Significant contributions of Dr Chandra Sekhar Bal in Medical-Sciences (Nuclear Medicine) based on the work done in India

Detailed Work

My work has significantly impacted the field of radionuclide theranostics, spanning over three decades and leading to important advancements in the treatment of differentiated thyroid cancer (DTC). Notably, my contributions influenced two major recommendations in the American Thyroid Association (ATA) 2015 Thyroid Cancer Guidelines. In a landmark clinical trial published in JCEM, I examined the optimal dose of radioiodine for remnant ablation in DTC patients. Conducted between July 1995 and January 2002, the study included 509 patients and evaluated different doses of ^{131}I for remnant ablation, starting at 15 mCi and increasing in increments of 5 mCi up to 50 mCi. The trial demonstrated that patients receiving at least 25 mCi of ^{131}I had a significantly higher rate of successful remnant ablation compared to those receiving lower doses. The overall ablation rate across all groups was 77.6%, with no significant differences in outcome for doses between 25, 30 and 50 mCi. This study provided critical data on the effectiveness of radioiodine doses for remnant ablation and established that any activity of 25–50 mCi is sufficient for achieving successful ablation in most patients. (***C. S. Bal,*** *Ajay Kumar, G. S. Pant.* ***Radioiodine Dose for Remnant Ablation in Differentiated Thyroid Carcinoma: A Randomized Clinical Trial in 509 Patients, The Journal of Clinical Endocrinology & Metabolism, Volume 89, Issue 4, 1 April 2004, Pages 1666–1673, https://doi.org/10.1210/jc.2003-03115) Impact factor: 6.1.***

Additionally, my recent research published in The Journal of Clinical Endocrinology & Metabolism explored the use of cumulative radioiodine activities in metastatic DTC patients, providing critical insights into optimizing treatment efficacy while mitigating potential adverse effects. This research has refined treatment protocols, improving outcomes for patients with challenging forms of thyroid cancer**.** ***[****Bharadwaj MS, Ballal S,* ***Bal C. Optimal Cumulative I-131 Activity in Metastatic Differentiated Thyroid Cancer: Balancing Efficacy and Adverse Events. J Clin Endocrinol Metab. 2024 Jan***

12:dgae024. doi: 10.1210/clinem/dgae024. Epub ahead of print. PMID: 38214553.]Impact factor: 6.1

At AIIMS, New Delhi, my work with pediatric thyroid cancer patients has been instrumental, particularly in studying the clinical characteristics and long-term outcomes of those undergoing radioiodine therapy. I have extensively compared outcomes across different age groups and played a pivotal role in advancing dynamic risk-stratification for pediatric DTC. This has led to the development of more targeted and age-appropriate treatment protocols for younger populations affected by thyroid cancer.

At AIIMS, New Delhi we are lucky to have access to treat both adult and pediatric DTC. Thus, my contributions to the field, particularly my research in pediatric thyroid cancer and my exploration of optimal radioiodine doses, have had a profound impact on treatment strategies and have significantly improved patient outcomes in both adult and pediatric populations.

Over the last one decade, my research was primarily focus on two key areas: advancing therapeutic strategies for radioiodine-refractory differentiated thyroid cancer (RR-DTC) and optimizing novel treatment approaches for medullary thyroid cancer (MTC). These areas need innovative radionuclide therapies, targeted agents, and the integration of precision medicine to improve patient outcomes in these challenging thyroid cancer subtypes.

My research in neuroendocrine tumor (NET) imaging began in 2006, followed by work in ^{177}Lu-SSTR agonist peptide receptor radionuclide therapy (PRRT) in 2007. ***[Clin Nucl Med. 2017, (impact factor: 10.6)].*** I have been a pioneer in advancing the use of PRRT for advanced-stage neuroendocrine tumors, particularly through the clinical application of radiolabeled somatostatin analogs.

