4th Theranostics World Congress 2016

7–9 November 2016, Melbourne Convention & Exhibition Centre, Melbourne

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Integrating cancer genomics with imaging
Ben Lawrence
Auckland City Hospital, Auckland, New Zealand.

Abstract unavailable at the time of publishing

OC2

Production of Ga-68 radiotracers under GMP and regulatory aspects – a German perspective
Oliver Neels
German Cancer Research Center, Heidelberg, Baden-Württemberg, Germany.

Radiopharmaceuticals labelled with the positron emitter Gallium-68 have had an enormous impact on the diagnostic imaging of neuroendocrine tumors using somatostatin receptor ligands and in recent years on the diagnosis of prostate cancer using PSMA ligands and subsequently their application for radio-endotherapy using Yttrium-90, Lutetium-177 or more recently Actinium-225. The release of the monographs for 'Gallium-68 chloride solution for radiolabelling' and 'Gallium-68 Edotreotide injection' within the European Pharmacopoeia in 2013 tightened the requirements for specifications of Gallium-68 labelled radiotracers and will be enhanced with the ongoing elaboration of monographs for 'Gallium-68 DOTA-TATE injection', 'Gallium-68 DOTA-NOC injection' and '68Ga-PSMA'. In the same way the work environment of the responsible radiochemists and radiopharmacists in terms of quality control has been improved but also the workload has reached a high level with the increasing number of clinical applications and the limitation of the maximum achievable amount of starting activity from the currently available generators and therefore a limited dose number. The change of conditions for the production and quality control of Gallium-68 labelled radiopharmaceuticals will be reviewed with regards to legislating and practical aspects from 'on bench' to 'full GMP' preparation linked to the specific requirements for a multi-centre clinical trial using 68Ga-PSMA-11 in high-risk prostate cancer.

OC3

Optimised production of ^{64}Cu-SARTATE for a phase 1 clinical trial
Peter Roselt[1], Wayne Noonan[1], Charmaine Jeffery[2,3], Roger Price[3] & Amos Hedt[2]
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A new radiopharmaceutical using the somatostatin analogue octreotide has been developed for use in humans. SARTATE consists of the novel bifunctional chelator, MeCOSar, conjugated to (Tyr^3)-octreotate. MeCOSar is a superior chelator for copper over a wide pH range and at room temperature, which allows for SARTATE to be used as an imaging/therapy pair when radiolabelled with copper-64 and copper-67.
^{4}Cu-SARTATE was produced by radiolabelling SARTATE (AusPep, Victoria) with cyclotron-generated copper-64-chloride (Sir Charles Gairdner Hospital, Western Australia). Previous pre-clinical development work had shown that ^{64}Cu-SARTATE was stable *in vivo* (Paterson *et al*., 2014). Experiments were then undertaken to adapt the pre-clinical manual radiolabelling method for use in humans, which aimed to optimise conditions for reaction time, temperature, ligand amount, column cartridge purification and the use of quench agents to limit radiolysis. Four validation studies, requiring full quality control per production, were performed on the final method. Ten productions were made for human clinical PET/CT imaging. The production yield for each synthesis was calculated to monitor the performance and efficiency of the synthesis. The radiochemical purity of the final product was assessed by HPLC.
Discussion
^{64}Cu-SARTATE had shown it was susceptible to radiolysis at activity levels required for human imaging. This required optimisation of the HPLC analysis to separate and quantify radiolysis products – which could not be accurately assessed by TLC. Several stability studies looking at the addition of quench agents to limit radiolysis were then carried out. ^{64}Cu-SARTATE was ultimately prepared by radiolabelling for 30 min at room temperature, followed by SPE using a C18 cartridge. The susceptibility to radiolysis was overcome through the use of quench agents.
Conclusion
A consistent and reliable non-automated method for producing ^{64}Cu-SARTATE for clinical trials was developed, and successfully used in a Phase 1 clinical trial of ten patients.
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OC4

^{68}Ga, ^{64}Cu labelling and affinity study of NODAGANOC, a NODAGA conjugated somatostatin analogue
Rana Ben Azzouna[1,2,3], Faisal Al-Shoukr[4], Fabien Hyafil[2,3,4], François Rouzet[2,3,4], Denis Guilloteau[5] & Dominique Le Guludec[2,3,4]
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Introduction
DOTANOC is a largely used somatostatin analogue in NETs investigations. In NODAGANOC, the DOTA is replaced by NODAGA, a chelator derivative from NOTA which is the 'gold standard' for Ga^{3+} and Cu^{2+} chelation because it forms more stable complexes than DOTA.[1] The aim of our study is to evaluate the affinity of NODAGANOC for somatostatin receptors (sst) and to develop a ^{68}Ga and ^{64}Cu labelled NODAGANOC for a future use in PET imaging.
Material and methods
The affinity of NODAGANOC was evaluated ($n=3$) in AR4-2J rat pancreatic cell line which express mRNA of $sst_{1,2,3,5}$.[2] IC$_{50}$ values for the binding to living AR4-2J cells were determined from competition experiments between NODAGANOC (Concentrations from 1.7×10^{-12} to 10^{-6}M) and 15.10^{-9}M ^{68}Ga-DOTANOC.
Radiolabelling
^{68}Ga-NODAGANOC was prepared instantly at RT by mixing the fraction of eluate containing $>90\%$ (613 ± 54MBq) of the available generator activity with 35 nmol of peptide and 800 µl of 1M ammonium acetate buffer (pH 4.4) without further purification of the final product. ^{64}Cu-NODAGANOC was prepared after incubation 15 min at RT of 10 nmol of conjugate with 50 µl of ^{64}CuCl$_2$ (67MBq) in ammonium acetate buffer (0.1 M, pH 8.54)[3]. The radiochemical purities (RCP) were determined by RP-HPLC. The stabilities of the labelled compounds were evaluated by HPLC at RT and in human plasma for 2 h.
Results
The competition curve was analyzed with GraphPad Prism Software, the IC50 of NODAGANOC is 1.2 ± 0.5 nM. The labelled products were obtained with high radiochemical purities ($>95\%$ for ^{68}Ga-NODAGANOC and 100% for ^{64}Cu-NODAGANOC) without purification of the final product. In all cases, RCP remains $>90\%$ for 2 h.
Conclusion
The nanomolar affinity for living cells AR4-2J makes NODAGANOC a potential interesting vector for targeting of pathologies overexpressing the sst. The radiolabelling described methods can be performed without costly equipment and allows to ^{68}Ga and ^{64}Cu-NODAGANOC with high radiochemical purities without further purification.
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OC5

Influence of the radiopharmaceutical affinity and peptide content on the pharmacokinetics: [^{68}Ga]Ga-DOTATOC and [^{68}Ga]Ga-DOTATATE

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The common perception is that receptor targeting peptide radiopharmaceuticals of high affinity should be prepared and administered in high specific radioactivity and thus low peptide content in order to assure high contrast uptake in the target tissue. However, both pre-clinical and clinical studies have demonstrated complexity of the translation of the observations *in vitro* to *in vivo* pharmacokinetics. The investigation of the phenomenon for clinically used radiopharmaceuticals is of outmost importance and is exemplified using clinically established [^{68}Ga]Ga-DOTATOC and [^{68}Ga]Ga-DOTATATE. The affinity and biodistribution of [^{68}Ga]Ga-DOTATOC and [^{68}Ga]Ga-DOTATATE were compared *in vitro* and *in vivo* both pre-clinically and clinically. The influence of the injected peptide mass was studied pre-clinically and clinically for [^{68}Ga]Ga-DOTATOC. The choice of the specific radioactivity value of the radiopharmaceutical depends on the application. Determination of the affinity *in vitro* by frozen tissue section autoradiography was possible with [^{68}Ga]Ga-DOTATOC only of highest specific radioactivity. On the contrary *in vivo* in humans the target tissue uptake improved with lower specific radioactivity. The clinical study indicated importance of the optimization of the administered peptide amount in order to assure accurate quantification of the target receptors and subsequent radiotherapy planning. The interpatient variation stressed the importance of the individualized treatment approach. The effect of affinity difference between [^{68}Ga]Ga-DOTATOC and [^{68}Ga]Ga-DOTATATE on the targeting properties could not be detected *in vivo* in rats and humans. However, there was a slight thought statistically significant difference in some healthy organs, e.g. liver and gallbladder as well as excretion.The pre-clinical and clinical studies demonstrated necessity for the optimization of the specific radioactivity of the radiopharmaceuticals in each particular case and for the personalized patient management. Difference in affinity determined in cell cultures might not be essential in vivo in terms of radiopharmaceutical biodistribution, targeting and imaging properties.

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OC6

DNA damage assay in blood lymphocytes in peptide receptor radionuclide therapy patients with personalised high activities

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Objectives
Radiation induces DNA double strand breaks (DSBs) that can be visualized and enumerated as microscopic γ-H2AX and 53BP1 foci. This study analysed the dose- and time-dependency of the DNA damage in blood lymphocytes in patients after a personalised high-activity ^{177}Lu-DOTATATE treatment.
Methods
We investigated multiple blood samples of three patients up to 96 h after personalised high-activity peptide receptor radionuclide therapy (PRRT) (14.4GBq-19.3GBq). Background focus rates were determined in pre-therapeutic samples. Lymphocytes were isolated by density centrifugation and fixed in 70% ethanol. After two-color immunofluorescent staining co-localizing γ-H2AX + 53BP1 foci were counted manually using a red/green double-band-pass filter. The results were compared to a previous patient study (1) and an in-vitro calibration-curve (2)
Results
Blood samples of three patients receiving a personalised high activity therapy were evaluated for γ-H2AX+53BP1 DSB-indicating foci. Compared to the standard therapy (7.7GBq) the absorbed dose to the blood after 48 h was higher (mean: 78 mGy vs 186 mGy, resp.). In the first 4 h after administration of the

radiopharmaceutical there was a strong increase of the number of radiation-induced foci/cell (RIFPC) with the average RIFPC values being in accordance with our in-vitro calibration curve. Maximum foci numbers ranged from 0.8 – 1.1 RIFPC. At t=4 h in standard therapy the mean RIFPC values normalised to the blood dose (0.019 RIFPC/mGy) were higher than those of the high-activity patients (0.012 RIFPC/mGy). The patient with the highest activity administered and highest absorbed dose to the blood had persisting RIFPC levels after 72 h, while for the two other high activity patients RIFPC levels decreased similar to patients receiving standard therapy.
Conclusions
This study provides a first analysis of DSB induction in lymphocytes of Lu-DOTATATE patients receiving personalised high-activity Lu-DOTATATE therapy. With the exception of a late time-point in one patient our findings align well with our previous results.

