximum benefit is usually achieved when the two treatments are given synchronously rather than sequentially (*51*).

A computational system that allows absorbed radiation dose from both sources to be summed, and which considers the different radiobiological effects of both treatments, is needed to safely progress this therapeutic strategy (*52*).

**Alternative radionuclides**

Most MRT to date has involved beta emitting radionuclides such as 131I and 177Lu. Their physical and radiobiological properties are well understood, and they are clearly effective. However alternative radionuclides which emit alpha particles or Auger electrons may have advantages in certain situations.

Alpha particles, emitted by radionuclides including 223Ra, 211At, 212Pb and 225Ac, offer at least two potential advantages over beta emitters. Firstly, they cause many more ionisation events along their path length. This higher linear energy transfer causes greater DNA damage with more double strand breaks, and a lower chance of repair. This means that cells are more likely to be killed. Secondly, their path length is much shorter than that of beta particles, simply a few cell diameters, so a greater proportion of the energy released is located within smaller micrometastases than is the case with, for example, 131I. While an analogue of mIBG labelled with 211At, meta astatobenzylguanidine ([211At]mABG) was first considered for use in neuroblastoma over 30 years ago but not developed further, there has recently been a resurgence of interest in its possible benefits (*6*). The shorter path length of these alpha particles may reduce hospital time and need for lead shielding compared to beta emitters.

Compared with alpha emitters, Auger electrons emitted by radionuclides such as 125I, 201Tl and 111In, have even shorter path lengths, but also have high linear energy transfer. If localized in the nucleus of a cell, and particularly if incorporated into DNA, or on the cell membrane, they are highly toxic. Additionally, Auger electrons may start a strong bystander response leading to cell death (*53*). While an interesting field of research, the use of Auger emitting radiopharmaceuticals has yet to find a place in the MRT of neuroblastoma.

**Radionuclide supply and radiopharmaceutical availability**

One of the biggest challenges facing the development of, and treatment with, MRT for neuroblastoma is the availability of radiopharmaceuticals. For example, [18F]mFBG and [124I]mIBG, mentioned above for imaging use, are not commercially available. There are worldwide shortages of nuclear reactors producing radioisotopes, and many of those which exist are nearing the end of their lives without replacements planned. The academic radiochemistry facilities lack capacity to make all the radiopharmaceuticals which might be useful in a timely way. Even the commercial supply of recognized products like [131I]mIBG has been erratic and unreliable for clinical users, with very late cancellation of orders to the detriment of patient care. This was a major factor in the premature closure of the VERITAS clinical trial previously mentioned. Despite the proven clinical value of [131I]mIBG, the only UK Medicines and Healthcare products Regulatory Agency recognized supplier, GE Healthcare, has stopped supplying it across Europe from the end of 2024. One commercial supplier remains in Europe; whether or not there is sufficient production capacity for all users remains unclear. Previously, there were two [131I]mIBG suppliers in North America.  Production of a no-carrier added formulation has been discontinued by Lantheus and therefore only one supplier remains for all of North America.  Additional sources of production would ensure ongoing, reliable supply for this critical medication across both continents.

A multistakeholder group, *Radionuclides for Health UK*, has been formed to raise awareness of these difficulties, and to campaign for resources for better radionuclide and radiopharmaceutical provision. Its publication *Radionuclide Supply in the UK: A Path to a Cancer Breakthrough* sets out a strategy to address this issue (*54*).

**Patient and Public Involvement and Engagement**

Children with neuroblastoma are the focus of our efforts to improve treatment, and so it is crucial that we listen to the views of their parents who advocate for them (55). Charities are central to this, and work with clinical trials groups both in the UK and internationally. Patient advocates should be included in developing research priorities, and in the design and delivery of clinical trials. In addition, advocates can play an important role in expanding access to theragnostics facilities such that more patients can be treated closer to home. As new facilities are developed, advocates can lend the patient voice to design of patient and family rooms to maximise patient and family comfort during therapy.

**Clinical Service Delivery**

Hospitals which provide theragnostics for children with neuroblastoma must be appropriately equipped and staffed, not simply to provide excellent technical imaging and therapy, but also holistic family centred care. Many families travel very long distances, and are away from home for several weeks at a time. Just as every child is different, so families are different, with varying levels of support available. Adults are required to act as comforters and carers, and their personal radiation exposure must be kept as low as reasonably achievable. They, as well as ward staff, need specific radiation protection guidance and monitoring. Specialist staff, such as therapeutic radiographers, are essential to deliver a high-quality service.

**DISCUSSION**

This symposium brought together an international group of over 40 individuals from a wide range of professional backgrounds, and also patient advocates, all interested in further developing theragnostics for neuroblastoma. There were active discussions, and new preliminary research ideas were generated, which will be considered further. Figure 2 illustrates the range of priorities participants identified.

