Role of Medical Internal Radiation Dose (MIRD) 2020 in evolving paradigms of use for internal emitters for radiotherapy of human cancers

Clinical radiotherapy is always a tradeoff between cure and toxicity, finding the acceptable therapeutic balance. Radiation oncologists, using external beam radiation to control primary tumors, have worked for decades to find this balance between cure of local tumor and normal tissue toxicity. In the last decade, based on advances in radiation dosimetry, and in instrumentation, they can now consistently achieve controlled radiation delivery that provides local tumor control while minimizing radiation toxicity to normal surrounding tissues. For targeted radionuclide therapy, key questions arise: *How can we accurately and practically measure tumor and normal tissue dosimetry of internal emitters? What are the radiation absorbed doses that are achievable by tumors and can be tolerated by normal radiosensitive tissues?* Now is the time to plan for a similar balance with targeted radiotherapy of internal emitters.

The new *Primer 2020* (S-1) "reflects the dramatic evolution of the field of nuclear medicine, more specifically, of molecular imaging and radiopharmaceutical therapy and of the complementary advances in technology, radiochemistry, and radiation biology" …It also emphasizes the important distinction between dosimetry for risk assessment in diagnostic imaging (Primer 1) versus dosimetry for treatment efficacy and toxicity evaluation related to therapy (Primer 2020). Accordingly, guidance on treatment planning for radioimmunotherapy, radiopeptide therapy, and radiopharmaceutical therapy generally is provided. The MIRD schema (Primer 1) long the standard in the field for "guidance on internal dosimetry-related tasks that may be faced by nuclear medicine and other healthcare professionals, including the dosimetric requirements for regulatory

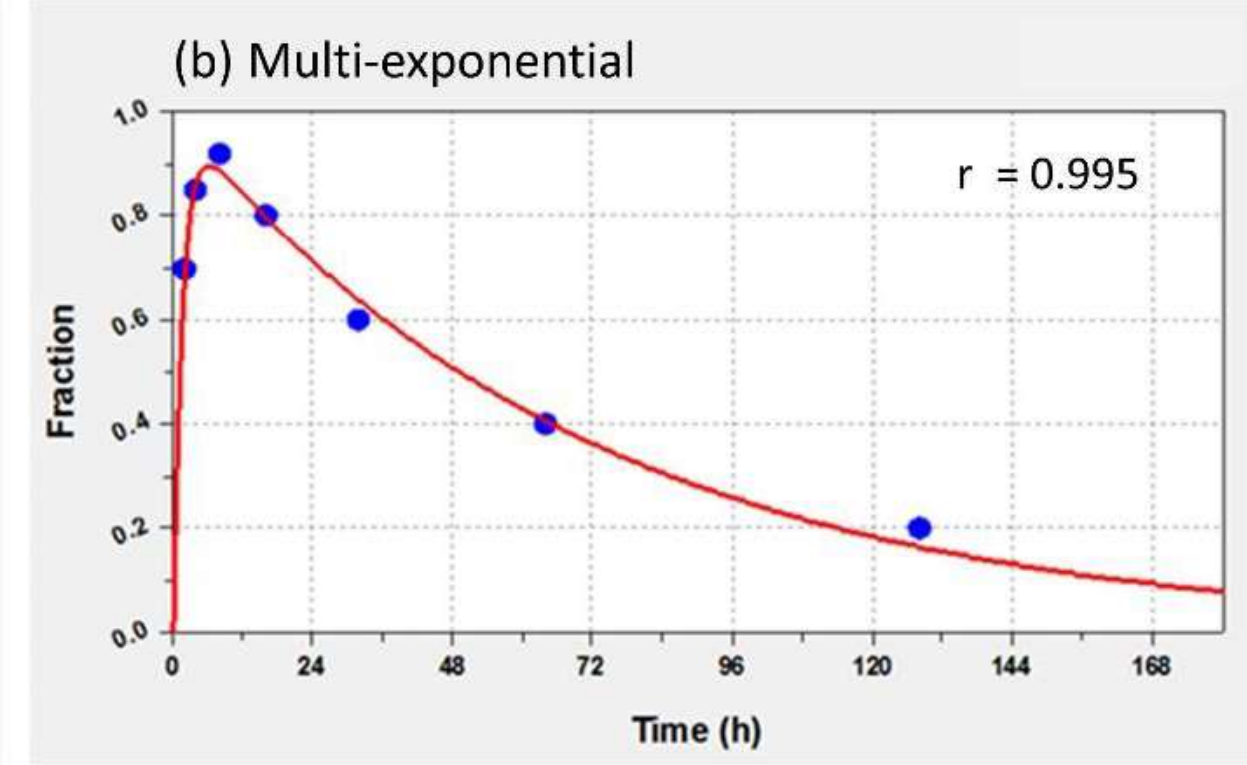
approval of new radiopharmaceuticals" has now expanded its applications to include details about how tumor specific radiopharmaceutical time-activity data can be acquired clinically and pre-clinically - for example, for patient-specific dosimetry in the context of radiopharmaceutical therapy - and how acquired data are analyzed to yield time-integrated activities (Chapter 5). For further details please consult MIRD *Primer 2020* (see Supplemental Figure 1 for an additional example).