One of my significant contributions has been the development and assessment of [^{225}Ac]Ac-DOTATATE, a targeted alpha therapy that has become a cornerstone in NET treatment. My work, was adjudged as international best abstract of the year twice by North American Society of Nuclear medicine and Molecular Imaging 2021 &2022 in their Annual meetings, and published as feature article and images from the manuscript featured on the cover of the *Journal of Nuclear Medicine*, ***[J Nucl Med.***

2022 Jul 21:jnumed.122.264043. doi: 10.2967/jnumed.122.264043, (Impact factor: 11.06)] demonstrated the effectiveness of this therapy in improving long-term survival and quality of life in patients with advanced or refractory neuroendocrine tumors even those who have progressed on ^{177}Lu-PRRT.

In particular, my research has provided critical real-world data on survival outcomes in patients with metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) treated with a combination of [^{225}Ac]Ac-DOTATATE and Capecitabine. This study offers key insights for clinical management, shaping treatment strategies for NETs and providing practical guidance for long-term patient care.

Key Contributions:

- **Innovation in Combination Therapy**: This was one of the first studies to assess the combined use of [^{225}Ac]Ac-DOTATATE and Capecitabine, introducing a novel therapeutic approach that improved tumor control and survival in metastatic GEP-NETs.
- **Long-term Efficacy Evidence**: The research highlighted the potential for extended survival with this combination therapy, offering hope to patients with limited treatment options and emphasizing the durability of targeted alpha therapies in neuroendocrine tumors.
- **Real-world Management Insights**: By focusing on real-world clinical practices, the study helped bridge the gap between controlled clinical trials and everyday patient care, offering actionable strategies for the effective administration of these therapies.
- **Survival Benefit Correlation**: The study established a clear correlation between the use of [^{225}Ac]Ac-DOTATATE and improved overall survival, reinforcing its role in the treatment of metastatic GEP-NETs and supporting more personalized treatment plans based on survival data.
- **Foundation for Future Research**: These findings have paved the way for future clinical trials to further evaluate combination therapies, potentially setting new standards of care for advanced neuroendocrine tumors.

I have also expanded the treatment landscape by incorporating antagonist-based PRRT for NETs that are unresponsive to agonist-based therapies. My work includes head-to-head studies comparing the efficacy of [^{68}Ga]Ga-DOTANOC and [^{68}Ga]Ga-DATA^{5m}-LM4 PET/CT imaging in NET patients, providing valuable insights into the performance of different imaging agents. [***Pharmaceuticals (Basel). 2024 Feb 22;17(3):275. doi: 10.3390/ph17030275. PMID: 38543061; PMCID: PMC10974918.(Impact factor: 4.3)]***

My research in radionuclide therapy for prostate cancer has focused on pioneering and advancing the use of [177Lu]Lu-PSMA-617 and [225Ac]Ac-PSMA-617. These targeted therapies have demonstrated significant efficacy in treating metastatic castration-resistant prostate cancer (mCRPC), offering promising outcomes, particularly for patients with limited therapeutic options.

Key Contributions:

1. Clinical Efficacy and Safety of [177Lu]Lu-PSMA-617:
My studies have thoroughly documented the therapeutic efficacy of [177Lu]Lu-PSMA-617, showcasing its potential to substantially reduce tumor burden with tolerable side effects. This radioligand therapy targets the prostate-specific membrane antigen (PSMA) expressed on prostate cancer cells. In patients with mCRPC, [177Lu]Lu-PSMA-617 has been shown to deliver precise doses of radiation to tumors, leading to improved disease control and symptom relief. These studies have underscored the safety of this therapy, with most adverse events being mild and manageable, enabling its adoption in clinical practice for mCRPC patients who have progressed on conventional treatments.

2. Long-Term Outcomes of [177Lu]Lu-PSMA-617:
By extending the research to long-term follow-up, my work has demonstrated the durability of [177Lu]Lu-PSMA-617 therapy, with significant progression-free survival (PFS) and overall survival (OS) improvements in treated patients. The therapy's capacity to offer long-term disease control has reinforced its utility in the clinical management of mCRPC, potentially delaying the need for more aggressive interventions.

