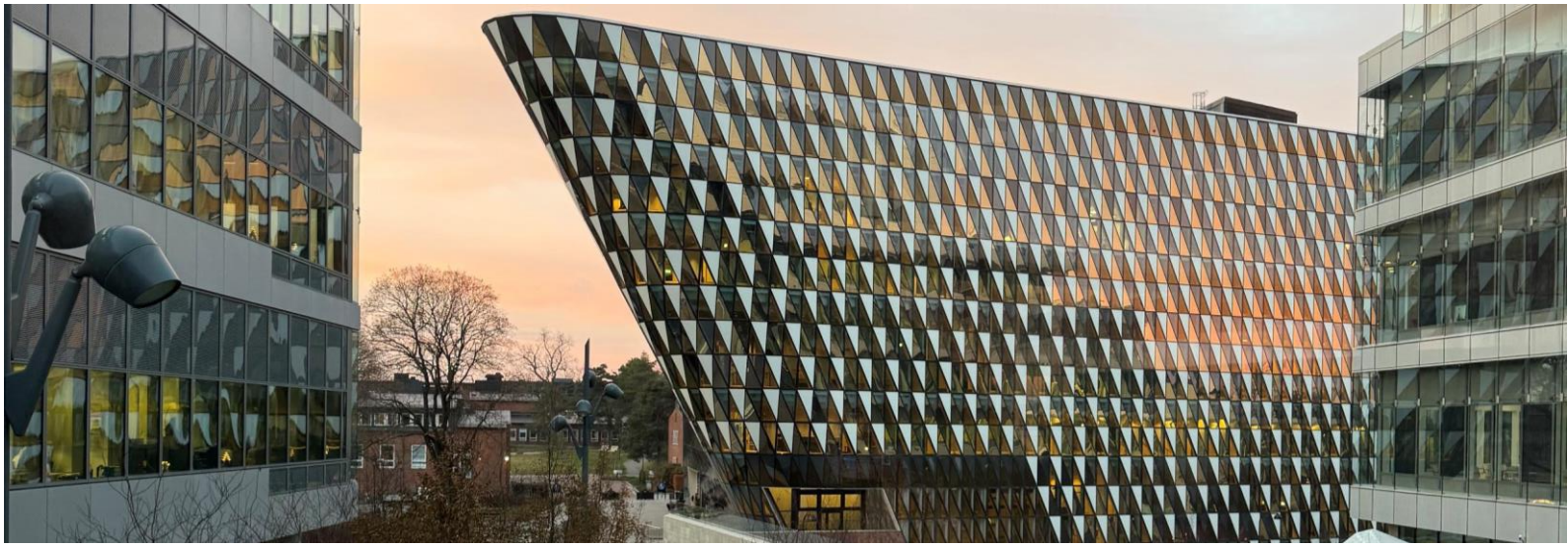

THERANOSTICS TRIAL CENTER INAUGURATION SYMPOSIUM
MAY 5, 2025

ABSTRACT BOOKLET

THERANOSTICS TRIAL CENTER
INAUGURATION SYMPOSIUM

KAROLINSKA UNIVERSITY HOSPITAL
SUNE BERGSTRÖMS AULA

5th May 2025

State-of-the-art overview of theranostics: use in clinical practice and ongoing trials

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Abstract

Theranostics has rapidly transitioned from a research concept to a pillar of precision oncology, integrating diagnostic imaging with targeted radionuclide therapy. This talk reviews approved theranostic pairs ^{68}Ga-DOTATATE/^{177}Lu-DOTATATE in neuroendocrine tumors and ^{68}Ga-PSMA-11/^{177}Lu-PSMA-617 in prostate cancer, summarizing key clinical efficacy, safety data, and real-world outcomes. Emerging applications in novel targets and next-generation alpha-emitters (such as ^{225}Ac-labelled compounds) are highlighted alongside ongoing multicenter trials (NETTER-2, VISION-2, COMPETE) that explore optimized patient selection, dosimetry personalization, and combination strategies with immunotherapies. Advances in quantitative imaging, radiomics, and AI-driven dosimetry are underscored as critical enablers for standardized reporting and multidisciplinary collaboration. Looking ahead, harmonized protocols and data sharing will be essential to accelerate translation and broaden patient access to these life-extending treatments.

Development of protein-based theranostics pairs from an industrial perspective

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Abstract

In patient molecular diagnostic targeting of disease to assess therapeutic potential, followed by administration of the therapeutic agent itself using the theranostic concept, is scientifically appealing and holds promise for more precise patient management. From a practical industrial perspective the concept may, however, be discussed. Breast cancer is a major cause of cancer related morbidity among women and will be used as an example to discuss development of protein-based theranostic pairs from an industrial perspective. HER2 is an important oncogenic driver in a large subset of breast cancers. The Affibody based HER2 specific imaging agent tezatabep matraxetan has demonstrated pharmacological access to the target in women with metastatic disease. The therapeutic drug ABY-271 is incorporating the same targeting vector with a biodistribution enhancing albumin binder and the payload lutetium-177 and is entering clinical trials for targeted radioligand therapy.

Development of radiopharmaceutical therapy in pediatric neuroblastoma

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Abstract

Background and aims

Radiopharmaceutical therapy with ^{131}I-mIBG has been widely used as a second line therapy in neuroblastoma since the 1980's. Alternative radioligands targeted at the SSTR2 receptor are now being assessed in several ongoing clinical trials. We are currently leading a multicenter, phase II, single arm, two stage clinical trial assessing the efficacy of a dosimetry-guided, higher activity schedule of ^{177}Lu-DOTATATE in relapsed or refractory high-risk neuroblastoma (LuDO-N). The trial is sponsored by the Karolinska University Hospital, and it has opened in 7 European countries with a combined population of 196 million.