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OC7

Two Decades of THERANOSTICS in Neuroendocrine Tumors – Past, Presence and Future of Peptide Receptor Radionuclide Therapy (PRRT)

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OC8

NETTER-1 Phase III in Patients with Midgut Neuroendocrine Tumors Treated with 177Lu-Dotatate: Efficacy, Safety, QoL Results and Subgroup Analysis

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Background
Currently, there are limited therapeutic options for patients with advanced midgut neuroendocrine tumors progressing on first-line somatostatin analog therapy.
Methods
NETTER-1 is the first phase III, randomized trial evaluating ^{177}Lu-DOTA^0-Tyr^3-Octreotate (Lutathera$^®$) in patients with progressive, somatostatin receptor positive midgut NETs. 230 patients were randomized to receive Lutathera 7.4 GBq every 8 weeks (x4 administrations) versus Octreotide LAR 60 mg every 4 weeks. The primary endpoint was PFS (RECIST 1.1). Secondary objectives included ORR, OS, toxicity, and quality of life (QoL) based upon EORTC QLQ-C30 and QLQ-G.I.NET21 questionnaires. Subgroup analysis of PFS was performed to assess impact of potential prognostic factors.
Results
The centrally confirmed disease progressions or deaths were 23 in the Lutathera arm and 68 in the Octreotide LAR 60 mg arm. The median PFS was not reached for Lutathera and was 8.4 months with control, $P<0.0001$, HR 0.21. At the time of the NDA/MAA submission, interim OS analysis (14 deaths in Lutathera group and 26 in control group; $P=0.0043$) suggested an improvement in OS. Subgroup analyses for PFS confirmed consistent benefits of Lutathera irrespective of stratification and prognostic factors including tumor grade, age, gender, tumor marker levels, and levels of radiotracer uptake. Grade 3 or 4 neutropenia, thrombocytopenia and lymphopenia occurred in 1%, 2% and 9% of patients in Lutathera arm vs. none in controls. Health related QoL surveys indicated a moderate improvement in the global health status in the Lutathera treatment arm, demonstrating that the treatment benefit of Lutathera is not offset by a negative impact on patient quality of life.

Conclusions

The phase III NETTER-1 trial provides evidence for a clinically meaningful and statistically significant increase in PFS, and suggests an OS benefit in patients with advanced midgut NETs treated with Lutathera. Subgroup analysis demonstrates consistent benefit across prognostic factors. The Lutathera safety and QoL profile was found to be favorable.

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2. Markey Cancer Center, University of Kentucky, Lexington, KY, USA
3. University of Texas MD Anderson Cancer Center, Houston, TX, USA
4. Dana-Farber Cancer Institute, Boston, MA, USA
5. University of Iowa, Iowa City, IA, USA
6. Royal Free Hospital, London, United Kingdom
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8. Stanford University Medical Center, Stanford, CA, USA
9. Mayo Clinic College of Medicine, Rochester, MN, USA
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12. Advanced Accelerator Applications, New York, NY, USA
13. Erasmus Medical Center, Rotterdam, The Netherlands
14. Hopital Beaujon, Clichy, France

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OC9

Clinical Perspective: The 'difficult development situation': how to approach and overcome challenges from a regulatory perspective

Hans-Georg Eichler

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A range of innovative treatment approaches present 'difficult development situations' for drug developers and decision makers including medicines regulators. Treatment concepts where conventional development pathways and evidence standards may be difficult to apply include some cell therapies, gene therapies, personalised treatments, personalised treatment combinations and theranostics.

The recently elaborated concept of adaptive pathways (AP) may be useful to facilitate the development and licensing of treatments that represent difficult development situations. AP is based on stepwise learning under conditions of acknowledged uncertainty, with iterative phases of data gathering and regulatory evaluation. This approach allows approval to align more closely with patient needs for timely access to new technologies and for data to inform medical decisions.

With AP, evidence will be based on a diverse family of data sources and methodologies complementing randomised controlled trials.

This session will discuss difficult development situations, reflect on the associated methodological challenges for evidence generation, and outline the basic concept of AP.

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OC10

The Cruel Wait for PRRT

Paul Stephensen

Unicorn Foundation, Blairgourie, VIC, Australia.

If you are unfortunate enough to get NETs, and with surgical options not on the table, then at least I thought I had a reasonable head start to access the only other demonstrable treatment regime…PRRT?

The equation:

Australian patient + Victorian patient + Under direct care of Peter Mac team + PET scans with tumours demonstrating strong take-up of GaTate = Early Treatment

Instead of a relatively short lead-in period, it turned into an 'endurance event', required to wait for the tumours to advance (in number and size), and symptoms to become stronger.

Frustrating, stressful and anxious times.

My talk will cover the timeline from diagnosis, through to PRRT treatment and, 2 years on, the wait for action/next steps is being repeated.

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OC11

The challenges of waiting for RCTs vs treating patient's now

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Background

2016 marks the 20th anniversary of PRRT and may mark the year that a commercially available PRRT product is approved in the United States for the treatment of Neuroendocrine Tumors (NETs). During these 20+ years PRRT was available to many in either small institutional studies or via single center compassionate care programs. Many retrospective analysis were done on this data showing the extended progression free survival (PFS) compared to drugs approved for the treatment of NETs. Over the past 20 years thousands of patients traveled the world in search of PRRT at centers that were able to offer PRRT. Thousands more were unable to make this journey due to lack of resources or knowledge about this treatment, or were steered away by members of the medical community that would not recommend a treatment before a randomized control trial was complete.

Observation

As patients we seek the best chance to live a longer life or find a cure, we tend to overlook the details of why a treatment is offered in one country over another only to assume that it is over regulation in one country vs another, we mostly fail to look at the underlying issues and challenges regarding drug development in our respective countries. The pathway that PRRT was developed on, while allowing many of us to have access to treatment, hindered the wider NET population of having access to a therapy that may greatly lengthening the quality and quantity of our lives.

Conclusion

As a community we must work harder to have focused investigational periods where patients can benefit from new treatment while at the same time having some common methodology among institutions so that the time to a randomized control trial and the length of the trail can be considerable shorter than 20 years.

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OC12

PET/CT based dosimetry for ^{90}Y-DOTATOC treatment of neuroendocrine cancer

John Sunderland, Mark Madsen, Molly Martin, Len Watkins, Tom O'Dorisio, Yusuf Menda, Michael Schultz, David Bushnell & M. Sue O'Dorisio

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Introduction

Determining the radiation dose to both the kidneys and malignant lesions from therapeutic administrations of Y-90 DOTATOC is critical for optimal management of neuroendocrine cancer patients. Here, a new dosimetric approach uses PET/CT to quantify the absolute activity of Y-90 immediately after administration to calibrate subsequent tissue clearance monitored with bremsstrahlung SPECT. The dosimetric information is used to personalize subsequent Y-90 DOTATOC doses to optimize therapeutic effect while keeping renal dose below toxic levels.

Methods

Patients with nonresectable or metastatic neuroendocrine tumors were treated with three cycles separated by 6 weeks. For the 1st treatment cycle, adult subjects received 4.44 GBq of Y-90 DOTATOC. PET/CT imaging was acquired after amino acid infusion and was used to quantify the renal uptake of ^{90}Y-DOTATOC. Bremsstrahlung SPECT/CT was acquired immediately after the PET/CT study and was repeated at 24, 48 and 72 h to obtain the time activity curves from the kidneys and lesions in the field of view. Tissues masses were determined from the CT and the radiation dose to these tissues was determined using OLINDA/EXM. The administered activity in subsequent cycles was modified based on the kidney dose determined from the previous cycle.

Results

Eighteen patients have been treated with at least one cycle of ^{90}Y-DOTATOC. The mean kidney uptake at the time of PET/CT imaging was 2.2% of the administered activity resulting in a mean kidney dose of 1.4 mGy/MBq (range 0.6–2.7 mGy/MBq). The dose to the kidney tended to vary between cycles indicating the need to monitor dose with each administration. Based on the measured kidney doses, the administered activity was reduced in 6 and increased in 20 treatment cycles.

Conclusion
PET/CT-based Y-90 DOTATOC dosimetry combined with Bremsstrahlung SPECT allows patient-specific optimized therapeutic dosing. This general dosimetric methodology is applicable to any Y-90 based therapeutic.

OC13

Personalized ^{177}Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumors: a simulation study

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Aim
It is common practice to administer peptide receptor radionuclide therapy (PRRT) at fixed injected activity (IA) per cycle. This results in highly variable radiation doses to critical organs and undertreatment of most patients. We conceived a personalized PRRT (P-PRRT) system enabling delivery of a prescribed dose to the kidney over four cycles. Our goal was to assess the potential of P-PRRT to safely increase radiation dose rate to tumors, by performing a simulation in a retrospective cohort.