3. Development and Advancement of [225Ac]Ac-PSMA-617 Therapy: In parallel, my research on [225Ac]Ac-PSMA-617 has provided groundbreaking insights into the enhanced therapeutic potential of this alpha-emitting radionuclide. Actinium-225's short-range, high-energy alpha particles that results in double-stranded DNA-breaks make it particularly effective in targeting and destroying cancer cells, even in cases of low PSMA expression. Unlike the beta/gamma radiation, 225Ac alpha particle breaks DNA-double strand, independent of hypoxic conditions of tumor microenvironment. The localized radiation damage minimizes collateral effects on surrounding healthy tissues, which is crucial in patients with metastatic disease. My work has illustrated that [225Ac]Ac-PSMA-617 offers a potent treatment option, particularly for patients with mCRPC who have become refractory to [177Lu]Lu-PSMA-617, improving their survival prospects.

4. Dosimetry and Dosing Protocol Optimization: Refining the dosimetry protocols for both [177Lu] and [225Ac] PSMA therapies has been a critical component of my work. By carefully calibrating radiation doses based on individualized patient characteristics, I have contributed to the development of safer, more effective treatment regimens that balance therapeutic benefit with the risk of adverse effects. These refined protocols have optimized patient outcomes by enhancing the specificity of tumor targeting while preserving healthy organ function.

5. Expansion into Hormone-Sensitive Prostate Cancer: Additionally, I have expanded the therapeutic use of [177Lu]Lu-PSMA-617 to patients with high-volume metastatic hormone-sensitive prostate cancer. This represents a broadening of the clinical application of PSMA-targeted radioligand therapy, potentially shifting the treatment paradigm earlier in the disease course and offering hope to a wider group of prostate cancer patients.

Published Research:

- Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, **Bal C.** *Post-therapeutic dosimetry of 177Lu-DKFZ-PSMA-617 in the treatment of patients with metastatic castration-resistant prostate cancer.* Nucl Med Commun. 2017.

- Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, **Bal C.** *177Lu-DKFZ-PSMA-617 therapy in metastatic castration-resistant prostate cancer: safety, efficacy, and quality of life assessment.* Eur J Nucl Med Mol Imaging. 2017.

- Ballal S, Yadav MP, Satapathy S, Raju S, Tripathi M, Damle NA, Sahoo RK, **Bal C**. *Long-term survival outcomes of salvage [225Ac]Ac-PSMA-617 targeted alpha therapy in patients with PSMA-expressing end-stage metastatic castration-resistant prostate cancer: a real-world study.* Eur J Nucl Med Mol Imaging. 2023.

- Sathekge MM, Lawal IO, **Bal C,** Bruchertseifer F, Ballal S, Cardaci G, Davis C, Eiber M, Hekimsoy T, Knoesen O, Kratochwil C, Lenzo NP, Mahapane J, Maserumule LC, Mdlophane AH, Mokoala KMG, Ndlovu H, Pant V, Rathke H, Reed J, Sen IB, Singh A, Sood A, Tauber R, Thakral P, Yadav MP, Morgenstern A.*Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study.* Lancet Oncol. 2024.

Conclusion:

These contributions underscore the transformative impact of radionuclide therapies on prostate cancer treatment, particularly for patients with advanced, resistant disease. The success of [177Lu]Lu-PSMA-617 and [225Ac]Ac-PSMA-617 therapies continues to drive innovation in nuclear medicine and oncology, offering new hope for patients facing limited treatment options.

As the co-inventor of the [177Lu]Lu-DOTAGA.Glu.FAPi dimer (***USA Patent Application No.: 18/567,891 dated December 7, 2023; Confirmation no.: 4027 dated May 6, 2024***), I have pioneered a novel therapeutic strategy targeting the tumor microenvironment, which has significantly broadened the scope of radionuclide therapy. This dimer targets fibroblast activation protein (FAP) in cancer-associated fibroblasts (CAFs), a key component of the tumor stroma that supports cancer growth and invasion. The innovation offers a promising new treatment for advanced cancers that are resistant to conventional therapies.