As a metaphor for planning safe and efficacious targeted radiotherapies, we look for an "optimized treatment path," in which we take the narrow road between guardrails of 1) efficacy: cGy to tumor sufficient for complete responses and even cures, and 2) safety: high enough TIs (therapeutic indices) for sensitive tissues like lung, kidney, and especially bone marrow, to avoid lasting radiation damage, whether deterministic or stochastic (see below). We remind the reader that that relative biologic effectiveness of external beam radiation, and β^- rays from internal emitters, is quite similar: around 1 (ICRP Publication 92).

S-1 MIRD Primer 2020: A Complete Guide to Radiopharmaceutical Dosimetry

Prepared by the MIRD Committee of the Society of Nuclear Medicine and Molecular Imaging: Rachel M. Bartlett, Wesley E. Bolch, A. Bertrand Brill, Yuni K, Dewaraja, Frederic H. Fahey, Darrell R. Fisher, Robert F. Hobbs, Roger W. Howell, Ruby F. Meredith, Joseph G. Rajendrana, George Sgouros (Immediate Past Chairman), Pat Zanzonico (Chairman).

Supplemental Figure 1. From Figure 5.8b of the MIRD Primer 2020. Data points obtained from regions of interest using quantitative imaging of a hypothetical tumor metastasis showing an uptake followed by exponential clearance. Data were uncorrected for radioactive decay. Function fit by least squares regression to the data were a sum of 2 exponentials with 4 parameters (a, b, c, and d) of the form $y = a \exp(-bt) + c \exp(-dt)$. Analytic solution of the integral of the curve is a/b + c/d. Integral can be converted to μC-hour/gram * total mCi dose administered. Radiation absorbed dose in cGy is obtained by simple multiplication of D decay constant in gm-rad/μCi-hr for the radionuclide in question. In this case, the shape of the curve and kinetics would be typical for ^{131}I-localization into a well differentiated thyroid cancer metastasis after oral administration during radioactive iodine therapy.



SUPPLEMENTAL Table 1. Select milestones in PRID/PRIT development

Year	Milestone	Preclinical or clinical?	Target	Radioisotope	References
1986-1988	Anti-chelate mAb radiopharmaceutical delivery (passive tumor targeting)	Preclinical	N/A	^{111}In	(*1,2*)
1987	In vivo biotin-streptavidin PRID	Preclinical	N/A	^{111}In	(*3*)
1988	Application of multivalent haptens during in vivo anti-tumor antigen/anti-hapten BsAb PRID	Preclinical	Murine Lyb8.2	^{125}I ^{111}In	(*4*)
1990	First-in-human studies of biotin-streptavidin PRID	Clinical	CEA	^{111}In	(*5*)
1991	First-in-human studies of BsAb PRID	Clinical	CEA	^{111}In	(*6*)
1991	First-in-human studies of biotin-streptavidin PRIT	Clinical	CEA	^{90}Y	(*7*)
mid-1990's	First-in-human studies of affinity enhancement system BsAb PRID	Clinical	CEA	^{111}In	(*8,9*)
2010	First-in-human studies of dock-and-lock BsAb PRID	Clinical	CEA	^{111}In	(*10*)
2010	In vivo bioorthogonal inverse electron demand Diels-Alder (IEDDA) PRID	Preclinical	TAG72	^{111}In	(*11*)
2017-2018	In vivo bioorthogonal IEDDA PRIT	Preclinical Preclinical	CA19.9 CA19.9 gp72	^{177}Lu ^{225}Ac ^{212}Pb	(*12-14*)
2019	Anti-tumor/anti-Pb-DOTAM BsAb PRIT	Preclinical	CEA	^{212}Pb	(*15*)
2021	BsAb self-assembling and disassembling PRIT platform	Preclinical	GD2	^{177}Lu ^{225}Ac	(*16*)