Methods
Twenty-two patients underwent a four-cycle, empiric-IA induction course of ^{177}Lu-octreotate PRRT (29.6 ± 2.4 GBq cumulative IA), with quantitative SPECT/CT-based dosimetry. Kidney, bone marrow (BM) and maximum tumor doses were 16.2 ± 5.5, 1.3 ± 0.8 and 114 ± 66 Gy, respectively. We simulated P-PRRT, in which the renal dose per IA is predicted by the body surface area and glomerular filtration rate for the first cycle, and by prior cycle(s)' dosimetry data for subsequent cycles. Personalized IA is determined at each cycle, in order to reach the prescribed renal dose of 23 Gy over four cycles (25–50% reduction if impaired renal or BM function). Simulated IAs and doses were based on actual patients' characteristics, lab values and doses per IA delivered at each of the 88 cycles.

Results
P-PRRT would have allowed increasing cumulative IA to 43.7 ± 16.5 GBq over four cycles, which would have increased kidney, BM and maximum tumor doses to 21.5 ± 2.5, 1.6 ± 0.6 and 156 ± 82 Gy, respectively. There was an average 1.45-fold increase of tumor dose over empiric PRRT (range: 0.68–2.34 folds; $P=0.0025$).

Conclusion
By standardizing the dose rate to the kidney instead of the IA per cycle, P-PRRT offers the prospect of significantly increasing tumor radiation doses, and thus the likelihood of therapeutic benefits, while limiting the risk of toxicity. We are currently evaluating this approach in a registered prospective trial.

OC14

[68]Ga-Pentixafor-PET/CT for Imaging of Chemokine Receptor 4 Expression in Neuroendocrine Tumors – a head-to-head comparison with DOTATOC and FDG PET/CT

Michael Lassmann[1], Rudolf A. Werner[1,2], Alexander Weich[3], Hans-Juergen Wester[4,5], Michael Scheurlen[3], Takahiro Higuchi[1,2], Samuel Samnick[1], Christina Bluemel[1], Martina Rudelius[6], Andreas K. Buck[1], Constantin Lapa[1] & Ken Herrmann[1,7]

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Introduction
Diagnostic imaging of neuroendocrine tumors (NETs) is the domain of somatostatin receptor (SSTR) agonists as well as FDG PET/CT in dedifferentiated tumors. SSTR also serves as target for receptor directed peptide therapy. More recently, specific ligands targeting the chemokine receptor 4 (CXCR4) were introduced potentially offering an additional theranostic option in NETs. Here we evaluated the CXCR4 expression using ^{68}Ga-Pentixafor PET/CT in NET patients in comparison to ^{68}Ga-DOTATOC and ^{18}F-FDG PET/CT.

Material and methods
Eleven consecutive patients with histologically proven advanced NETs were retrospectively analyzed (three female; mean age, 69 ± 10 years; Ki67 36 ± 36%). 5/11 (45%) suffered from pancreatic NETs, 3/11 (27%) from ileum NETs, 2/11 (18%) from cancer of unknown primary and 1/11 (9%) was classified as a gastric NET. DOTATOC, FDG and Pentixafor PET/CT were performed in all patients within 4 weeks to confirm target expression of SSTR, CXCR4 and to detect dedifferentiated tumor lesions. Image analysis was performed visually. Immunohistochemical CXCR4 expression was evaluated in biopsy samples using monoclonal anti-human anti-CXCR4 antibodies.

Results
7/11 (63%) initially presented with lymph node metastases, 3/11 (27%) with bone metastases, 9/11 (82%) with liver metastases, 2/11 (18%) with lung metastases and 1/11 (9%) with a brain metastasis. On visual analysis, Pentixafor was positive in 4/11 (36%), FDG in 9/11 (82%) and DOTATOC in 9/11 (82%) patients, respectively. Of the nine SSTR positive patients seven and three were also FDG- and CXCR4-positive. Two DOTATOC negative patients were FDG positive and one of them also Pentixafor positive. Three patients were positive on all three PET/CT scans. In 2/4 Pentixafor-positive patients, biopsy samples revealed intense CXCR4 expression.

Conclusions
In this pilot study, one third of NET patients were CXCR4 positive. However, one NET patient without SSTR expression was Pentixafor positive. Hence, CXCR4-directed radionuclide therapy can be envisioned for selected patients with SSTR-negative tumors.
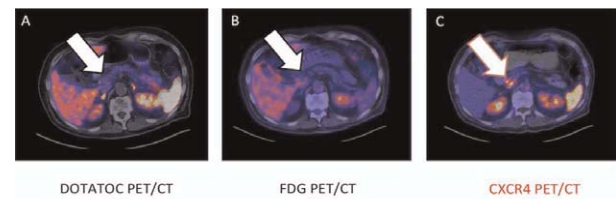

Figure 1 DOTATOC (A), FDG (B) and pentixafor/CXCR4 (c) PET/CT of a 69-year old male patient suffering from a pancreatic NET with a Ki67 0f 85%. Papilla of the pancreas demonstrated neither uptake in the DOTATOC nor in the FDG PET/CT (black arrows) whereas a Pentixafor scan was positive (red arrow)

OC15

Evaluation of somatostatin, CXCR4 chemokine and endothelin a receptor expression in a large series of paragangliomas

Daniel Kaemmerer[1], Joerg Saenger[2], Ruza Arsenic[3], Jan G. D'Haese[4], Jens Neumann[5], Aviral Singh[6], Richard P. Baum[6], Stefan Schulz[7] & Amelie Lupp[7]

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Background
Paragangliomas are predominantly benign tumors, but in some cases invasive growth and also metastasis is observed. Given the limited number of nonsurgical treatment options, novel target structures for diagnostics and therapy of this tumor entity are urgently needed.

Aims
In the present study the expression of the five somatostatin receptor (SSTR) subtypes as well as of the chemokine receptor CXCR4 and of the endothelin receptor A (ETA) was evaluated.

Methods
Receptor expression was assessed by means of immunohistochemistry using a panel of novel rabbit monoclonal antibodies in a total of 54 paraffin-embedded paraganglioma tumor samples from 43 patients. The stainings were rated by means of the Immunoreactive Score and correlated to clinical data.

Results
The SSTR2 was by far the most prominent receptor in the paragangliomas investigated. It was present in all samples at a high intensity, followed by the SSTR5, the SSTR1, the SSTR3 and the SSTR4. The CXCR4 and the ETA were seen only in a few cases on the tumor cells. However, with respect to the tumor blood vessels, in all cases an exceptionally strong staining for the ETA and in the majority of the samples also for the CXCR4 was noticed.

Conclusions
Due to the high expression rate found in the present study, paragangliomas seem to be well suited for SSTR2-based diagnostics and therapies. Additionally, an indirect targeting of these highly vascularized tumors via the CXCR4 or the ETA may represent a promising future strategy.

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OC16

Benefits and challenges of translating pre-clinical studies into clinical practice
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Radiolabeled peptides that target with high affinity and specificity their receptors on tumor cells are being applied as nuclear tracers for both diagnostic imaging and targeted radionuclide therapy with great success. It is an extensive process to bring a newly designed radiolabelled peptide molecule from its design into the clinic however and from a vast number of newly designed and developed radiolabeled peptides only few will finally meet the conditions for clinical application. So, in tracer development, preclinical work in different models with different levels of complexity has to be performed, ranging from studies using isolated cells or cell membranes to validate receptor affinity and specificity to imaging and therapy studies *in vivo* in animal models. The radiolabeled peptides that successfully pass all the desired preclinical tests, including toxicological studies and established radiopharmaceutical preparation, may enter clinical studies in humans. This lecture will focus on translational studies to be performed for translation into the clinic of novel peptide tracers from different peptide families and will focus on experimental conditions, hurdles, pitfalls, and opportunities related to preclinical evaluation. In this lecture also examples of peptide molecules that have been successful and peptide molecules that failed will be given.

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OC17

Dosimetry in ^{177}Lu treatment: what we know and what we do not know
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^{177}Lu-labelled compounds show many advantages for dosimetry assessments due to the attractive physical properties of the isotope which comprise a clearly separated gamma peak at 208 keV and low abundance of photons which permits reliable quantitative imaging after therapy. In addition, the low range of beta particles is advantageous for radiation protection. This talk mainly focuses on dosimetry methodology which includes consideration of the number and time points of scans, quantitative imaging, methods for integrating time-activity curves and calculating absorbed doses. The most recent results of absorbed dose calculations for the kidneys, bone marrow, and tumors will be presented. Reasons are given why the absorbed doses reported for radiopeptide therapies using ^{177}Lu labelled compounds taken from clinical studies show a high variability. For radiopeptide therapies with ^{177}Lu labelled compounds the widely assumed dose-limit to the kidneys is 23–25 Gy. This value is based on data from external beam therapy; a dose-response for kidney toxicity after ^{177}Lu radiopeptide therapies has not been observed. Therefore, further clinical studies are suggested to establish such a dose-limit for kidney toxicity. The results of such studies might lead to further optimization of treatments with ^{177}Lu labelled compounds. In addition, new studies which link DNA damage to internal dosimetry will be presented as this might bring new insights in the individual patients' radiation sensitivity associated with PRRT therapy.

