Celebrating 80 years Anniversary of Radioiodine for Use in Thyroid Cancer and Perspectives for Theranostics

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Abstract

In 1942, eighty years ago, Dr. Hertz first conducted radioiodine (RAI) therapy for thyroid cancer patient followed by the successful diagnosis of thyroid disorders using RAI. In 2022, memorial 80 years later, alpha emitter astatine (^{211}At), an analogue for iodine, was successfully administered to a patient with refractory thyroid cancer in Japan as a phase-1 clinical trial (first-in-human). Over the past two decades, the use of ^{68}Ga labeled peptides for somatostatin receptor (SSTR)-targeted PET imaging followed by beta or alpha emitters labeled SSTR-analogues for peptide receptor radionuclide therapy (PRRT) has demonstrated remarkable success in the management of neuroendocrine neoplasms. In addition, theranostics targeting prostate specific membrane antigen (PSMA) has dramatically changed the management and treatment of advanced prostate cancer patients. Novel radionuclides and new targets, ligands targeting the tumor microenvironment, optimized peptides and antibodies, combinations of radioligands with immunotherapy, radioprotectors and radiosensitizers as well as new delivery strategies are currently systematically explored. Now the dream of conquering cancer, that Saul Hertz began eight decades ago is coming to fruition.

Radionuclide Therapy for Thyroid Cancer

Dr. Saul Hertz (1905-1950) was the first to diagnose thyroid disorders by radioiodine (RAI) (Fig.1) and went on to advance the use of RAI to successfully treat thyroid disorders [1,2]. Dr. Hertz envisioned, “My new research project is in Cancer of the Thyroid which I believe, holds the key to the larger problem of Cancer in general.” Hertz’s use of uptake testing, dosimetry, RAI as a tracer and biomarker are essential to his targeted approach.

In 1942, eighty years ago, Dr. Hertz conducted RAI thyroid carcinoma studies that were reported to the Markle Foundation, funding his research. He was quoted predicting,” ...demand is expected for radioactive iodine and as research develops in the field of cancer and leukemia, for other radioactive medicines." Dr. Hertz advanced the use of RAI to diagnose and successfully treat thyroid cancer as well as exploring the use of other radioisotopes and hormones to treat additional forms of cancer. The Harvard Crimson, featured the headline "Hertz to Use Nuclear Fission in Cure for Cancer" [3].

Almost 80 years after the start of RAI treatment for fighting thyroid cancer by Dr. Hertz, astatine (^{211}At) has been attracting attention as an analogue for iodine. ^{211}At is an accelerator-produced alpha-emitter (half-life: 7.2 hours) which shows - as a halogen element - a similar behavior to iodine. It accumulates in the normal thyroid and in thyroid cancer via uptake enabled by the sodium iodide symporter (NIS) [4,5]. Using xenograft models of differentiated thyroid cancer, substantial treatment effects were seen by inducing more double-strand breaks of deoxyribonucleic acid (DNA) compared to ^{131}I [5,6]. In Japan, a phase-1 clinical trial (first-in-human) has been conducted since Nov. 2021

(NCT05275946) [7]. [^{211}At]NaAt was successfully administered to a patient refractory to RAI in 2022 - 80-years after the first RAI treatment by Dr. Saul Hertz. Targeted alpha therapy using ^{211}At seems to be a promising approach to further enhance the potential of radionuclide therapy in nuclear medicine.

Progress of Theranostics beyond RAI

Today's renaissance in Theranostics began with the treatment using ^{90}Yttrium-DOTATOC [8,9]. Since then, Radiomolecular Precision Oncology has been driven by rapid advances in novel diagnostics and therapeutic interventions, with dramatically expanded radiopharmaceuticals toolbox over the last few years. As part and integral in the current era of precision oncology, theranostics aims to identify the appropriate molecular targets in neoplasms (diagnostic tool), so that the optimal ligands and radionuclides (therapeutic tool) with favorable labeling chemistry can be selected for personalized management of a specific disease, taking into consideration the specific patient, and subsequently monitor treatment response for personalized cancer care. The rapid development and availability of new isotopes and agents has fundamentally changed the landscape for radiomolecular targeted therapy.

Over the past two decades, the use of ^{68}Ga labeled peptides for somatostatin receptor (SSTR)-targeted PET imaging followed by beta emitters like ^{177}Lu and ^{90}Y or alpha-emitters like ^{213}Bi, ^{225}Ac and ^{212}Pb labeled SSTR-analogues for peptide receptor radionuclide therapy (PRRT) has demonstrated remarkable success in the management of neuroendocrine neoplasms and paved the way to other theranostics indications. PRRT lends a significant benefit in PFS in

metastasized NENs as compared to other treatment modalities and quality of life is significantly improved [10].

In addition, theranostics targeting prostate specific membrane antigen (PSMA) has dramatically changed the management and treatment of advanced prostate cancer patients (Fig.2). ^{177}Lu-PSMA – first used early in 2013 [11] - has been shown to be safe and effective with appropriate selection/follow-up of patients by ^{68}Ga- or ^{18}F-PSMA PET/CT. A prospective, randomized, controlled study (the VISION trial) demonstrated prolonged overall survival compared to the standard treatment alone in advanced metastatic castration resistant prostate cancer patients [12].