Neuroblastoma is genetically and phenotypically diverse. This disease heterogeneity is important, and so individualisation should be considered when selecting the most appropriate therapy. One strength of molecular imaging is to identify the better target for the individual patient. The main conclusions were that efforts need to be directed at addressing both logistic constraints and promoting further research in imaging and treatment to optimise clinical outcomes. Clearly increased funding is important, as both aspects require significant investment.

Radiopharmaceutical production needs strengthening, especially for orphan drugs which may be of great value for a small number of patients, but which are not commercially profitable. Similarly, greater academic radiopharmacy capacity is needed to prepare novel compounds in a timely way for research. Additional clinical facilities for treating young children would be advantageous as currently there are too few, resulting in geographical inequity of service provision.

Research priorities include both preclinical endeavours to evaluate innovative ideas, and an expanding portfolio of clinical trials to assess different strategies to improve results including radiosensitisation, radiation and immunotherapy combinations, and novel agents. These will establish evidence and guide sequencing of therapies.

Given the multidisciplinary effort required to move the field forward and to implement theragnostic advances, it is essential that leading individuals from different specialties work together with patient advocates to raise awareness of the potential of molecular radiotherapy, and lobby nationally and through international collaboration for better resourcing.

**CONCLUSION**

Theragnostics is an important area of research and clinical practice as part of the multimodality treatment of neuroblastoma. International multidisciplinary collaboration is they key to advancing understanding of the use of radiopharmaceuticals in the diagnosis and treatment of this childhood cancer of unmet need.

**TABLE 1. Recent molecular radiotherapy trials for neuroblastoma.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Short name****clinicaltrials.gov number** | **Full title****(Organisation)** | **Radiopharmaceutical Trial type****Dates** | **Status** |
| **Completed and published** |
| LuDO | A phase IIa trial of molecular radiotherapy with 177-lutetium DOTATATE in children with primary refractory or relapsed high-risk neuroblastoma. (University of Birmingham) | [177Lu]DOTATATEPhase II 2013-2017 | Published 202027 |
| NANT 2011-01NCT02035137 | Randomized Phase II Pick the Winner Study of 131I-MIBG, 131I-MIBG With Vincristine and Irinotecan, or 131I-MIBG With Vorinostat for Resistant/ Relapsed Neuroblastoma(NANT) | [131I]mIBGRandomized Phase II2014-2019 | Published 202137 |
| MIITOPNCT00960739 | Phase II study of (131) I-metaiodobenzylguanidine with 5 days of topotecan for refractory or relapsed neuroblastoma(Centre Oscar Lambret) | [131I]mIBGPhase II2008-2015 | Published 202321 |
| **Accrual completed – awaiting maturation of data** |
| ANBL1531 NCT03126916 | Testing the Addition of 131I-MIBG or Lorlatinib to Intensive Therapy in People with High-Risk Neuroblastoma (COG) | [131I]mIBGRandomized phase III2018-2024 | Closed to accrual |
| MINIVANNCT02914405 | Phase I Study of 131I mIBG Followed by Nivolumab & Dinutuximab Beta Antibodies in Children With Relapsed/​Refractory Neuroblastoma(University Hospital Southampton) | [131I]mIBGPhase I2018-2024 | Closed to accrual |
| OPTIMUMNCT03561259 | A Phase II, Open Label, Two-Arm Study of Therapeutic Iobenguane (131I) as Single Agent or in Combination With Vorinostat for Recurrent or Progressive High- Risk Neuroblastoma Subjects (Jubilant DraxImage Inc.) | [131I]mIBGNon-randomized Phase II2019-2023 | Closed to accrual |

|  |  |  |  |
| --- | --- | --- | --- |
| VERITASNCT03165292 | Evaluation of 2 Intensification Treatment Strategies for Neuroblastoma Patients With a Poor Response to Induction (SIOPEN) | [131I]mIBGRandomized Phase II2018-2023 | Closed to accrual (terminated prematurely) |