Methods

^{177}Lu-DOTATATE treatment is delivered in 2 doses, 2 weeks apart, at Karolinska and at the Prinses Máxima Center. The aim was to administer ^{177}Lu-DOTATATE, corresponding to a cumulative whole-body dose of 2.4 Gy, but not exceeding a renal dose of 23 Gy. A weight-based activity of 200 MBq/kg is used for the first dose and the second dose is adjusted based on dosimetry. Response evaluation is performed at 1 and 4 months after end-of-treatment according to the revised INRC criteria. Follow-up for survival will continue for 5 years.

Results

The first stage of the trial has been completed with 14 patients aged 2-15 years, from 6 European countries included and treated. 182 AEs and 5 SAEs have been recorded, and 4 patients have died of disease. A stem cell re-infusion has been required in 2 cases. Objective responses have been recorded in the soft tissue and bone marrow compartments and disease stabilization has also been observed. A stop/go decision for the second stage is expected in May 2025.

Conclusions

^{177}Lu-DOTATATE is well tolerated with limited toxicity. Detailed data on efficacy will be disclosed upon trial completion.

INVITED SPEAKER
MARIKA NESTOR, PROFESSOR

THERANOSTICS TRIAL CENTER
INAUGURATION SYMPOSIUM

Translating innovation: Advancing the cancer radiopharmaceutical 177Lu-AKIR001 to clinical trials

Marika Nestor

Professor in Biomedical Radiation Science, Department of Immunology, Genetics and Pathology, Uppsala University

Chief Executive Officer Akiram Therapeutics

Abstract

Expanding radiopharmaceutical therapy beyond traditional targets, 177Lu-AKIR001 combines precision antibody engineering with localized radiation to tackle CD44v6-positive cancers. Exceptional preclinical results show potent tumor eradication and minimal off-target effects, paving the way for ongoing clinical trials. This presentation follows the journey from molecular design to first-in-human translation.

Physicist perspective – dosimetry of new radiotheranostic products

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Abstract

The numbers of diagnostic and therapeutic nuclear medicine agents under investigation are rapidly increasing, and both novel emitters and novel carrier molecules require careful selection of dosimetry procedures. This talk will provide a short introduction to different emitters and carrier molecules, as well as potential dosimetric solutions. Some recommendations from the “EANM guidance document: dosimetry for first-in-human studies and early phase clinical trials” from 2024 will be included. While the focus is on clinical settings, it will give perspectives on both clinical and preclinical dosimetry for new radiotheranostics.

Astatine-211 and beyond

Stig Palm

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Abstract

Astatine-211 (^{211}At) with a half-life of 7.2 hours is one of the candidates for targeted alpha therapy (TAT). Advantages, compared to most suggested alternatives, include (1) a near-instant 100% delivery of an alpha-particle with each decay; (2) simultaneous delivery of characteristic X-rays that facilitates quantification and gamma-camera imaging; (3) unlimited raw material (of stable Bi-209) for production via the ^{209}Bi(α,2n)^{211}At production route; and (4) daughter elements (^{207}Bi, ^{210}At and ^{210}Po) that do not pose any radiation safety concern for normal clinical use.

Development is today hindered by (1) relatively low access to nearby production; (2) challenges in radiochemistry; (3) uncertainties in quantification; (4) lack of large-scale industrial funding; in addition to a general stigma for work with alpha-emitters.

A completed European COST project (NOAR) originally formed to address the various challenges has now been fused to the world astatine community (WAC). Two European IHI and one Euramet project are currently focusing on At-211 therapies.

Completed clinical trials have been reported from USA, (East) Germany and Sweden. Countries with on-going trials include Japan. Many others have declared interest and are awaiting regulatory approval.

As with all radiation therapy, the radiation absorbed dose to tumour must be optimized with respect to absorbed dose to critical healthy tissues. Therefore, ^{211}At holds most promise for loco-regional therapy of single cells or micrometastases. Intra-thecal therapy with ^{211}At would theoretically be highly beneficial for a small group of neuroblastoma

patients. In Gothenburg (Sweden), we have clinical experience on using ^{211}At for loco-regional (intraperitoneal) therapy of recurrent ovarian cancer. Since some patients are still alive 15+ yrs following treatment, possible long-term risks need to be evaluated.

Advances and future perspectives of ^{161}Tb-labeled radiopharmaceuticals

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Abstract

In recent years, radioligand therapy, has garnered growing interest for the treatment of disseminated cancer, largely due to the approval of ^{177}Lu-based radiopharmaceuticals for neuroendocrine neoplasms and metastasized prostate cancer. Despite these successes, radioligand therapy remains insufficiently effective in achieving a durable response. Targeted alpha therapy using ^{225}Ac-based radiopharmaceuticals offers significantly greater potency, however, it may be associated with severe side effects. At the Center for Radiopharmaceutical Sciences, our research has focused on the development and investigation of terbium-161, a promising new radionuclide with unique properties to enable more effective treatment of micrometasases without increasing the risk of damaging healthy tissue. This presentation will provide an overview of the development of ^{161}Tb-based radiopharmaceuticals from the initial stage of terbium-161 production to the ongoing clinical Phase I studies. It will also address the opportunities and challenges associated with the application of terbium-161 and related radiopharmaceuticals in preclinical research and clinical trials.