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Spotlight on Prostate Cancer
OC18

The Holy Grail: individualised dosimetry for radionuclide therapy
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Historically, many radionuclide therapy (RNT) procedures practiced in nuclear medicine have employed standardised amounts of a radionuclide for the therapy. This often neglects factors such as patient size, tumour burden, rate of disease progression and intra-lesional heterogeneity. At the opposite end of the spectrum, treatment procedures using external beam radiotherapy (EBRT) have become increasingly individualised to maximise the dose to target whilst minimising radiation dose delivered to normal tissues. Currently, the majority of RNTs still follow the former paradigm. Individualising dosimetry can have two differing aims: (i) to deliver what is believed to be a tumouricidal dose of radiation to the target to attempt to effect local control or (ii) to limit the radiation exposure of dose-limiting organs whilst achieving a measure of tumour control. Dose-limiting organs often include bone marrow and kidneys. Inevitably, treatment planning may try to attempt to achieve both of these sometimes competing aims simultaneously. One limitation in implementing image-based treatment planning for RNT has been the compromised data format when using 2D (planar) whole-body images from the gamma camera (e.g., I-131, Lu-177) to measure the biodistribution over time. These data are typically not quantitative and suffer from significant organ and tissue overlap, such that individual organs and lesions cannot be readily interrogated in isolation. This problem does not exist with PET imaging (e.g., I-124, Cu-64) for treatment planning as the images are inherently 3D and quantitative. Recent advances in gamma camera imaging, driven by the introduction of combined SPET/CT systems and improved iterative reconstruction algorithms, provide the potential for quantitative whole-body (3D) SPECT imaging. This overcomes a number of issues and the remaining challenge for planning RNT with g-emitting radionuclides will be the need to acquire data at a number of time points to study the individual biodistribution. The compromise situation, which may well prevail, is to start a course of RNT with a standard dose and acquire the necessary data to individualise subsequent treatments.

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OC19

The history of PSMA and future directions
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The World Cancer Research Fund International predicts the number of prostate cancer (PCa) cases will approach 1.7 million by 2030. Patient-specific staging drives the demand for sensitive and specific imaging of PCa including intraprostatic disease as well as local and distant metastases. Definitive therapy such as surgery or radiation is highly effective, but if the tumor escapes the gland, treatment options are limited. New imaging approaches that can more accurately assess the status of disease are needed and targeted radiotherapy could be a powerful treatment for refractory PCa (mCRPC). Prostate specific membrane antigen (PSMA) may be the ideal target for PCa due to its near universal expression on PCa cells and recent significant clinical success in translating radiolabeled small molecule PSMA inhibitors for imaging and therapy. Early work on the development of inhibitors of NAALADASE, a glutamate carboxypeptidase II enzyme, identified a number of small molecule inhibitors of this enzyme. Ultimately, the identification of the structural and functional homology between NAALADASE and PSMA opened the possibility of using small molecules for the targeted treatment and imaging of PCa. The first published demonstration of PET imaging of PCa with small-molecule PSMA inhibitor in animals was described in 2002 using 11C. The first major clinical step forward was realized in 2008 with the first human experience with 123I-MIP-1972 and 123I-MIP-1095. A 'theranostic' breakthrough followed in 2011 with the first clinical demonstration of successful endoradiotherapy of mCRPC using 131I-MIP-1095. That same year 68Ga-PSMA-11 was introduced for PET imaging which rapidly spread worldwide. New 18F based tracers such as 18F-DCFPyL and 18F-PSMA-1007 followed. The promising results of 131I-MIP-1095 in mCRPC patients stimulated development of 177Lu labeled compounds, such as DKFZ-617 and PSMA I&T. These DOTA containing analogs represent a novel class of PSMA-targeting theranostics allowing the use of 68Ga for PET imaging and 177Lu (beta) and 225Ac (alpha) for endoradiotherapy. The latter recently introduced into the clinic and thereby creating a new theranostics paradigm. The promise of theranostics is powerfully demonstrated in the application of small molecule PSMA inhibitors to PCa.

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OC20

Evolving evidence of PSMA PET/CT

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Since its introduction as an imaging agent in humans in 2011, Ga PSMA PET CT has been rapidly embraced clinically for the imaging of prostate cancer both in the setting of biochemical failure and as a staging procedure. The increased sensitivity of the technique in comparison to previously available imaging modalities, and the startling images, have led to a paradigm shift in the treatment of prostate cancer, particularly in the setting of biochemical failure. This talk will give an overview of the evolving evidence for the use of Ga PSMA in prostate cancer and discuss the need for ongoing research into a promising technique that has turned the management of prostate cancer on its head in recent years.

OC21

Should PSMA PET/CT replace conventional imaging?

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Introduction
Conventional imaging for prostate cancer typically utilizes cross-sectional CT and MRI scanning, along with Tc99 bone scanning for bone metastases. All of these modalities have relatively poor sensitivity and specificity, particularly for men with suspected recurrence following radical prostatectomy or radiotherapy. PSMA PET is rapidly emerging as a superior imaging option.
Objective
To give a clinical perspective of the role PSMA PET for staging recurrent and high-risk prostate cancer.
Evidence overview
PSMA PET has provided a significant advance in imaging sensitivity and specificity for men with biochemical recurrence following previous definitive treatment. Recurrence can be identified in up to 50% of men with PSA levels below 0.5 ng/ml post-radical prostatectomy. However the decision impact of this is unclear. PSMA PET also appears sensitive for recurrence following primary radiotherapy. The role of PSMA PET for staging primary localised prostate cancer, especially lymph node staging in high-risk localised prostate cancer, is under evaluation with encouraging early data. Overall, PSMA performs much better than conventional imaging and much better than other PET tracers such as choline. It is also much more accessible and affordable in regions in which is has become popularised. PSMA PET also offers theranostic possibilities adding another dimension to its utility.
Conclusions
PSMA PET is an exciting new option for imaging in prostate cancer and greatly outperforms existing imaging modalities for recurrent and higher risk localised prostate cancer. However prospective studies are required to define its optimal role and to measure decision impact. Theranostic possibilities are also of clinical interest for advanced prostate cancer.

OC22

PET/MRI: better AND worse than PET/CT for PSMA PET imaging

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Currently national and international guidelines for imaging procedures for high risk and advanced prostate cancer (PCa) include abdomino-pelvic cross sectional imaging, multiparametric prostate MRI, bone scintigraphy and in the case of therapy monitoring of mCRPC whole body cross-sectional imaging mainly by means of computed tomography. Positron emission tomography (PET) has become increasingly important in the work-up of prostate cancer. Recently, a ^{68}Gallium-labelled ligand of the prostate-specific membrane antigen (^{68}Ga-PSMA) has been introduced in PET-imaging of PCa with first promising results. Due to relatively exclusive expression of PSMA in prostatic tissue as well as increased expression in PCa ^{68}Ga-PSMA was reported to exhibit a favourable lesion to background ratio compared to presently used choline- or fluorodesoxyglucose-based PET examinations. Together with the novel development of combined

PET/MR, the combination of excellent morphological detail, multiparametric functional information and molecular PET data might lead to a significant improvement in detection and staging of PCa and thus may help to optimize oncological treatment. Teaching and learning contents of the talk will include:
1. The molecular basis of prostate cancer imaging targeting the prostate-specific-membran antigen (PSMA), review of the various PSMA-tracers
2. The diagnostic performance and potential role of PSMA PET/CT and PET/MR for high-risk primary and advanced prostate cancer
3. Challenges using Ga-labelled PSMA-agents in PET/MR
4. Comparison of the workflow for integrated PET/MR vs PET/CT
5. Outline of a potential approach for patients selection towards PET/MR vs PET/CT

OC23

Imaging the expression of gastrin releasing peptide receptors in prostate cancer using Ga-68 labeled antagonists

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Abstract unavailable at time of publishing.

OC24

How to get away with PET+MRI

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Stanford University has installed the first GE SIGNA PET+MRI world-wide in December 2013 as part of a comprehensive research program expanding the successful Radiological Sciences Laboratory (RSL) MRI research and the Molecular Imaging Program at Stanford (MIPS) expertise. The presentation will address the challenges, opportunities and success stories of the program after 3 years of research activities.

OC25

Re-assessing gallium-67 as a therapeutic radionuclide

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Background
Despite its desirable half-life and high-energy Auger electrons, ^{67}Ga has been neglected as a therapeutic Auger electron emitter, due in part to lack of suitable chelators and targeting molecules.
Objective
Here, ^{67}Ga is compared with Auger electron emitter ^{111}In as a therapeutic radionuclide in prostate cancer and breast cancer cell lines.
Method
Plasmid pBR322 studies allowed direct comparison between ^{67}Ga and ^{111}In (1 MBq) in causing DNA damage, including the effect of chelators EDTA and DTPA and the effects of free radical scavenger DMSO. The cytotoxicity of internalized (using oxine) and non-internalized ^{67}Ga and ^{111}In was measured in cancer cells after a one-hour incubation using cell viability and clonogenic studies.
Results
Plasmid DNA damage caused by ^{67}Ga was comparable to ^{111}In and was reduced in the presence of EDTA, DTPA and DMSO. The A_{50} values (internalized activity of oxine complexes per cell required to kill 50% of cells) as determined by trypan blue staining was 1.0 Bq/cell for both ^{67}Ga and ^{111}In; the A_{50} values determined by clonogenic assay were 0.7 Bq/cell and 0.3 Bq/cell for ^{111}In and ^{67}Ga respectively. At the concentrations required achieving these uptake levels, non-internalized ^{67}Ga and ^{111}In caused no cellular toxicity.

Conclusion
[67]Ga causes as much damage as ^{111}In to plasmid DNA in solution and is more toxic than ^{111}In at equivalent internalized activity per cell in the cell types studied. [67]Ga therefore deserves further evaluation for radionuclide therapy.