SUPPLEMENTAL TABLE 2. Overview of select PRID/PRIT clinical trials

Year	First Author(s)	Phase	Disease	PRIT method	Radiohapten(s)	Target/Antibodies	References
1990	Kalofonos	?	lung	biotin-streptavidin	^{111}In-biotin	CEA/HMfg1-St	(*5*)
1991	Stickney	?	colorectal	BsAb	^{111}In-EOTUBE	CEA/ZCE-025	(*6*)
1991	Paganelli	?	multiple (GI, thyroid, lung, breast)	biotin-streptavidin	^{111}In-biotin	CEA/FO23C5	(*7*)
1993	Le Doussal	?	colorectal	BsAb	^{111}In-DPTA-TL, ^{111}In-DPTA	CEA/F6-734	(*8*)
1993	Peltier	I,II	thyroid	BsAb	^{111}In-DPTA-TL	CEA/F6-734	(*9*)
1996, 1998	Bardies, Barbet	?	thyroid	BsAb	^{131}I-,^{111}In-DPTA-TL	CEA/F6-734	(*17,18*)
1999	Kraeber-Bodere	I,II	thyroid	BsAb	^{131}I-DPTA-TL	CEA/F6-734	(*19*)
1999	Breitz	?	multiple (GI, lung, bladder, breast, ovarian)	biotin-streptavidin	^{90}Y-biotin	EpCAM/NR-LU-10	(*20*)
2000	Knox	II	colorectal	biotin-streptavidin	^{90}Y-biotin	EpCAM/NR-LU-10	(*21*)
2000	Weiden	I,II	lymphoma	biotin-streptavidin	^{186}Re-, ^{111}In-, ^{90}Y-biotin	CD20/C2B8-StA (Rituximab StA)	(*22*)
2003	Kraeber-Bodere	I	lung	BsAb	^{131}I-DTPA	CEA/hMN14-m734	(*23*)
2004	Forero	I	lymphoma	biotin-streptavidin	^{111}In-, ^{90}Y-biotin	CD20/B939FP	(*24*)
2005	Shen	I	colorectal	biotin-streptavidin	^{111}In-, ^{90}Y-biotin	TAG72/CC49	(*25*)
2006	Kraeber-Bodere	I	thyroid	BsAb	^{131}I-DTPA	CEA/hMN14-m734	(*26*)
2006	Chatal	Two successive phase I studies	thyroid	BsAb	^{131}I-DTPA	CEA/hMN14-m734 vs F6-734	(27)
2013, 2014	Schoffelen	I	colorectal	DNL BsAb	^{111}In-, ^{177}Lu-IMP288	CEA/TF2	(*28*)
2015	Bodet-Milin	I	lung	DNL BsAb	^{111}In-, ^{177}Lu-IMP288	CEA/TF2	(*29*)
2016	Bodet-Milin	I	thyroid	DNL BsAb	^{68}Ga-IMP288	CEA/TF2	(*30*)
2020	Rousseau	?	breast	DNL BsAb	^{68}Ga-IMP288	CEA/TF2	(*31*)
2021	Bodet-Milin	?	thyroid	DNL BsAb	^{68}Ga-IMP288	CEA/TF2	(*32*)
2021	Touchefeu	?	colorectal	DNL BsAb	^{68}Ga-IMP288	CEA/TF2	(*33*)

References

1. Goodwin DA, Meares CF, McTigue M, David GS. Monoclonal antibody hapten radiopharmaceutical delivery. *Nucl Med Commun.* 1986;7:569-580.

2. Goodwin DA, Meares CF, McCall MJ, McTigue M, Chaovapong W. Pre-targeted immunoscintigraphy of murine tumors with indium-111-labeled bifunctional haptens. *J Nucl Med.* 1988;29:226-234.