While beta-emitters have demonstrated efficacy, alpha-emitters have a 100-fold higher LET. Remarkable results have been achieved by switching non-responders from ^{177}Lu- to ^{225}Ac-PSMA demonstrating excellent results in refractory cases of beta-therapy [13]. Recent experiences indicate that the combination of ^{225}Ac and ^{177}Lu labeled PSMA ligands for TANDEM treatments are feasible, safe, and effective, and also suggest a potential synergistic effect.

FAP is overexpressed on cancer-associated fibroblasts (CAFs) in over 90% of all malignancies. The worldwide first clinical experience of FAP-targeted peptide targeted radionuclide therapy (PTRT) using ^{177}Lu-FAP-2286 has been reported [14] and improved peptides for PTRT (e.g., 3BP-3940) are currently explored for a theranostic approach applying ^{68}Ga-3BP-3940 for PET/CT imaging and selection of the patients for PTRT with ^{177}Lu, ^{90}Y, ^{225}Ac and combinations of these radioisotopes for TANDEM-PTRT. The initial clinical results of 3BP-3940

PTRT provide evidence for the feasibility of radiomolecular precision theranostics in a number of advanced, therapy-refractory adenocarcinomas.
The combination of radioligand therapy with immunotherapy (e.g., immune check point inhibitors like PD-L1 mAb) is a novel promising approach that could reprogram the tumor microenvironment (TME) from “cold” to “hot”, i.e., to make low immunoactivity tumors sensitive to therapy (RadioVaccination).
Novel radionuclides (e.g., ^{212}Pb, ^{211}At, Terbium and other radioisotopes) and new targets, ligands targeting the tumor microenvironment, optimized peptides and antibodies, combinations of radioligands with immunotherapy, radioprotectors and radiosensitizers as well as new delivery strategies are currently systematically explored [15,16].
Personalized, molecular radiotherapy of many different malignancies, tailored to the individual patient in a PRECISION ONCOLOGY setting (including genetics and omics) is becoming more and more a clinical reality, and large patient populations are expected to be in the mainstream of future applications.
The dream of conquering cancer, that Saul Hertz began eight decades ago is coming to fruition.

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Fig.1

The picture of Dr. Saul Hertz (right) demonstrating the measurement of thyroid uptake in a patient using the multi-scaler. It was the beginning of theranostics.

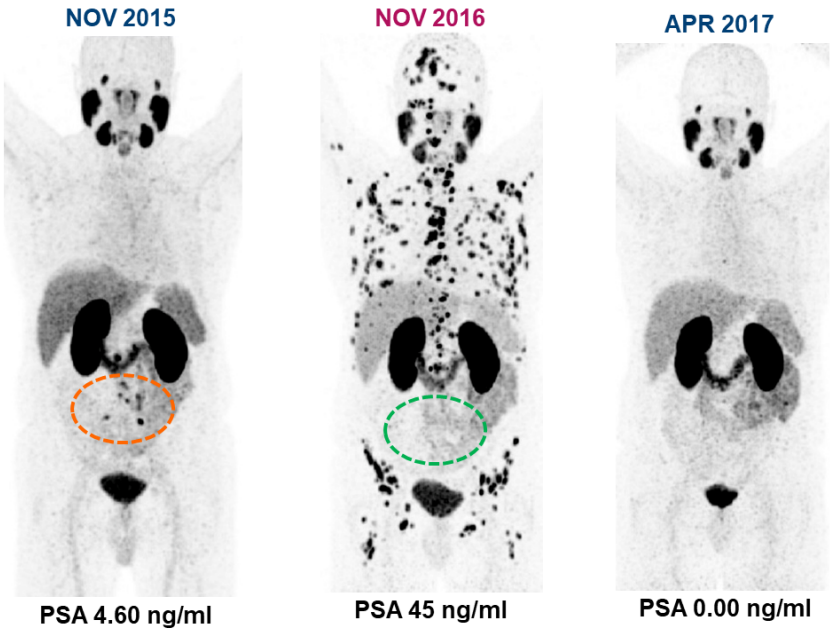

Fig. 2

62-year-old patient with metastatic prostate carcinoma after surgery, radiotherapy and tumor progression despite hormone therapy (PSA increase from <1 to 4.6 ng/ml). PSMA-PET/CT (left) showed lymph node metastases in the abdomen (see circle). Costly hormone blockade (Abiraterone/Zytiga) and repeated external beam radiotherapy were performed.

1 year later, PSA had risen to 45 ng/ml and PSMA PET/CT (middle) now revealed extensive metastasis throughout the skeletal system with the exception of the irradiated lymph nodes (green circle). This patient had two cycles of ^{177}Lu-PSMA I&T therapy.

Several months later, PSMA PET/CT control (right) revealed a complete regression of the metastases and the serum PSA was no longer measurable. The patient is still alive today.