OC26

^{177}Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: safety, efficacy and quality of life assessment

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Purpose
The purpose of this study was to evaluate the efficacy and safety of a novel theranostic agent, ^{177}Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer (mCRPC).
Methods
31 mCRPC patients with progressive disease despite second line hormonal therapy and/or Docetaxel chemotherapy were recruited for the study. All patients underwent diagnostic[68]Ga-PSMA-HBED-CCPET/CT, prior to inclusion for therapy. Included patientsthen underwent quarterly ^{177}Lu-DKFZ-PSMA-617 therapy. Hematological, kidney function, liver function tests and serum PSA levels were recorded before and after therapy at 2 weeks, 4 weeks and 3 month intervals. Biochemical response was assessed with trend in serum PSA levels. Metabolic response was assessed by PERCIST 1 criteria. Clinical response was assessed by visual analogue score (VASmax) analgesic score (AS), Karanofskys performance status (KPS) and Toxicity and response criteria of the Eastern Cooperative Oncology Group (ECOG) criteria.
Results
The mean age of patients was 65.93 ± 9.77 years (range: 38–81 years). The mean activity administered in the 31 patients was 5069 ± 1845 MBqranging from 1–4 cycles. There was a decline in the mean serum PSA levels from the baseline (baseline: 275 ng/ml, post 1st cycle therapy: 141.75 ng/ml). Based on biochemical response criteria 2/31, 20/31, 3/21 and 6/31 had complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD), respectively. Metabolic response revealed 2/6 patients with CR, and remaining 3/6 patients with PR and 1/6 patients with SD. The mean VASmax score decreased from 7.5 to 3. The mean analgesic score reduced from 2.5 to 1.8 after therapy. The mean KPS score improved from 50.32 to 65.42 after therapies. The mean ECOG performance status improved from 2.54 to 1.78 after therapy. Two patients experienced grade I and grade II hemoglobin toxicity each.None of the patients experienced nephrotoxicity or hepatotoxicity.
Conclusion
^{177}Lu-DKFZ-PSMA-617 radionuclide therapy is a safe and effective approach in the treatment of mCRPC patients.

OC27

Initial experience with aggressive treatment of metastastic prostate cancer using 3 cycles of 7.4 GBq [177Lu]-PSMA every 4 weeks

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Aim
Given the aggressive biological features of metastatic prostate cancer, a more aggressive treatment with [177Lu]-PSMA might be appropriate.
Materials and methods
We have treated 15 patients (mean age 69 years) with intended 3 cycles of [177Lu]-PSMA every 4 weeks. All patients have been examined with [68Ga]-PSMA PET/MRI to validate PSMA expression of all metastatic lesions. We monitored haemoglobin (Hb), platelets (Pl), leucocytes and creatinine for assessment of toxicity. The highest toxicity grade until 3 months after the last cycle was assessed. Scintigraphy of the salivary glands before treatment, and after the third cycle has been used to assess salivary toxicity. For treatment response we evaluated PSA values before the first and after the third cycle. For RECIST based response 12/15 patients were examined with [68Ga]-PSMA PET/MRI 4 weeks after the last cycle.

Results
12/15 patients were treated with all 3 cycles; In 2/15 treatment was stopped after the second cycle due to progressive disease, in 1/15 patient treatment was stopped due to PSA response (-52%) and minimal tumor load. 11/15 patients (73%) had a decreasing PSA (mean -53%), 6/15 (40%) with a decline of more than 50%. According to RECIST 5/12 patients showed PR (42%), 4/12 SD (33%) and 3/12 PD (25%). Treatment was excellent tolerated with no grade 2 toxicity. 1/15 patients showed an increase of Hb toxicity of grade 0 to 1; 2/15 had an increase of Pl toxicity from grade 0 to 1 and 4/15 of leucocytes toxicity, which resolved after 3 months, respectively. We experienced no toxicity regarding creatinine. We did not experience any relevant loss of function neither in scintigraphic monitoring of the salivary glands nor from patient reports.
Conclusion
Aggressive [177Lu]-PSMA treatment was safe and effective and might better reflect the more aggressive nature of castration resistant metastatic prostate cancer.

OC28

Theranostic in early detection of recurring prostate cancer: [64]CuCl$_2$

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Aim
To evaluate the use of PET/CT with [64]CuCl$_2$ in recurring prostate cancer after surgery in patients with low PSA level (<2).
Introduction
Previous works* demonstrated as [64]CuCl$_2$ is a PET probe in prostate cancer in mice with xenografts of prostate cancer.Moreover, it was described** in seven patients the role of [64]CuCl$_2$ PET/CT in staging of prostate cancer.
Method
32 Patients with low PSA level (<2) in recurring prostate post-surgical cancer were studied with [64]CuCl$_2$ PET/CT executed at 1, 3 and 24 h after injection of 200–400 MBq (medium activity 4 MBq/kg). A dosimetric analysis was done with manual VOI on various organs (Liver, Kidneys, Spleen, lumbar spine L4-L5 and Prostate as target). Coregistered imaging with CT to calculate VOIs, specific activity (Bq/ml) and SUVmax were executed. We analyzed time/activity curve with Olinda/EXM software to calculate absorbed dose. All patients had a control of PSA 10 days after PET/CT scan.
Results
The PSA value was 1.1 ng/ml (0.4–1.9 ng/ml). All patients showed lesions with an uptake of [64]CuCl$_2$ with a ratio lesion/background grate than 10. The positive lesions ($n=63$) had a medium dimension of 5.2 mm (3–9 mm) in linfonodes ($n=46$), Prostatic lodge ($n=13$) and Bone ($n=4$). After 10 days all patients presented a reduction of PSA with a medium of 0.3 ng/ml (0.1–0.5). Sensibility 90%.
Conclusion
PET/CT scan with [64]CuCl$_2$ is a high sensitivity method to detect early recurring prostate cancer after surgery. The possibility to see the lesions in early stage and in low dimensions (3–9 mm) opens a new possibility for theranostic application. The reduction value of PSA after 10 days could be related to the therapeutic effect of [64]CuCl$_2$. When the lesions are very small, a diagnostic dose could be also therapeutic. Further studies are necessary, but this could be a new approach in theranostic application.
*F.Peng et al. – J.Nucl.Med. 2006; **E.Capasso et al. – Ann.Nucl.Med. 2015

OC29

A short history of transforming the diagnostic tracer PSMA-11 into the theranostic variant PSMA-617

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PSMA-11 belongs to the substance class of peptidomimetic prostate-specific membrane antigen (PSMA) inhibitors. In general, the class of urea-based PSMA inhibitors was firstly described by Kozikowski et al. in 2001 [1] and one of the first preclinical imaging studies using PSMA radioligands in PSMA-positive

tumor xenografts were reported by Pomper *et al.* in 2005 [2]. PSMA is an optimal target both for imaging and therapy of prostate cancer. The now well established PSMA radioligand Ga-68-PSMA-11 for PET imaging of PSMA-positive prostate cancer was clinically introduced in 2011. The first clinical papers on Ga-68-PSMA-11 PET/CT imaging were published in 2012 and 2013 by Afshar-Oromieh *et al.* [3]. Ga-68-PSMA-11 was developed by the Heidelberg group at the German Cancer Research Center (DKFZ) Heidelberg. Eder *et al.* published the synthesis and the preclinical evaluation of Ga-68-PSMA-11 [4] which encouraged the aforementioned clinical introduction in Heidelberg. The complexing agent HBED-CC was conjugated to the pharmacophore Glu-urea-Lys. The resulting conjugate PSMA-HBED-CC (PSMA-11) cannot bind clinically relevant therapeutic radiometals such as Lu-177 or Ac-225. PSMA-11 can thus only be used for diagnostic purposes. However it soon became clear that PSMA inhibitors can also be used for PSMA radioligand therapy (PSMA-RLT) of prostate cancer. The first published clinical theranostic approach using radioiodinated versions of the PSMA inhibitor MIP-1095 was reported in 2014 [5]. MIP-1095 was in fact firstly described by Babich *et al.* in 2009 [6]. As a consequence the Heidelberg group started an initiative to transform the diagnostic tracer PSMA-11 into the theranostic variant PSMA-617 which can also be radiolabelled with the therapeutically relevant trivalent radiometals Lu-177 for beta therapy and Ac-225 for alpha therapy [7], [8]. Consequently, the here intended presentation will describe the chemical transformation of Ga-68-PSMA-11 into Lu-177-PSMA-617 which is currently one of the main candidates for endoradiotherapy (PSMA-RLT) of prostate cancer.

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OC30

Beyond wizardry: creating high level evidence for PSMA PET Imaging and Theranostics

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Ga-68 PSMA PET/CT is producing images with astounding tumour-to-background contrast for staging prostate cancer. Defining the extent of prostate cancer spread with imaging is of utmost importance for therapeutic decision-making. Relapse following curative-intent treatment is not uncommon despite careful selection of patients with CT, MRI and bone scintigraphy prior to surgery or radiotherapy, highlighting the limited sensitivity of conventional imaging. Imaging with PSMA-PET may improve patient outcomes by redirecting patients with metastatic disease from curative-intent local treatments destined to fail to more appropriate management. This presentation will detail the 'ProPSMA' multi-centre, randomised controlled trial designed to provide robust data on the diagnostic accuracy, management impact and economic benefits of using PSMA-PET for primary staging of high-risk prostate cancer.

On the other end of the spectrum, patients with established metastatic disease remain incurable. Although androgen deprivation and chemotherapy may control disease, patients relapse with limited therapeutic options. Lutetium-177 PSMA has emerged as a promising theranostic pair for patients with metastatic PSMA-avid disease. Emerging evidence suggests high response rates but the data are from single centre, retrospective studies with non-uniformity of protocols, potential selection bias and lack of robust follow-up or control arm. The early results of the first Australian prospective trial and plan for a multi-centre randomised controlled trial will be presented.