Key Contributions:

1. Development of [177Lu]Lu-DOTAGA.Glu.FAPi Dimer:

The [177Lu]Lu-DOTAGA.Glu.FAPi dimer has transformed the therapeutic landscape by enhancing the binding affinity and improving the pharmacokinetics of the FAP-targeting agent. As a homodimer, it exhibits superior tumor retention compared to monomeric FAP inhibitors, allowing for more precise targeting of the tumor microenvironment. This molecule not only accumulates in cancer cells but also disrupts the supporting stroma, leading to improved tumor control.

This therapeutic innovation has demonstrated efficacy in a wide variety of malignancies, including radioiodine-refractory thyroid cancers, medullary thyroid cancer (MTC), advanced prostate cancer, neuroendocrine tumors (NETs), and other refractory solid tumors such as triple-negative breast cancer (TNBC) and glioblastoma multiforme (GBM). The FAP-targeting approach has opened the door to new treatment possibilities for patients who previously had limited options.

2. Advancements in Imaging for Radioiodine-Resistant Thyroid Cancers and MTC:

My research has contributed significantly to the imaging of radioiodine-refractory differentiated thyroid cancers (RR-DTCs) and MTCs, utilizing novel fibroblast activation protein inhibitors (FAPIs). The introduction of [68Ga]Ga-DOTA.SA.FAPi as a diagnostic imaging agent offers a distinct advantage over conventional imaging techniques. My head-to-head comparison studies, such as those involving [68Ga]Ga-DOTA.SA.FAPi and [18F]F-FDG PET/CT, have demonstrated substantial improvements in diagnostic accuracy and patient monitoring, leading to better-informed treatment strategies in nuclear medicine.

For instance, in MTC patients, [68Ga]Ga-DOTA.SA.FAPi has shown superior sensitivity in detecting recurrent or residual disease compared to other imaging modalities. This work has not only refined imaging protocols but has also provided critical insights into the tumor biology of thyroid cancers.

3. Breakthrough in Therapy for Radioiodine-Resistant Thyroid Cancers:

Through my co-invention of the [177Lu]Lu-DOTAGA.FAPi dimer, I have opened new therapeutic pathways for the treatment of thyroid cancers that are resistant to radioiodine therapy. This innovation represents the first major advance in thyroid cancer treatment since the introduction of radioiodine

therapy over eight decades ago. By leveraging the tumor microenvironment's susceptibility to FAP inhibition, [177Lu]Lu-DOTAGA.FAPi dimer offers a targeted approach to treat patients whose tumors no longer respond to traditional therapies. This theranostic agent has exhibited promising outcomes in terms of tumor control, progression-free survival, and quality of life improvement in patients with aggressive thyroid malignancies.

Published Research:

- *Martin M, Ballal S, Yadav MP,* ***Bal C,*** *Van Rymenant Y, De Loose J, Verhulst E, De Meester I, Van Der Veken P, Roesch F. Novel Generation of FAP Inhibitor-Based Homodimers for Improved Application in Radiotheranostics.* ***Cancers (Basel). 2023****. This study outlines the design and synthesis of homodimeric FAP inhibitors, including [177Lu]Lu-DOTAGA.Glu.FAPi, highlighting their enhanced efficacy and pharmacokinetics in cancer models.*

- *Ballal S, Yadav MP, Roesch F, Raju S, Satapathy S, Sheokand P, Moon ES, Martin M, Awarwal S, Tripathi M,* ***Bal C.*** *Head-to-Head Comparison of [68Ga]Ga-DOTA.SA.FAPi and [68Ga]Ga-DOTANOC PET/CT Imaging for the Follow-Up Surveillance of Patients with Medullary Thyroid Cancer.* ***Thyroid. 2023****. This paper presents a comprehensive comparison between FAPi and somatostatin analog (DOTANOC) PET/CT imaging, demonstrating the superior diagnostic capability of FAPi in MTC.*

- *Ballal S, Yadav MP, Roesch F, Satapathy S, Moon ES, Martin M, Wakade N, Sheokand P, Tripathi M, Chandekar KR, Agarwal S, Sahoo RK, Rastogi S,* ***Bal C.*** *Head-to-Head Comparison of [68Ga]Ga-DOTA.SA.FAPi with [18F]F-FDG PET/CT in Radioiodine-Resistant Follicular-Cell Derived Thyroid Cancers.* ***Eur J Nucl Med Mol Imaging. 2023****. This pivotal study shows the increased accuracy of FAPi PET/CT over FDG in identifying lesions in RR-DTC, leading to better treatment planning and disease management.*