3. Hnatowich DJ, Virzi F, Rusckowski M. Investigations of Avidin and Biotin for Imaging Applications. *J Nucl Med.* 1987;28:1294-1302.

4. Le Doussal JM, Martin M, Gautherot E, Delaage M, Barbet J. In vitro and in vivo targeting of radiolabeled monovalent and divalent haptens with dual specificity monoclonal antibody conjugates: enhanced divalent hapten affinity for cell-bound antibody conjugate. *J Nucl Med.* 1989;30:1358-1366.

5. Kalofonos HP, Rusckowski M, Siebecker DA, et al. Imaging of tumor in patients with indium-111-labeled biotin and streptavidin-conjugated antibodies: preliminary communication. *J Nucl Med.* 1990;31:1791-1796.

6. Stickney DR, Anderson LD, Slater JB, et al. Bifunctional antibody: a binary radiopharmaceutical delivery system for imaging colorectal carcinoma. *Cancer Res.* 1991;51:6650-6655.

7. Paganelli G, Magnani P, Zito F, et al. Three-step monoclonal antibody tumor targeting in carcinoembryonic antigen-positive patients. *Cancer Res.* 1991;51:5960-5966.

8. Le Doussal JM, Chetanneau A, Gruaz-Guyon A, et al. Bispecific monoclonal antibody-mediated targeting of an indium-111-labeled DTPA dimer to primary colorectal tumors: pharmacokinetics, biodistribution, scintigraphy and immune response. *J Nucl Med.* 1993;34:1662-1671.

9. Peltier P, Curtet C, Chatal JF, et al. Radioimmunodetection of medullary thyroid cancer using a bispecific anti-CEA/anti-indium-DTPA antibody and an indium-111-labeled DTPA dimer. *J Nucl Med.* 1993;34:1267-1273.

10. Sharkey RM, Rossi EA, McBride WJ, Chang C-H, Goldenberg DM. Recombinant bispecific monoclonal antibodies prepared by the dock-and-lock strategy for pretargeted radioimmunotherapy. *Semin Nucl Med*. 2010;40:190-203.

11. Rossin R, Verkerk PR, van den Bosch SM, et al. In vivo chemistry for pretargeted tumor imaging in live mice. *Angew Chem Int Ed Engl.* 2010;49:3375-3378.

12. Houghton JL, Membreno R, Abdel-Atti D, et al. Establishment of the In Vivo Efficacy of Pretargeted Radioimmunotherapy Utilizing Inverse Electron Demand Diels-Alder Click Chemistry. *Mol Cancer Ther.* 2017;16:124-133.

13. Poty S, Carter LM, Mandleywala K, et al. Leveraging Bioorthogonal Click Chemistry to Improve (225)Ac-Radioimmunotherapy of Pancreatic Ductal Adenocarcinoma. *Clin Cancer Res.* 2019;25:868-880.

14. Shah MA, Zhang X, Rossin R, et al. Metal-Free Cycloaddition Chemistry Driven Pretargeted Radioimmunotherapy Using alpha-Particle Radiation. *Bioconjug Chem.* 2017;28:3007-3015.

15. Frost S, Pichard A, Haas A, et al. Preclinical evaluation of CEA-PRIT, a novel pretargeted alpha therapy regimen for treatment of CEA-positive tumours with Pb-212 [abstract]. *Eur J Nucl Med Mol Imaging.* 2019;46:S56-S57.

16. Santich BH, Cheal SM, Ahmed M, et al. A Self-Assembling and Disassembling (SADA) Bispecific Antibody (BsAb) Platform for Curative Two-step Pretargeted Radioimmunotherapy. *Clin Cancer Res.* 2021;27:532-541.

17. Bardies M, Bardet S, Faivre-Chauvet A, et al. Bispecific antibody and iodine-131-labeled bivalent hapten dosimetry in patients with medullary thyroid or small-cell lung cancer. *J Nucl Med.* 1996;37:1853-1859.

18. Barbet J, Peltier P, Bardet S, et al. Radioimmunodetection of medullary thyroid carcinoma using indium-111 bivalent hapten and anti-CEA x anti-DTPA-indium bispecific antibody. *J Nucl Med.* 1998;39:1172-1178.

19. Kraeber-Bodéré F, Bardet S, Hoefnagel CA, et al. Radioimmunotherapy in medullary thyroid cancer using bispecific antibody and iodine 131-labeled bivalent hapten: preliminary results of a phase I/II clinical trial. *Clin Cancer Res.* 1999;5:3190s-3198s.