OC31

First in-man study of ^{68}Ga-THP-PSMA PET in patients with primary prostate cancer: initial results

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Ga-68 labelled urea-based inhibitors of the prostate specific membrane antigen (PSMA), such as ^{68}Ga-HBED-PSMA-11, are promising peptides for targeting prostate cancer. The tris(hydroxypyridinone) (THP) ligand rapidly complexes ^{68}Ga^{3+} at room temperature, at very low concentration and over a wide pH range, making it possible for the direct elution from a ^{68}Ge/^{68}Ga generator into a cold radiopharmaceutical kit in one step without any manipulation. This first in-man study aimed to assess the safety and biodistribution of ^{68}Ga-THP-PSMA (ACTRN: 12615001324505).

Methods
Eight patients with pathologically proven prostate cancer scheduled to undergo prostatectomy were recruited (mean age 61, range 46–71; Gleason score 7–10; PSA mean 7.8, range 5.4–10.6). ^{68}Ga-THP-PSMA was administered with whole body PET/CT imaging performed at multiple time-points from administration to 180 min. Patients were followed-up for 24 h to evaluate for adverse events. All patients proceeded to prostatectomy with PSMA immunohistochemistry performed. Seven patients also underwent pelvic nodal dissection.

Results
No adverse events occurred. Six of eight patients had increased uptake in the prostate above background (at 2 h imaging: average SUV$_{max}$ 5.1, range 2.4–9.2; volume 4.1 mL, range 1.4–10.4). Physiologic activity was seen in salivary glands, liver, spleen and duodenum; activity in these organs was significantly lower than our experienced with ^{68}Ga-HBED-PSMA11, although direct comparison was not performed. 3+ immunohistochemistry staining was seen in 6 THP-PSMA positive scans, and 1+/2+ staining in the 2 THP-PSMA negative scans. Patients with SUV$_{max}$ over five all had 3+>80% PSMA staining. Pathologic pelvic nodal involvement was identified in two patients although <1 mm in size and therefore not visualised on PET. One patient had focal uptake in sub-cm pelvic nodes without pathologic abnormality; follow-up is awaited to see if this represented sampling error.

Conclusion
^{68}Ga-THP-PSMA is safe. Focal uptake in prostate adenocarcinoma correlates with high PSMA expression.

OC32

Prostate specific membrane antigen targeted radioligand therapy of metastatic castration-resistant prostate cancer using Lu-177 PSMA-617: safety, efficacy and dosimetry in comparison with Lu-177 PSMA I&T

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Aim
To analyze the safety, efficacy and dosimetry of Lu-177 labeled prostate specific membrane antigen (PSMA) ligand 617 in patients with progressive metastatic castration-resistant prostate cancer (mCRPC), in comparison with Lu-177 PSMA I&T.

Methods
Lu-177 PSMA-617 radioligand therapy (PRLT) was performed in 64 mCRPC patients. The median administered activity per treatment was 6 GBq. Ga-68 PSMA PET/CT was used for patient selection and follow-up. Hematological status, renal and hepatic function and serum prostate specific antigen (PSA) levels were documented before and after therapy.

Results
Lu-177 PSMA-617 demonstrated intense accumulation in the metastases. The absorbed tumor dose was 6.3 mGy/MBq (median). Parotid glands received a higher dose (1.0 mGy/MBq) than kidneys (0.65 mGy/MBq). All patients tolerated the therapy well without any acute adverse effects. Mild xerostomia was observed in five patients. G1 hematological toxicity was noticed in 13 patients, G2 in five and G3-4 pancytopenia in two patients. Mild erythrocytopenia was the commonest sequel. Higher-grade toxicity was observed in patients ($n=7$) having received chemotherapy or Ra-223 treatment before. The severity of pain was

significantly reduced in 6/17 (35.3%) symptomatic patients after PRLT. Decrease in PSA was noted in 48/64 (76.9%) patients. Molecular response evaluation (Ga-68 PSMA PET/CT) in 29 patients followed up after at least two cycles revealed complete remission (CR) in three, partial remission (PR) in 12, stable disease (SD) in five and progressive disease (PD) in nine patients. CT exhibited PR in eight, SD in 14, and PD in seven patients. The median overall survival is yet to be reached and progression-free survival was 12.3 months.

Conclusion

Lu-177 PSMA-617 appears to be safe and effective in progressive mCRPC. The kinetics and dosimetry are similar to Lu-177 PSMA-I&T, the first-ever PSMA inhibitor used at our center.

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OC33

Molecular imaging with ^{64}Cu-PSMA PET/CT in Theranostics of prostate cancer

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Objectives

Copper-64 (^{64}Cu, T1/2 = 12.7 h; Eβ+ max = 0.65 MeV (17.9%); Eβ− max = 0.57 MeV (39%)) is suitable for *in-vivo* PET imaging. Prostate specific membrane antigen (PSMA) is significantly over-expressed in undifferentiated prostate cancer tissue. We report the initial molecular imaging results with ^{64}Cu-PSMA PET/CT in patients with prostate cancer.

Methods

^{64}Cu labeled PSMA (mean administered radioactivity – 260 MBq) was administered to nine patients referred for restaging following elevation of PSA. Whole-body PET/CT (Biograph mCT Flow 64) was performed up to 17 h p.i. All ^{64}Cu-PSMA-positive lesions were counted and SUV$_{max}$ recorded. Comparison was made with previous and concurrent imaging, and therapy response evaluation was performed according to RECIST/PERCIST.

Results

Seven (77.7%) patients had previous prostatectomy. Two (22.2%) patients had uptake in the prostate bed, suggestive of local recurrent disease. Lymph node metastases were seen in five (55.5%) patients. Skeletal metastases were detected in four (44.4%) patients. Two (22.2%) patients demonstrated no pathological tracer uptake, compatible with bio-chemical recurrence post-prostatectomy. Three patients had stable disease (SD), despite PSA increase. Progressive disease (PD) was observed in four (44.4%) patients, out of which, three were recommended ^{177}Lu-PSMA radioligand therapy (PRLT). No adverse effects were observed in any patient.

Conclusion

Molecular imaging with ^{64}Cu-PSMA PET has potential for prostate cancer staging, restaging, and ^{177}Lu-PRLT planning. High resolution images were obtained. Late imaging, up to 17 h.p.i., is possible due to the longer half-life of ^{64}Cu. ^{64}Cu can be produced centrally and distributed to distant centers without a cyclotron or where ^{68}Ga-generator facilities are not available. ^{64}Cu-PSMA was found safe for human use. Future applications as Theranostics 'matched pair' using beta-emitting Copper-67 maybe possible. Clinical studies directly comparing other PET radiopharmaceuticals, such as ^{68}Ga- or ^{18}F- PSMA or ^{18}F-Choline are warranted to establish the specific role of ^{64}Cu-PSMA PET imaging in patients with prostate cancer.

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OC34

Radiolabelling of DOTA^{MZOL} with ^{68}Ga and ^{44}Sc for clinical application

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Objectives

DOTA^{MZOL} is a DOTA-conjugated bisphosphonate which can be used for diagnostic (^{44}Sc, ^{68}Ga) or therapeutic (^{177}Lu) applications. The aim of this study was to evaluate the adaption of the radiolabelling process on an automated module utilizing NaCl-post processing, with regard to clinical application and additional radiation protection point of view.

Methods

^{68}Ga was obtained from a 1.5 years old 1.85 GBq ^{68}Ge/^{68}Ga-generator (iThemba, South Africa). ^{44}Sc was obtained from a 180 MBq ^{44}Ti/^{44}Sc-generator (Johannes Gutenberg-University institute of nuclear chemistry Mainz, Germany). DOTA^{MZol} was provided from ITG Garching (Germany). Radiolabelling was performed on an automated cassette module (GAIA, Elysia-Raytest GmbH, Germany). Compared to standard ^{68}Ga-synthesis in hard-, software and reagent were made. Synthesis route based on Meckel *et al.* was used[1], but had to be optimized in terms of temperature, reaction time, buffer, pH-value, reaction vial and quality control. These optimization on ^{68}Ga-Sythesis could be transferred and used for radiolabelling with ^{44}Sc.

Results

The reactor screening showed DOTA^{MZOL} is sensitive to reaction vials and therefore in need of a specific vial, otherwise unplanned side products are obtained. Furthermore an automated method was obtained for ^{68}Ga and a manual method for ^{44}Sc which both could be validated and established. The new quality control gives clear and reliable evidence on impurities.

Conclusion

A new Synthesis route for DOTA^{MZOL} was developed with reduced manual interference which reduced radiation exposure of the operator. It was possible to minimize the effect of the reactor and develop an automated method for modules. The procedures guarantee save preparation and high purity of ^{68}Ga-DOTA^{MZOL} as well as ^{44}Sc-DOTA^{MZOL} for clinical application.

Acknowledgement

We thank ITG Garching for support and put DOTA^{MZOl} at our disposal.