New Possibilities with Whole-body PET/CT cameras

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Abstract

Recently long axial field-of-view (LAFOV) positron emission tomography (PET) scanners have been introduced into the clinic. Compared with conventional short axial field-of-view systems, these new scanners have a larger axial coverage of the body and, thereby, a substantially higher system sensitivity. This provides new opportunities for applying PET in clinical practice. Some examples are reduction of scan time duration for example in intensive care unit patients; reduction of the amount of radiotracer administered to the patient, which is very important when imaging younger patients or pregnant women; longitudinal or delayed imaging for using short- and long-lived radiotracers; and applications of whole-body dynamic imaging, facilitating pharmacokinetic modelling. In addition to this, the total dose to the patient can also lowered by applying low mAs, and a thin filter during CT acquisition needed for attenuation correction of PET images. New emerging techniques, such as imaging with multiple radiotracers will also be addressed. The main objective of this presentation is to highlight these opportunities and to indicate future directions with LAFOV PET from a clinical perspective at the University Medical Center Groningen (UMCG).

A new SPECT agent for PSMA visualization, [^{99m}Tc]Tc-BQ0413: preclinical evaluation and preliminary results of Phase I clinical study

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Introduction

Development of radiopharmaceuticals for the SPECT imaging of PSMA might improve the availability of PCa diagnostics. We have designed a molecule BQ0413 and performed preclinical and Phase 1 clinical evaluation of imaging properties of [99mTc]Tc-BQ0413.

Methods

BQ0413was labeled with Tc-99m and studied in vitro in PSMA-expressing cells. In vivo biodistribution and tumor targeting were studied in mice bearing PSMA-expressing xenografts. Dosimetry was estimated in NMRI mice. [99mTc]Tc-BQ0413 was studied in a single-centre diagnostic Phase I open-label exploratory study. A whole body planar scintigraphy and SPECT/CT imaging were performed 2, 4, and 6 h after administration of 50, 100, or 150 μg (680 ± 140 MBq) of [99mTc]Tc-BQ0413 in five PCa patients.

Results

[99mTc]Tc-BQ0413 bound specifically to PC3-pip cells with affinity of 33 ± 15 pM. The tumor uptake (38 ± 6 %IA/g in PC3-pip) was dependent on PSMA expression. The dosimetry estimations predicted an effective dose of 0.0018 mSv/MBq. In patients, all injections of [99mTc]Tc-BQ0413 were well tolerated. The elimination was predominantly renal. Average effective doses were 0.007 ± 0.001, 0.0049 ± 0.0003, 0.0062 ± 0.0008 mSv/MBq for 50, 100, and 150 μg/injection respectively. With given activity, the radionuclide-associated dose burden per patient was 4-7 mSv/study. Uptake of [99mTc]Tc-BQ0413 in primary tumors was identified in all patients (SUVmean increased from 3.4 ± 1.4 [1.15–4.82] for 50 μg/dose to 5.1 ± 1.2 [3.86-7.01] for 150 μg/dose). Uptake in lymph node and bone metastases was the highest at 100 μg/dose (SUVmean 29.6 ± 28.9 [12.34-62.99] and 20.0 ± 12.3 [6.41-30.29]).

Conclusions

[99mTc]Tc-BQ0413 demonstrated specific binding to PSMA with binding affinity in low picomolar range. The results of the Phase I study showed that injections of [99mTc]Tc-BQ0413 were well-tolerated, safe and associated with low absorbed doses. SPECT/CT imaging using [99mTc]Tc-BQ0413 enabled visualization of primary prostate cancer lesions, as well as lymph nodes and bone metastases.

Real-time characterization of 177Lu-DOTATATE binding, internalization and excretion

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Introduction

The efficacy of molecular radiotherapy is highly influenced by cellular binding and trafficking of radiopharmaceuticals. However, methodologies to study these, often complex, interactions in a dynamic manner are limited. Therefore, this study aimed to explore how real-time interaction analysis on cells can be applied to quantify the binding rate constants of complex biological systems as well as gain understanding of the dynamics of cellular processes. In particular, the goals is to deepen the knowledge of the binding and trafficking of 177Lu-Tyr3-DOTA-octreotate (177Lu-DOTATATE) to somatostatin receptors (SSTRs) on cancer cells in vitro.

Methods

The interaction between 177Lu-DOTATATE and cancer cells was studied in real-time using LigandTracer, with varying concentrations and incubation times. Non-internalizing settings (e.g. formalin fixation or lowered assay temperature) were compared to internalizing conditions. The obtained real-time interaction curves were analysed with kinetic binding models to evaluate binding rate constants. The distribution between internalized and membrane-bound 177Lu-DOTATATE was quantified using acid wash. Inhibitors of receptor trafficking were applied to investigate intracellular sorting of the ligand-receptor complex.

Results

177Lu-DOTATATE displayed a heterogeneous binding pattern, with two distinct interactions corresponding to affinities of approximately 0.5 and 25 nM. The interaction pattern was highly influenced by addition of pertussis toxin, indicating the identified interactions were connected to G protein activity. Internalization of 177Lu-DOTATATE exhibited rapid kinetics, 82% of the total bound ligands were internalized after 30 minutes

incubation. However, approximately 60% of the internalized ligands were recycled back out to the cell surface and replaced by new ligands within 3 hours.