20. Breitz HB, Fisher DR, Goris ML, et al. Radiation absorbed dose estimation for 90Y-DOTA-biotin with pretargeted NR-LU-10/streptavidin. *Cancer Biother Radiopharm.* 1999;14:381-395.

21. Knox SJ, Goris ML, Tempero M, et al. Phase II trial of yttrium-90-DOTA-biotin pretargeted by NR-LU-10 antibody/streptavidin in patients with metastatic colon cancer. *Clin Cancer Res.* 2000;6:406-414.

22. Weiden PL, Breitz HB, Press O, et al. Pretargeted radioimmunotherapy (PRIT) for treatment of non-Hodgkin's lymphoma (NHL): initial phase I/II study results. *Cancer Biother Radiopharm.* 2000;15:15-29.

23. Kraeber-Bodere F, Faivre-Chauvet A, Ferrer L, et al. Pharmacokinetics and dosimetry studies for optimization of anti-carcinoembryonic antigen x anti-hapten bispecific antibody-mediated pretargeting of Iodine-131-labeled hapten in a phase I radioimmunotherapy trial. *Clin Cancer Res.* 2003;9:3973S-3981S.

24. Forero A, Weiden PL, Vose JM, et al. Phase 1 trial of a novel anti-CD20 fusion protein in pretargeted radioimmunotherapy for B-cell non-Hodgkin lymphoma. *Blood.* 2004;104:227-236.

25. Shen S, Forero A, LoBuglio AF, et al. Patient-specific dosimetry of pretargeted radioimmunotherapy using CC49 fusion protein in patients with gastrointestinal malignancies. *J Nucl Med.* 2005;46:642-651.

26. Kraeber-Bodere F, Rousseau C, Bodet-Milin C, et al. Targeting, toxicity, and efficacy of 2-step, pretargeted radioimmunotherapy using a chimeric bispecific antibody and 131I-labeled bivalent hapten in a phase I optimization clinical trial. *J Nucl Med.* 2006;47:247-255.

27. Chatal JF, Campion L, Kraeber-Bodere F, et al. Survival improvement in patients with medullary thyroid carcinoma who undergo pretargeted anti-carcinoembryonic-antigen radioimmunotherapy: a collaborative study with the French Endocrine Tumor Group. *J Clin Oncol.* 2006;24:1705-1711.

28. Schoffelen R, Boerman OC, Goldenberg DM, et al. Development of an imaging-guided CEA-pretargeted radionuclide treatment of advanced colorectal cancer: first clinical results. *Br J Cancer.* 2013;109:934-942.

29. Bodet-Milin C, Ferrer L, Rauscher A, et al. Pharmacokinetics and Dosimetry Studies for Optimization of Pretargeted Radioimmunotherapy in CEA-Expressing Advanced Lung Cancer Patients. *Front Med (Lausanne).* 2015;2:84.

30. Bodet-Milin C, Faivre-Chauvet A, Carlier T, et al. Immuno-PET Using Anticarcinoembryonic Antigen Bispecific Antibody and 68Ga-Labeled Peptide in Metastatic Medullary Thyroid Carcinoma: Clinical Optimization of the Pretargeting Parameters in a First-in-Human Trial. *J Nucl Med.* 2016;57:1505-1511.

31. Rousseau C, Goldenberg DM, Colombie M, et al. Initial Clinical Results of a Novel Immuno-PET Theranostic Probe in Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer. *J Nucl Med.* 2020;61:1205-1211.

32. Bodet-Milin C, Faivre-Chauvet A, Carlier T, et al. Anti-CEA Pretargeted Immuno-PET Shows Higher Sensitivity Than DOPA PET/CT in Detecting Relapsing Metastatic Medullary Thyroid Carcinoma: Post Hoc Analysis of the iPET-MTC Study. *J Nucl Med.* 2021;62:1221-1227.

33. Touchefeu Y, Bailly C, Frampas E, et al. Promising clinical performance of pretargeted immuno-PET with anti-CEA bispecific antibody and gallium-68-labelled IMP-288 peptide for

imaging colorectal cancer metastases: a pilot study. *Eur J Nucl Med Mol Imaging.* 2021;48:874-882.