Literature

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Innovative Theranostics
OC35

Kit-based Ga-68 PET imaging

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The 68Ge/68Ga generator has the potential to greatly expand positron emission tomography (PET) imaging to benefit more patients, by allowing many PET applications in hospitals without immediate access to cyclotrons and costly radiochemistry facilities. It is often suggested that '^{68}Ga is the new ^{99m}Tc,' drawing parallels with conventional radiopharmacy practice where radiopharmaceuticals are prepared with little more complex equipment than a syringe and a vial. However, there are further barriers to overcome to realise this potential, and current ^{68}Ga labelling methods are more like those associated with^{18}F than ^{99m}Tc. Half a century of experience with ^{99m}Tc tells us that simple kit-based chelation chemistry is the key to wider patient benefit. To meet this challenge, we need chemistry that satisfies several requirements: labelling should be complete ($>95\%$) quickly (<5 min) at 20°C without additional steps to concentrate, purify or buffer; high kinetic stability *in vivo*, against transchelation by Fe3+-chelating endogenous proteins such as transferrin, is needed during the imaging period of a few hours; chelation should compete with hydroxide formation, to which Ga3+ is vulnerable, at near-neutral pH; chelation should be robust and unaffected by common trace metals present in water and equipment; conjugation and labelling should not induce isomerism or high lipophilicity that would delay renal clearance. Most ^{68}Ga-chelating chemistries that may already be described as 'conventional' do not meet these requirements. This presentation will summarise progress with the tris(hydroxypyridinone) (THP) ligands as representatives of a new generation of chelators designed to address these issues. THP ligands show good selectivity for gallium over other major contaminating biometals except iron. They can be labeled efficiently within a few minutes at room temperature, low concentration, neutral pH, without problems of isomerism. They have been used successfully to label a range of small molecules, peptides and proteins with ^{68}Ga, and they perform well in direct competitive experiments alongside a range of other ^{68}Ga chelators currently being evaluated.

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OC36

Bone seeking bisphosphonate therapy
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Metastatic bone lesion is a common syndrome of many cancer diseases in an advanced state. The major symptom is severe pain, spinal cord compression and pathological fracture, associated with an obvious morbidity. Common treatments including systemic application of bisphosphonate drugs aim on pain reduction and on improving the quality of life of the patient. Particularly patients with multiple metastatic lesions benefit from bone-targeting therapeutic radiopharmaceuticals.
The traditional design of bone volume seeking radiopharmaceuticals based on e.g. trivalent radionuclides is to form radiometal-bisphosphonate complexes, with the bisphosphonate moieties being directly involved in the coordination chemistry of the radiometal.
Here, we propose a new design, disconnecting the bisphosphonate moiety and the radiometal coordination moiety by introducing a separate, physiologically inert chelate for the radiometal.
Several DOTA- and DO2A-based bisphosphonates, including monomeric and dimeric structures and one NO2A derivative, were synthesized and labelled with both 68Ga and n.c.a. 177Lu. Radiolabeling yields for 68Ga- and 177Lu-DOTA and NO2A bisphosphonate complexes was >98% within 15 min. Within a series of next-generation bisphosphonates, a zoledronate derivative appeared to be superior to any other compounds tested.
Ex vivo biodistribution experiments and dynamic *in vivo* SPECT/CT measurements were performed in healthy rat for 1 h time points. Data on %ID/g or SUV for femur, blood and soft tissue organs were analysed. All radiopharmaceuticals showed exclusively accumulation in the skeleton. Blood clearance and renal elimination were fast. SUV data in the femur ranged from 3.34 to 5.67 at 60 min after injection in rat.
In patients, 68Ga-bisphosphonate PET imaging is (at least) as good as with 18F-fluoride. Preliminary human data demonstrate high uptake with SUVs reaching 100 and even 200. The 177Lu-complexes of macrocyclic bisphosphonates might be become therapy options for skeletal metastases. Together with analogue 68Ga bisphosphonates for PET/CT diagnosis, the new design provides excellent examples of radio-theranostics.

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OC37

The development of copper-based imaging and therapeutics agents
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Radioactive isotopes of copper are of interest in the development of imaging agents for positron emission tomography (PET) and companion therapeutics. The synthesis of a ligand, 5-(8-methyl-3,6,10,13,16,19-hexaaza-bicyclo[6.6.6]icosan-1-ylamino)-5-oxopentanoic acid (MeCOSar), designed to form stable complexes with radioactive copper isotopes that can be tethered to tumour targeting peptides and antibodies will be presented.
The MeCOSar ligand has been conjugated to Tyr[3]-octreotate and the conjugate radiolabelled with [64]Cu[II] to form [64]CuSarTATE. *In vitro* and *in vivo* evaluation of [64]CuSarTATE demonstrated its high selectivity for tumour cells expressing somatostatin receptor 2 (sstr2) resulting in with high-quality PET images with excellent tumour to background ratios at 24 h post injection.
The use of MeCOSar to radiolabel antibodies will also be discussed. Attaching the chelator to the antibody or fragment requires careful consideration to avoid compromising the affinity of the antigen-binding site for the target. The use of enzyme-mediated bioconjugation for the site-specific incorporation of a radioactive metal complex into antibodies will be presented. The chemistry presented opens up opportunities for combined imaging and therapy using a combination of [64]Cu[II]- and [67]Cu[II] complexes.

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OC38

How I do it; delivering outpatient theranostics
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Outpatient theranostics began 30 years ago in Western Australia with world-first phase 1/11 clinical trials of Samarium-153-EDTMP for pain palliation of skeletal metastases prospective individualised dosimetry in each patient, based upon a calculated maximum radiation absorbed dose of 2Gy to haemopoietic marrow was performed by quantitative whole-body gamma imaging, to prescribe the safe effective administered therapeutic activity, which was then given on the same day as an outpatient.
The same simple, practical outpatient theranostic methodology was subsequently applied to Rhenium-188-HEDP, prepared in-house using an on-site Tungsten-188/Rhenium-188 generator for inexpensive, sustainable, practical control of bone cancer pain.
In 1999, we introduced Iodine-131 rituximab radioimmunotherapy (RIT) of relapsed/refractory non-Hodgkin Lymphoma (NHL) using an outpatient theranostic approach with a prescribed individual administered activity (GBq) on the basis of a prospectively measured whole body radiation absorbed dose of 0.75Gy (predicated upon 2Gy to red marrow). The efficacy and lack of toxicity of this theranostic approach was subsequently demonstrated in first-line outpatient RIT of advanced follicular NHL. Our contemplated introduction of Lutetium-177-rituximab will obviate the requirement for such patient isolation within the community.
We have administered Lutetium-177-octreotate exclusively as an out-patient therapy of NETs for over a decade. The radiation safety of this simple, practical and relatively inexpensive outpatient approach has been documented in a formal study of radiation exposure to hospital personnel, patient's family members and the public and measured rates are in conformity with international guidelines.
The enhanced efficacy of our outpatient theranostic Lutetium–177-Octreotate PRRT of GEP-NETs, when combined with radiosensitizing chemotherapy with capecitabine and temozolomide is currently under formal multicentre randomised controlled trial throughout Australia–CONTROL–NETs (ACTRN12615000909527).
We have recently reviewed the short-term and long-term myelotoxicity of our outpatient theranostic Lutetium-177-Octrotate capecitabine/temozolomide PRRT of GEP-NETs and shown it to be modest, provided that patients have not been heavily pre-treated with alkylating agents. We are now currently reviewing the myelotoxicity profile of our out-patient theranostics Lutetium-177-PSMA radiopeptide therapy of advanced prostate cancer.

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OC39

The success and failure of radioimmunotherapy for lymphoma
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Two anti-CD-20 radioantibody therapies: Y-90 ibritumomab tiuxetan (Zevalin) and I-131 tositutumomab (Bexxar) were approved in the USA in the early 2000s. The safety and efficacy of both Bexxar and Zevalin were proven relative to rituximab. While Zevalin remains on the market, sales are reportedly low. Bexxar exited the market in 2014 after low sales. Bexxar cost $26K USD, 'very expensive' by early 21st century standards, but low compared to cancer therapies in 2016. The challenges with Bexxar in the USA marketplace occurred at a time when private practice oncologists received the majority of their compensation from the mark up of drug prices between the wholesale and retail prices. Oncologists could prescribe

rituximab at an infusion center, making money on every patient they treated. Prescribing radioimmunotherapy meant they would lose that revenue stream. In addition, there were logistical issues with radiopharmaceutical therapy, notably Bexxar, which had personalized dosimetry and challenges related to use I-131 as an inpatient in many locales. Other issues included US Medicare paying less than the cost of the dosimetric or therapeutic agent and a logistical arrangement which paid none of the providers much for their time. Both Bexxar and Zevalin have suffered from having multiple commerical owners of the key technology. Oncologists also had concerns of patients developing myelodysplastic syndromes, which could be fatal. In time, other therapies emerged, while the RIT were mainly static in their technologies such as Bendamustine and idelalisib.

A trial comparing 554 patients randomized to chemotherapy + rituximab or chemotherapy + Bexxar showed comparable outcomes. Bendamustine + ritiuximab appears to be even more effective. Zevalin remains available, as well as I-131 rituximab in Australia, but both are 'underutilized' relative to their efficacy. Lessons from these agents should serve to inform and caution the theranostics community. Theranostic agents need to 'work' in the disease and 'work' in the marketplace to succeed.

OC40

PSMA in breast cancer
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The prostate specific membrane antigen (PSMA) has been reported to be selectively overexpressed in the tumor-associated neovasculature of a wide variety of solid tumors including breast carcinoma, and growth and progression of breast cancers are accompanied by increased neovascular-ization (angiogenesis). In this context, the robust expression of PSMA by breast cancer lesions as evidenced using PSMA-PET/CT makes PSMA an interesting potential target for antiangiogenic therapy of breast carcinoma. Furthermore, the 68Ga-PSMA avid lesions encourage ongoing exploration about the potential therapeutic application of PSMA-targeted radioligand therapy (PSMA-RLT) against breast cancer. PSMA can be probably be seen as one of the most interesting molecular imaging and therapeutic probe that may provide new opportunities in the design of individually suited therapies and response evaluation.

OC41

Theranostics for the invasive cancer phenotype: uPAR targeted theranostics
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Abstract unavailable at time of publishing.