Conclusion

These results exemplify how combining real-time binding assays with kinetic modelling allows quantification of cellular binding, internalization and excretion of radiopharmaceuticals. Deepening the understanding of radiopharmaceutical trafficking can improve several aspects of radionuclide therapy, including decision-making in drug development and dosimetry calculations.

[^{68}Ga]Ga-ABY-025 PET in HER2-positive breast cancer: assessment of small axillary lesions

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Introduction

[68Ga]Ga-ABY-025 PET may function as a useful tool for quantification and treatment response prediction in advanced stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC). This study aims to further assess [68Ga]Ga-ABY-025 PET for staging, highlighting potential pitfalls and changes in uptake patterns associated with previous treatments.

Methods

[68Ga]Ga-ABY-025 PET and [18F]FDG PET images from 50 patients with biopsy confirmed HER2 positive breast cancer were examined. Each patient underwent both scans within 1 week. A second [18F]FDG PET was performed following 2 courses of HER2-targeted treatment to assess metabolic response.

Results

Three patients presented with a more extensive local spread which was only detectable using [68Ga]Ga-ABY-025 PET. Based on [68Ga]Ga-ABY-025 PET findings, disease extent was reassessed in two of the three cases, both of which had lobular carcinoma, and resulted in modifications in treatment plans. All three patients showed early metabolic response, with two achieving complete response after HER2-targeted therapy. Two other patients showed elevated [18F]FDG PET uptake near the thyroid with low [68Ga]Ga-ABY-025 PET uptake. Biopsies excluded malignancy but were inconclusive. Two other patients who received the COVID19 vaccine shortly prior to PET scans showed high uptake on [18F]FDG PET in lymph nodes ipsilateral to the vaccine injection site, but not on [68Ga]Ga-ABY-025 PET. In the entire cohort, [68Ga]Ga-ABY-025 physiological uptake in the thyroid and axillary sweat glands was inversely correlated to

the number of previous treatments.

Conclusion
[68Ga]Ga-ABY-025 PET provided additional information that, in conjunction with [18F]FDG PET findings, helped in accurate staging, particularly in cases with small harder to detect lesions. It also helped reduce false positive results as [68Ga]Ga-ABY-025 uptake spared non-malignant inflammatory lesions.

Targeting brain tumours with radiolabelled chlorotoxin, a scorpion venom peptide

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Introduction

Chlorotoxin (CTX) is a 36-amino acid peptide found in the venom of the deathstalker scorpion (Leiurus quinquestriatus). Being a neurotoxin, it has evolved to cross the blood-brain barrier (BBB) to target sites in the central nervous system (1). Previous studies have demonstrated that CTX has an exceptional specificity for brain tumour cells, making it an interesting vector for the delivery of therapeutic radionuclides to brain tumours, in particular the therapeutic alpha emitter astatine-211 (211At) (2). Here, we present our initial proof-of-concept studies with iodine-125 (125I)-labelled CTX as a chemically similar but preclinically more practical surrogate for 211At-labelled CTX (3).

Methods

N-succinimidyl-3-(trimethylstannyl)-benzoate (m-MeATE)-functionalised CTX was radiolabelled with 125I using the chloramine-T method. Its ability to cross the BBB was evaluated in glioma and medulloblastoma organoid models containing an artificial BBB. Validation was obtained in subcutaneous and intercranial models of glioma and medulloblastoma. Blocking studies were performed using Tamoxifen (chloride channel block).

Results

Radiolabelled CTX (8 GBq/mg) was indeed able to cross the BBB and penetrate into the core of glioma ($P=0.03$) and medulloblastoma ($P<0.01$) organoids, whereas its control (IgG) was not. Blocking studies demonstrated good in vivo specificity of radiolabelled CTX for subcutaneous glioma ($P=0.02$) and medulloblastoma ($P=0.02$) tumours. Uptake of radiolabelled CTX in the intercranial glioma model was significantly higher for the tumour than for control brain regions ($P=0.04$), with a consistent and significantly larger increase

in tumour-to-blood ratio than for the radiolabelled IgG control (P=0.02).

Conclusions

We demonstrated that radiolabelled CTX is able to cross the BBB to specifically bind to glioma and medulloblastoma in organoid and murine models. Therefore, CTX is a promising vector for the delivery of 211At to brain tumours. Currently, we are further investigating this approach to, ultimately, develop an effective targeted radiopharmaceutical therapy strategy for patients with brain cancer.

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Acknowledgements

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Evaluation of [177Lu]Lu-radiolabelled bombesin antagonists as potential candidates for prostate cancer theranostics

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Introduction

The gastrin-releasing peptide receptor (GRPR) is an important target for prostate cancer radiotheranostics due to its high-density expression in the majority of primary and metastatic prostate lesions. This study is focused on the evaluation of the following GRPR-targeting analogs: AU-RM26-M2 (DOTAGA-PEG2-Pip-[Sar11]RM26), AU-RM26-M4 (DOTAGA-Arg-Arg-Pip-[Sar11]RM26), AU-SAR-M1 (DOTAGA-AMA-Dig-D-Phe-Gln-Trp-Val-Sar-His-Leu-NHEt) and AU-SAR-M2 (DOTAGA-Arg-AMA-Dig-D-Phe-Gln-Trp-Val-Sar-His-Leu-NHEt) labeled with the therapeutic radionuclide Lu-177.

Methods

After labelling with Lu-177, the radiopeptides were compared in vitro and in vivo. The specificity and cellular uptake over time were tested in PC-3 cells. In vivo stability was analyzed on healthy NMRI mice (with/without sacubitril pre-treatment), 5 min pi. Biodistribution 4h and 23h pi was assessed in PC-3 xenografed mice, pre-treated with sacubitril. Additionally, dosimetry studies for [177Lu]Lu-AU-SAR-M1 were performed.