- *Ballal S, Yadav MP, Raju S, Roesch F, Martin M, Tripathi M,* ***Bal C.*** *[177Lu]Lu-DOTAGA.Glu.(FAPi)2 Radionuclide Therapy: a New Treatment Option for Patients with*

Glioblastoma Multiforme. ***Nucl Med Mol Imaging 2024 Feb;58(1):32-34****. https://doi.org/10.1007/s13139-023- 00814-5.*

- *Yadav MP, Ballal S, Martin M, Roesch F, Satapathy S, Moon ES, Tripathi M, Gogia A,* ***Bal C.*** *Therapeutic potential of [177Lu]Lu-DOTAGA-FAPi dimers in metastatic breast cancer patients with limited treatment options: efficacy and safety assessment.* ***Eur J Nucl Med Mol Imaging. 2024 Feb;51(3):805-819.*** *doi: 10.1007/s00259-023-06482-z. Epub 2023 Nov 7. PMID: 37932560.*

- *Ballal S, Yadav MP, Moon ES, Roesch F, Kumari S, Agarwal S, Tripathi M, Sahoo RK, Mangu BS, Tupalli A,* ***Bal C.*** *Novel Fibroblast Activation Protein Inhibitor-Based Targeted Theranostics for Radioiodine-Refractory Differentiated Thyroid Cancer Patients: A Pilot Study.* ***Thyroid. 2022 Jan;32(1):65-77.*** *doi: 10.1089/thy.2021.0412. Epub 2021 Dec 31. PMID: 34641705.*

Conclusion:

As a co-inventor of [177Lu]Lu-DOTAGA.Glu.FAPi dimer and a leader in the field of radionuclide therapy, my work has significantly advanced the treatment of refractory cancers by targeting the tumor microenvironment. The development of this dimer and the comparative imaging studies in thyroid cancer patients mark critical milestones in the evolution of cancer theranostics, offering new hope for patients who have exhausted conventional treatment options.

Ongoing clinical trials

I am currently actively conducting two important clinical trials as the Principal Investigator for the projects. The first is titled "A Prospective, Randomized, Controlled, Open-label, Multicenter Trial to Evaluate Efficacy, Safety, and Patient-Reported Outcomes of Peptide Receptor Radionuclide Therapy (PRRT) with Lutetium (177Lu) Edotreotide Compared to Best Standard of Care in Patients with Well-Differentiated Aggressive Grade 2 and Grade 3, Somatostatin Receptor-positive (SSTR+), Neuroendocrine Tumors of Gastroenteric or

Pancreatic Origin (COMPOSE)." The duration of this study is 5 years, running from December 14, 2021, to December 14, 2026. The second study is "A Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Dabrafenib plus Trametinib in Previously Treated Patients with Locally Advanced or Metastatic, Radioactive Iodine Refractory BRAFV600E Mutation-Positive Differentiated Thyroid Cancer," funded by Novartis Healthcare Pvt Ltd, I oversee a study with the protocol number CDRB436J12301 and project code N2275. This project commenced on May 13, 2022, and is scheduled to run through May 12, 2026, spans a duration of four years.

Throughout my career, my research has been extensively published in leading journals and has encompassed key areas in theranostics, including treatment efficacy, safety assessments, and the exploration of novel systemic targeted therapies. My active involvement in international collaborations and clinical studies illustrates my capability to lead clinical programs focused on advancing nuclear medicine and improving patient outcomes through cutting-edge theranostic approaches.

C. S. Bal, M.D., D.N.B., MA(Economics), D.Sc.(H.C.)
FAMS, FNASc., FASc., FNA
Professor & Head, Department of Nuclear Medicine,
All India Institute of Medical Sciences, New Delhi, India, 110029.
E-mail: drcsbal@gmail.com , PHONE: +91-11-26593530; FAX: +91-11-26588993