|  |  |  |  |
| --- | --- | --- | --- |
| Omburtamab RadioimmunotherapyNCT03275402 | 131I-omburtamab Radioimmunotherapy for Neuroblastoma Central Nervous System/​Leptomeningeal Metastases(Y-mAbs Therapeutics) | [131I]-omburtamabPhase II2018-2023 | Closed to accrual |
| NANT 2017-01NCT03332667 | MIBG With Dinutuximab +/​- Vorinostat(NANT) | [131I]mIBGPhase I2018-2023 | Closed to accrual |
| **Open and recruiting** |
| LuDO-NNCT04903899 | 177Lutetium-DOTATATE in Children With Primary Refractory or Relapsed High-risk Neuroblastoma(Karolinska institute) | [177Lu]DOTATATEPhase II  | Open since 2021 and recruiting |
| NEUROBLU 02NCT03966651 | A Clinical Study Evaluating the Safety of Peptide Receptor Radionuclide Therapy (PRRT) With 177Lu-DOTA0-Tyr3-Octreotate in Children With Refractory or Recurrent Neuroblastoma Expressing Somatostatin Receptors. (Institut Claudius Regaud) | [177Lu]DOTATATEPhase I | Open since 2023 and recruiting |
| GD2-SADA :177Lu-DOTA complexNCT05130255 | GD2-SADA:177Lu-DOTA Complex in Patients With Solid Tumors Known to Express GD2 (Y-mAbs Therapeutics) | [177Lu] two-step radioimmunotherapy Phase 1 | Open since 2022 and recruiting. Amended 2024 to include neuroblastoma aged 18 or older  |
| **Planned** |
| MINT | A biomarker enriched phase I/II clinical trial of 131I-mIBG therapy with talazoparib for the treatment of relapsed and/or refractory neuroblastoma.(University of Birmingham) | [131I]mIBGPhase I/II | Funded, pending regulatory approval |

Selected clinical trials of molecular radiotherapy, past, present and future. Abbreviations: COG, Children’s Oncology Group; NANT, New Approaches to Neuroblastoma Therapy; mIBG, meta iodobenzylguanidine; SADA, self-assembling and disassembling; SIOPEN, European Neuroblastoma Clinical Trials Group.

**FIGURE 1**

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**Imaging and therapeutic radiopharmaceuticals for treating neuroblastoma and their molecular targets.** a) NET targeted by radioiodinated and radiofluorinated metabenzylguanidine analogues. b) SSTR2 can be targeted by the radiolabelled peptides DOTATOC and DOTATATE for PET imaging and therapy. c) GD2 has been targeted using a variety of radiolabelled antibodies, 3F8, Dinutuximab (ch14.18) and Dinutuximab beta (ch14.18/CHO). As well as using the (SADA) bispecific antibody for two-step pretargeted radioimmunotherapy. d) Finally, B7-H3 has been targeted with the radio-iodinated antibody, Omburtamab

Abbreviations: NET, norepinephrine transporter; SSTR2, somatostatin receptor 2; GD2, disialoganglioside; B7-H3, B7 Homolog 3. *Created in BioRender. Gawne, P. (2023)* BioRender.com/j40j096

**FIGURE 2**



**Suggestions for further research.** Word cloud to show ideas about where future efforts should be focused. Larger font size indicates a greater number of responses. Abbreviations: EBRT, external beam radiotherapy; mABG, meta astatobenzylguanidine; mFBG, meta fluorobenzylguanidine; mIBG metaiodobenzylguanidine; MRT, molecular radiotherapy; PROMs, patient reported outcome measures.

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**CONFLICTS OF INTEREST**

PJG reports travel expenses from Recordati Rare Diseases. SGD reports consulting fees from Amgen, Bayer, InhibRx, and Jazz and travel expenses from Loxo, Roche, and Salarius.

**ABBREVIATIONS**

Ac Actinium

At Astatine

B7-H3 B7 homolog 3

COG Children’s Oncology Group

CT Computed tomography

Cu Copper

DNA Deoxyribonucleic acid

EBRT External beam radiotherapy

F Fluorine

Ga Gallium

GA General anesthesia

GD2 Disialoganglioside

Gy Gray

I Iodine

In Indium

Lu Lutetium

MA Massachusetts

mABG meta astatobenzylguanidine

mFBG meta fluorobenzylguanidine

mIBG meta iodobenzylguanidine

MR Magnetic resonance

MRT Molecular radiotherapy

NANT New Approaches to Neuroblastoma Therapy

NET Norepinephrine transporter

NHS National Health Service

Pb Lead

PET Positron emission tomography

PARP Poly (ADP-ribose) polymerase

PD-1 programmed cell death protein 1

POLQ Polymerase theta

PROMs Patient reported outcome measures

Ra Radium

SADA Self-assembling and disassembling

SIOPEN European Neuroblastoma Clinical Trials Group

SPECT Single photon emission computed tomography

SSTR2 Somatostatin receptor subtype 2

Tl Thallium

UCL University College London

UK United Kingdom

USA United States of America

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| KEY POINTS:QUESTION: How can research and clinical practice in nuclear medicine imaging and molecular radiotherapy for neuroblastoma be enhanced and improved for patient benefit?Pages 4, 5PERTINENT FINDINGS: Carefully focused multi-professional and multi-disciplinary collaboration may determine clearer priorities for research and clinical practice in neuroblastoma theragnostics.Pages 6-14IMPLICATIONS FOR PATIENT CARE: Use of novel radiopharmaceuticals in clinical trials, aligned with the use of innovative technologies, may improve outcomes in this pediatric cancer of unmet need.Pages 16, 17 |

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