Results

All tested peptides were labeled with Lu-177 with high radiochemical yields (>98%) and purity (>97%). The radiotracers showed high specificity for GRPR and the cellular uptake demonstrated a typical internalization pattern for radioantagonists. Pre-treatment with sacubitril increased the intact peptide (stability improvement: 13-21%, reaching >80%).

Tumor's activity uptake 4h pi was the highest for [177Lu]Lu-AU-RM26-M4 (19.6 %IA/g), followed by [177Lu]Lu-AU-SAR-M1 (16.1 %IA/g) and [177Lu]Lu-AU-SAR-M2 (15.1 %IA/g), and the lowest for [177Lu]Lu-AU-RM26-M2 (4.7 %IA/g). [177Lu]Lu-AU-RM26-M4 had the highest kidney uptake at 4h pi (6.1 %IA/g), but there was no statistical difference between analogs at 23h. [177Lu]Lu-AU-SAR-M1 had the best biodistribution profile with fast non-tumor tissue clearance. Dosimetry studies of [177Lu]Lu-AU-SAR-M1 were crucial in designing an appropriate therapy study plan to eradicate the tumor while minimizing healthy tissue damage.

Conclusions

[177Lu]Lu-AU-RM26-M4, [177Lu]Lu-AU-SAR-M1, and [177Lu]Lu-AU-SAR-M2 demonstrated favorable properties as therapeutic radioligand, i.e. rapid clearance, high in vivo stability, high specific uptake in tumors, and low uptake in excretory organs. [177Lu]Lu-AU-RM26-M2 requires further structural modifications to improve its biodistribution properties. [177Lu]Lu-AU-SAR-M1 is the most promising for a follow-up therapy study.

Head-to-head evaluation of new GRPR-targeting theranostics labelled with Lu-177/Ga-68

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Introduction

GRPR is gaining popularity again as a biomolecular target for novel radiopharmaceuticals. It is overexpressed in various malignancies, including prostate and breast cancer rendering it an appealing biomolecular-target. One of the major hindrances for peptide-based radiopharmaceuticals is their rapid degradation in vivo. In order to improve upon the stability and thus the performance of AU-RM26-M2 [1], an α-methyl-L-tryptophan (MetTrp) was introduced at position 8 [2]. In addition, the impact of the chelator was accessed by exchanging DOTAGA (PK2) with DOTA (PK3)

Methods

All three analogues (AU-RM26-M2, PK2, PK3) were labelled with Lu-177 and PK2/PK3 were additionally labelled with Ga-68. Their cellular-uptake and receptor-specificity was accessed in PC-3 cells. The in vivo stability for the [177Lu]Lu-conjugated was evaluated in healthy mice. The biodistribution profile of all peptides was evaluated at 4h pi (Lu-177) / 2h pi (Ga-68) in PC-3 xenograft bearing mice.

Results

All three analogues were successfully labelled with Lu-177 and Ga-68, with RCY and RCP >95%. All compounds displayed high GRPR-mediated uptakes.
With both radiometals Lu-AU-RM26-M2 and Lu-PK2 had similar cellular-uptake, but PK3 had the highest uptake (10.88 ± 3% and 19.66 ± 0.52% of added activity for Lu-177/Ga-68 respectively). In all cases the majority of the cell-associated activity remaining on the membrane even after 24h.
At 5 min pi the amount of intact peptide detected in circulation was [177Lu]Lu-AU-RM26-M2: 76 ± 2%, [177Lu]Lu-PK2: 85 ± 6% and [177Lu]Lu-PK3: 91 ± 4%.

The biodistribution profiles of all three radiopeptides showed that the organs with the highest uptake were in series: tumours, kidneys and pancreas. Tumour values were: [177Lu]Lu-AU-RM26-M2–9.9 ± 0.75%IA/g [177Lu]Lu-PK2–16 ± 4%IA/g, [177Lu]Lu-PK3–24 ± 3%IA/g; [68Ga]Ga-PK2–16 ± 3%IA/g, [68Ga]Ga-PK3–17 ± 3%IA/g. With both radiometals PK3 displayed the highest tumour-to-kidneys rations (3.2 & 3.8 respectively).

Conclusions

MetTrp8 increases in vivo stability and thus the tumour-targeting. DOTA-chelator is preferred by our system, both in vivo and in vitro. Both [177Lu]Lu-/[68Ga]Ga-PK2 and [177Lu]Lu-/[68Ga]Ga PK3 showed high tumour uptake in vivo and rapid background clearance. With PK3 having an edge.

References

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Multidimensional diffusion MRI for monitoring radiotherapy response in human prostate cancer xenografts: A longitudinal pilot study

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Background

A new MRI technique can evaluate changes in intra-tumor heterogeneity during radiotherapy treatment, with the possibility of predicting treatment outcome and monitoring of treatment response. Recent results by Dr. Szczepankiewicz, in collaboration with Harvard Medical School (Boston, MA, USA), showed that information gained from multidimensional diffusion MRI could detect and identify tumor subtypes and with promising implications for diagnosis and treatment planning. In this work, we aim to explore potential biomarker candidates for prostate cancer by combining tensor-valued encoding with modulations of the diffusion time in a multidimensional approach and apply the method to monitor the response to radiotherapy in human PCa xenografts in mice.

Methods

8 nude mice (BALB/c, Foxnnu/nu) were subcutaneously inoculated with human prostate cancer cells (LNCaP) in the right flank (5-7·106 cells). The study was in accordance with national and local ethics regulations. The animals were monitored for tumor volume (caliper and ultrasound), body weight and signs of illness. After the final MRI, the mice were sacrificed, and tumors were dissected. 177-Lu-PSMA was injected i.v. in 4 mice and External beam irradiation was performed with a small animal radiotherapy system (Xstrahl XenX with average photon energy of 78 keV) in 4 additional mice. MRI was performed at 9.4 T (Bruker BioSpec Avance III). Each mouse was scanned under at four timepoints: one day before, 2-3 days after, 9-10 days after, and 14-15 days after radiotherapy.

Excised tumors were sectioned at 4 µm and stained with H&E and prostate-specific membrane antigen (PSMA).

Results

Preliminary results from mice treated with external beam radiotherapy using our novel MRI technique yielded novel imaging parameter related to microstructure, cell density variations, cell shapes, blood perfusion, and sizes of microscopic restrictions. Several MRI biomarkers changed after treatment, with effects most visible diffusivity and diffusional variance, believed to reflect cell density and its heterogeneity, respectively. The radiotherapy had a clear effect on tumor growth and morphology, however the effects manifested differently both within and between subjects.

Conclusions

• Radiotherapy induced a significant change in dMRI parameters within 1-15 days; the effect was heterogeneous across/within tumors.
• dMRI parameters can distinguish different effects of radiotherapy.
• dMRI parameters could detect and identify pathological tissue in an otherwise healthy context.

Novel Affibody-based tracer for radionuclide imaging of HER2: Clinical translation

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Introduction

A level of expression of human epidermal growth factor receptor type 2 (HER2) in breast and gastric cancers is a predictive biomarker for outcome of HER2-targeting treatments. Affibody molecules are small targeting proteins based on non-immunoglobulin scaffold, which provide highly sensitive molecular imaging at the day of injection. Clinical evaluation of 68Ga-labelled Affibody molecule ABY-025 showed that this imaging probe is capable of quantitative measure of HER2 expression in the breast cancer 3-4 h after injection [1]. Recent progress in development of SPECT/CT cameras enabled reasonable accuracy in quantitative measurement of activity concentration in vivo. Implementation of a 99mTc-labelled Affibody molecule would increase availability of HER2 imaging for clinical community. The aim of this study was to evaluate biodistribution dosimetry and safety of [99mTc]Tc-ZHER2:41071 Affibody molecule in a Phase I trial.

Methods

Biodistribution of [99mTc]Tc-ZHER2:41071 was studied in mice bearing HER2-expressing SKOV-3 xenografts. To evaluate dosimetry in humans, uptake values in mice was evaluated and absorbed doses were estimated using OLINDA/EXM 1.0 software. Phase I trial was a prospective, open-label, non-randomized Phase I diagnostic study in patients with untreated primary breast cancer (ClinicalTrials.gov Identifier: NCT05203497). Three cohorts of patients (injected with 500, 1000, or 1500 μg ZHER2:41071) with primary breast cancer were enrolled in the study. Each cohort included at least five patients with high HER2 expression (immunohistochemistry (IHC) score 3+ or IHC score 2+ and FISH positive) and five patients with low HER2 expression in tumors (IHC score 0, 1+ or 2+ and FISH negative). The injected activity was 451 ± 71 MBq. Planar scintigraphy was performed after 2, 4, 6 and 24 h and SPECT/CT imaging after the planar imaging 2, 4 and 6 h after injection. Vital signs were monitored before, during and after the imaging.

Results

Biodistribution results in murine model demonstrated that the tumor-to-kidney ratio and tumor-to-liver ratio were 2.2 ± 0.5 and 52 ±11 4 h after injection, respectively. microSPECT/CT imaging demonstrated a high-contrast visualization of HER2 expression. An evaluation of absorbed doses for humans demonstrated favourable dosimetry (effective dose of 0.00066 mSv/MBq). Phase I trial showed that there is no adverse events after injection of [99mTc]Tc-ZHER2:41071. Kidney was the normal organ with the highest accumulation. The effective dose was 0.019 ± 0.004 mSv/MBq. The best discrimination between HER2-positive and HER2-negative primary tumors was achieved in patients injected with 1000 μg. Already 2 h after injection, the uptake in tumors with high expression (SUVmax 16.9 ± 7.6) was significantly ($p<0.005$, Mann–Whitney U test) higher than in tumors with low expression (SUVmax 3.6 ± 1.4). [99mTc]Tc-ZHER2:41071 uptake in HER2-positive lymph node metastases was also significantly ($p < 0.05$) higher than in HER2-negative 2 h after injection of 1000 μg.

Imaging of HER2-positive breast cancer using scaffold proteins: direct clinical comparison of [99mTc]Tc-ADAPT6 and [99mTc]Tc-(HE)3-G3

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Abstract missing
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A scoping review of economic evaluations of theranostics

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Background

Theranostics is a novel approach of combining diagnostic imaging and targeted therapy to personalize treatment. Theranostics utilises advanced, high-cost technologies and could potentially provide great value for patients. However, little is known about the cost-effectiveness of theranostic interventions.

Methods

We conducted a scoping review of the available health economic literature covering - effectiveness analyses of theranostics . We adopted a snow-ball approach to identify additional publications that report economic evaluations of theranostics. The search string was iteratively constructed and included three main search blocks: economic evaluation, model based, and theranostics and only considered publications from 2015 or later. Blinded screening of titles and abstracts was conducted by two independent reviewers. Discrepancies or disagreements were resolved through adjudication by a third reviewer. Full text review was conducted by the same methodology.

Results

A total of 1161 records were identified in MEDLINE and an additional 5 records were obtained through snow-ball screening of identified publications. Nine (0.7%) records were included for full text screening. Three records (0.2%) met the inclusion criteria. Two records evaluated treatment selection in advanced female breast cancer (US, Belgium) and one treatment in metastatic prostate cancer (US). One analysis was based on a phase-two single arm trial, two were model based. The utilised modelling approaches were partitioned survival and a decision-tree informed Markov model.

Conclusion

Theranostics is a concept that holds potential to improve patient outcomes by tailoring treatment based on immediate information on expected treatment effectiveness. The literature is sparse and there is a need for further studies. Furthermore, a need for consolidation harmonization of methodological choices and valuation of these technologies is indicated. There is a need for alignment and standardization of terminology describing theranostics.

TEZATABEP MATRAXETAN (ABY-025) FOR MOLECULAR IMAGING OF HER2-EXPRESSING CANCERS

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Introduction

Human epidermal growth factor receptor 2 (HER2) is a key oncogenic driver in various cancers. HER2-targeted therapies are well-established in breast cancer, gastroesophageal adenocarcimona (GEAC), and HER2-mutated non-small cell lung cancers. Temporal and spatial heterogeneity of HER2 expression is a well-studied phenomenon. The inadequate detection of changes in target expression by standard biopsy analysis poses a significant challenge for HER2-directed therapies and can impact treatment success. We have therefore developed the molecular imaging tracer tezatabep matraxetan (ABY-025), derived from the Affibody® platform. The compound has picomolar affinity to HER2, carries a DOTA chelator for radiolabeling with gallium-68 or indium-111, and binds HER2 at a binding site distinct from those of the therapeutic antibodies trastuzumab and pertuzumab. As a result, patients can continue anti-HER2-therapy when undergoing molecular imaging with radiolabeled tezatabep matraxetan.

Methods

The 61-amino acid Affibody® molecule tezatabep matraxetan (ABY-025) was radiolabeled and used for PET or SPECT imaging in clinical trials with metastatic breast cancer patients. Studies are also exploring its use in GEAC, as well as breast cancer with low HER2 expression. A Swedish study (HER2-ExPET) initiated by investigators at the Karolinska University Hospital will analyze HER2-PET imaging before and after trastuzumab deruxtecan therapy in HER2-low expressing breast cancer.

Results

Early trials showed that radiolabeled tezatabep matraxetan effectively visualizes HER2-expressing breast cancer lesions, distinguishes HER2-positive from HER2-negative

disease, and predicts molecular response to HER2-targeted therapy. It also reveals disease heterogeneity and limitations of biopsy-based HER2 staging. Ongoing work indicates that HER2-expressing lesions can be detected by tezatabep matraxtean in patients diagnosed with HER2-low breast cancer.

Conclusions

Tezatabep matraxetan has proven useful in clinical trials, highlighting the need for better diagnostics beyond biopsy-based HER2 analysis. Further studies aim to make this tool available for personalized treatment decisions in HER2-expressing cancers.

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Investigator initiated clinical trials with tezatabep matraxetan were conducted by Jens Sörensen, Henrik Lindman, Ali Alhuseinalkhudhur, and team at Uppsala University Hospital; by Rimma Axelsson, Renske Altena, Antonios Tzortzakakis, and team at Karolinska University Hospital and Karolinska Institutet. Radiolabeling protocols were optimized and validated by Irina Velikyan, Uppsala University, and Thuy Tran, Karolinska Institutet. Preclinical investigations were conducted by Vladimir Tolmachev and Anna Orlova, Uppsala University. We thank they whole team at Affibody AB involved in the project, in particular Camilla Sandell.

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Development of Radiopharmaceutical Therapy for High-Risk Neuroblastoma

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Introduction

Neuroblastoma is the most common extracranial tumor in children, with most cases occurring in patients five years or younger. The survival rate remains low, at approximately 50% for this patient group. Current treatment is multimodal, incorporating chemotherapy, surgery, local radiation therapy, and maintenance therapy. The radiopharmaceutical therapy used today, ^{131}I-mIBG, was originally developed in the 1970s for adrenal medulla imaging and later introduced for neuroblastoma treatment. Another radiopharmaceutical, ^{177}Lu-DOTATATE, which binds to somatostatin type 2 receptors, is currently under evaluation in a clinical trial (Lu-DO-N).

While these radiopharmaceuticals have shown extended survival benefits, long-term survival and cure rates after relapse remain low. A major concern is that the radiation energy from β-radiation may not be sufficient to achieve a cytotoxic effect in single cells or small tumor clusters. A-radiation, with its shorter travel path and more concentrated energy deposition, could enhance cytotoxic effects and improve treatment outcomes. Additionally, current radiopharmaceuticals exhibit off-target binding, which can lead to damage in healthy organs.

Methods

Single-cell RNA sequencing (scRNA-seq) was used to identify novel therapeutic targets for neuroblastoma. Based on these findings, new targets in neuroblastoma are being investigated, and radiopharmaceuticals directed at these targets are under development. Candidate compounds are evaluated through cell-binding assays, and promising candidates undergo further assessment in in vivo models.

Results

Novel targets have been identified and confirmed through immunofluorescence staining. Radiopharmaceuticals targeting these newly identified neuroblastoma markers are currently under development.

Conclusion

We believe that improved radiopharmaceuticals can be developed to target neuroblastoma more selectively. By utilizing α-radiation, a more potent therapeutic effect may be achieved, potentially improving treatment outcomes with the aim to be curative.

Development of a Targeted Radiotherapeutic for Treatment of HER2 Expressing Cancers

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Introduction

HER2 is a prominent oncogenic driver. In spite of widely used HER2-targeted therapies, there is still a medical need for new treatments in both breast cancer, and other HER2 expressing cancers such as gastric cancer and HER2-mutated non-small cell lung cancer. We have developed a theranostic pair based on the Affibody® drug class, targeting HER2 with high affinity and specificity. This pair consists of the diagnostic Affibody® molecule tezatabep matraxetan designed for whole-body imaging of HER2 expression in cancer lesions (presented in a separate poster) and the therapeutic radioligand ABY-271. ABY-271 is a molecularly engineered version of the diagnostic Affibody® molecule with extended half-life for optimized biodistribution suitable for radiotherapy. The theranostic pair targets a different HER2 epitope compared to trastuzumab or pertuzumab or their ADC derivates, allowing them to be administered concomitantly.

Methods

Through protein engineering, molecular formatting, and addition of the proprietary albumin-binding domain Albumod, the HER2 targeting sequence of tezatabep matraxetan has been developed into the 106 amino acid long therapeutic candidate ABY-271. Radiolabeling with lutetium-177 via a DOTA chelator creates the therapeutic radioligand [177Lu]Lu-ABY-271. Preclinical utility and efficacy of [177Lu]Lu-ABY-271 were analyzed in biodistribution and therapy studies in a murine xenograft model. To prepare for clinical trials, a 28-day GLP toxicity study in rats was conducted. GMP-compliant processes for manufacture and radiolabeling of ABY-271 were established, and a 2-compartment dosimetry model was applied to define a safe starting dose for clinical trials. A first-in-human study is to start in 2025, evaluating safety and

biodistribution of [177Lu]Lu-ABY-271 in patients with metastasized HER2-positive breast cancer.

Results

The therapeutic candidate [177Lu]Lu-ABY-271 demonstrated a beneficial biodistribution profile in mice bearing HER2-expressing SKOV-3 xenografts, with a balanced blood and kidney clearance and accumulation in tumors that exceeded uptake in all other organs by the 24-hour timepoint. Median survival of xenograft-bearing mice receiving a single dose of 21 MBq [177Lu]Lu-ABY-271 was significantly longer than that of mice receiving vehicle control or trastuzumab, while combination treatment of [177Lu]Lu-ABY-271 and trastuzumab increased the number of complete tumor remissions. Histopathological evaluation of liver and kidney in this therapy study showed only mild changes following [177Lu]Lu-ABY-271 treatment. Further, the GLP toxicity study in rats demonstrated a beneficial safety profile of ABY-271. Human dosimetry estimates based on preclinical results predict that tumor doses in the range of approved therapeutic radioligands can be achieved.

First-in-human clinical trial outline

A first-in-human trial of ABY-271 is currently planned with first results anticipated during 2025. The trial involves a first part (part A) where biodistribution of a single, low radioactivity dose of [177Lu]Lu-ABY-271 is studied. Radioactivity dose will be the same in all patients and biodistribution of radioactivity will be assessed by SPECT/CT. Based on results obtained, the mass protein dose will be adjusted to optimize uptake in tumor vs. normal tissue.

In the second part (part B), two cohorts exploring higher radioactivity doses are included. Within each cohort, biodistribution of radioactivity at three different protein mass doses will be assessed.

Conclusion

In preclinical studies, [177Lu]Lu-ABY-271 demonstrated a favorable biodistribution profile and potent antitumor effect, which was further enhanced when combined with trastuzumab. A favorable safety profile has been demonstrated in a GLP-compliant toxicity study, GMP-compliant manufacture and labeling of ABY-271 has been established and a first-in human trial is under way.

Acknowledgements:

Calculations to predict safe starting dose in the first-in-human trial were conducted by Peter Bernhardt (Department of Medical Radiation Sciences, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden and Department of Medical Physics and Biomedical Engineering, Sahlgrenska University Hospital, Gothenburg, Sweden).
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The Autoradiography (ARG) core facility

Core facility or other infrastructure/resource

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The **Autoradiography Core facility** is included in the Division of Imaging Core Facilities (Department of Clinical Neuroscience) and is part of the Centre for Imaging Research (CIR).
Our facility is fully outfitted and staffed to support autoradiography (*in vitro & ex vivo*) and radioligand binding assays (whole cells or tissue homogenates) for different types of projects, e.g. target-specificity, binding affinity, drug screening. We can also perform GTPgammaS assays of GPCR activity. Our autoradiography service includes tritiated ligands as well as PET radioligands labelled with short-lived isotopes (e.g. ^{18}F). Depending on the project, we also can provide some human pathological tissue, non-human primate or rodent tissue for use on the assays requested by our users. We provide full service, including consultation, experimental design, tissue sectioning, assay execution, analysis and reporting. We also provide training and access to equipment for our users to carry out their studies on their own, booking lab space and instruments through our iLab page to do so.

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- Measure the maximum **density of the target protein** (e.g. receptor) available to the radioligand in a given tissue/organ.
- **Test drug candidates**, screening for compounds that compete with high affinity for binding to a particular target

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