OC42

Optimizing theranostics through pretargeting approaches
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The intrinsic selectivity and flexibility of bioorthogonal click chemistries make them an almost ideal synthetic methodology for the creation of radiolabeled PET imaging agents. One type of bioorthogonal reaction, the inverse electron demand Diels-Alder reaction between tetrazine and TCO, has particularly appealing characteristics for *in vivo* pretargeting applications. Simply put, the thrust of pretargeted imaging is to harness the exquisite tumor-targeting properties of antibodies while avoiding their slow pharmacokinetics and high background doses. To this end, pretargeting strategies decouple the targeting vector from the radioisotope at the time of injection. In the case of tetrazine/TCO pretargeting, a

TCO-labeled antibody could be injected days ahead of the actual imaging procedure. Then, only hours before imaging, a radiolabeled small molecule is administered which travels through the blood with a dramatically reduced blood half-life, either binding to the TCO-labeled antibody or quickly clearing from the patient.

Pretargeted approaches hold the promise of producing high activity uptake in tumors with extremely low levels of off-target radiation in non-target organs. In essence, this negates the biggest drawback of radiolabeled antibodies: the high radiation dose delivered to healthy tissues during long circulation times. These preclinical approaches illustrate the tremendous promise of the tetrazine/TCO reaction, establishing the basis for a clinical application of the methodology. In this R01, our goal is to translate this tetrazine/TCO-based pretargeting strategy to the clinic and to show that this technology can be superior to traditional PET imaging approaches using directly radiolabeled antibodies.

OC43

Initial South African experience on ^{68}Ga/^{213}Bi radiolabeling for prospective theranostics
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Background
The current focus of personalized medicine is towards the use of the theranostic approach – the development of an interdependent, collaborative targeted therapeutic and a companion diagnostic test. [DOTA^0,D-Phe^1,Tyr^3]-octreotate (DOTA-TATE) and ligands targeting prostate-specific membrane antigen (PSMA) have been introduced recently as ^{177}Lu-labeled theranostics for neuroendocrine tumors and prostate cancer respectively [1, 2]. DOTA-RP001 is a novel 11-mer peptide conjugate, envisaged as a theranostic agent against pancreatic cancer. For this study, ^{213}Bi which can be complexed by the DOTA-functionalized compounds for alpha-emitting radionuclide therapy is supported by ^{68}Ga, a PET-isotope prioritized for diagnostic imaging. ^{213}Bi was initially introduced clinically for radioimmunotherapy [3]. We report initial empirical values gained over the past 5 months on radiolabeling DOTATATE, PSMA^{HEBD}/DOTA-PSMA-617 and DOTA-RP001 with ^{68}Ga and ^{213}Bi, pioneering this procedure in South Africa.

Methods
^{68}Ga and ^{213}Bi were obtained by eluate fractionation from ^{68}Ga/^{68}Ge-generators (iThembaLABS, Somerset West, South Africa) and ^{225}Ac/^{213}Bi-generators (ITG, Garching, DE); sodium acetate buffered bioconjugates (pH 3.5–5) were incubated at 93–95 °C for 15 min followed by purification. Final solutions were sterilized by filtration directly to syringes diluted to ∼ 10 ml. Radiochemical purity and yields were assessed by HPLC/ITLC-SG.

Results
^{68}Ga-labeling succeeded using 0.05 mg DOTATATE and 0.005 mg PSMA$^{HEBD-CC}$; ^{213}Bi was quantitatively complexed using 0.1 mg DOTATATE or DOTA-PSMA-617. All patient administrations were successful. ^{68}Ga-DOTATATE-PET/CT was carried out (133–259 MBq, n=15) to support ^{213}Bi-DOTATATE treatment (259–370 MBq). ^{68}Ga-PSMA$^{HEBD-CC}$-PET/CT (120–240 MBq, n>20) was performed to facilitate ^{213}Bi-DOTA-PSMA-617 treatment (222–407 MBq). The method translated well to yield 77±20% (decay-corrected) ^{68}Ga-DOTA-RP001 (using 0.05 mg, RCP ≥96.4% after purification, 162–336 MBq, n=5) and a RCP of 65.7%, 91.2% and 97.5% for ^{213}Bi-DOTA-RP001 (using 0.05 mg, 222–259 MBq, n=3) after 5, 10 and 15 min incubation, respectively.

Conclusion
The data indicates that a robust preparation and safe administration to humans warrants prospective clinical studies with ^{68}Ga/^{213}Bi-theranostic agents.

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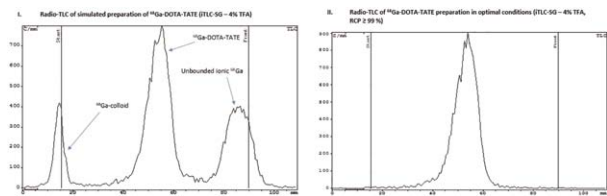
OC44

Critical aspects of radiochemical purity determination of ^{68}Ga-BCA-peptides and behavioral features of different ^{68}Ga species

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Determination of radiochemical purity (RCP) of radiopharmaceuticals based on ^{68}Ga-BCA-peptides (^{68}Ga-DOTA-TOC/-TATE, ^{68}Ga-NODAGA-RGD$_2$, ^{68}Ga-PSMA-HBED-CC, etc.) is an extremely important part of QC in routine clinical practice. Nature of gallium leads to formation of two major radiochemical impurities in the radiopharmaceutical: hydrolyzed [68]Ga (colloid) and unbounded ionic forms of [68]Ga. The amounts of each impurity and ^{68}Ga-BCA-peptide are strictly normalized in accordance with pharmacopoeial standards. In 8th EuPh there is no method allowing to separate all of radiochemical impurities in ^{68}Ga preparations. Normally it takes to use combination of two systems to separate them (iTLC-SG and 1M ammonium acetate/methanol 50:50 (V/V) and HPLC or iTLC-SG–citric buffer).

In the present study, effective iTLC method for the determination of RCP of ^{68}Ga-radiopharmaceuticals was developed (with no double-developing, changing of eluents or additional manipulation). In this method iTLC-SG strips and commonly used eluent TFA$_{aq}$. (3–5% (V/V)) are used. The method allows determining each of the key radiochemical forms of [68]Ga (colloid, bound, free ionic) separately with the peaks separation being no less than 7–8 σ. Rf =0.0–0.1 for ^{68}Ga-colloid; Rf =0.5–0.6 for ^{68}Ga-BCA-peptides; Rf =0.9–1.0 for ionic [68]Ga:

The method is simple and fast: for developing of 100 mm strip only 4–6 min is required (versus 18–20 min for pharmacopoeial method). The combination of typical chromatographic systems mentioned above as well as gel-electrophoresis and SPE were used as control.

The method has been tested on various compounds (including ^{68}Ga-DOTA-TOC/-TATE, ^{68}Ga-NODAGA-RGD$_2$, etc.) and mixtures with different values of RCP. It was found, that content of ^{68}Ga-colloid and ionic [68]Ga(III) determined with the method developed correlates with control results very well. It also was found, that in some cases HPLC shows wrong RCP values (erroneously high) not only due to presence of ^{68}Ga-colloid, but due to presence of other ^{68}Ga-ionic species as well.

OC45

Glioma tumors grade II/III – local alpha emiters targeted therapy with [213]Bi-DOTA-substance P

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Gliomas are a highly heterogeneous group of brain tumours that are refractory to treatment, and highly invasive. The treatment and prognosis depend upon the tumor grade. Treatment of Grade II/III gliomas typically consists of maximal safe resection, followed by external beam radiation therapy. Although less aggressive than GBM, mortality is high with a 5-year survival rate of only 25.9%. Glioma tumors has been demonstrated NK-1 receptor system and substance P can be used as a ligand for targeted therapy. Alpha emitter, like [213]Bi offers the new potential for selective irradiation of tumors, with minimizing damage to adjacent tissue.
Material and methods
50 patients with different glia tumors were treated in the study. Gliomas grade II/III was diagnosed in 12 patients with symptoms of progression of disease despite of standard therapy were performed. Following intracavitary or intratumoral insertion of catheter system, patients were treated with 2–8 doses of 2 GBq [213]Bi-DOTA-

Substance P ([213]Bi-SP) in intervals of 2 months. ^{68}Ga-DOTA-Substance P (^{68}Ga-SP) was co-injected with the therapeutic doses to assess biodistribution using PET/CT. Therapeutic response was monitored with MRI. Study was approved by the ethical committee of the Medical University of Warsaw.
Results
Treatment with activity up to 13 GBq [213]Bi-SP was tolerated well with only mild transient adverse reactions. PET/CT imaging showed high retention of the radiolabeled peptide at the tumor site.
Median progression free survival was 5.5 months. Median overall survival from the first symptoms of recurrence was 32.7 months, Survival time from the start of [213]Bi-SP was 30.2 months. Follow up of therapeutic responses and toxicity is continued and patient recruitment is ongoing.
Conclusions
Treatment of II/III grade gliomas with [213]Bi-SP is safe and well tolerated. Targeted alpha therapy with [213]Bi-SP may evolve as a promising novel option for treatment of II/III grade gliomas.

OC46

Spatially informed dose deposition of Auger electron-emitting radionuclides at a cell nucleus scale

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Aim
Auger electron (AE)-emitting radionuclides are well suited as molecularly targeted radionuclide therapeutics (MRT) due to the high energy deposition density in the immediate vicinity of the decay site which avoids to a large extent non-specific radiotoxicity. However, due to the short range of the low-energy Auger (and Coster-Kronig) electrons, it is imperative that the AE emitting agent is closely associated with the cell nucleus. In this study we evaluate the dose deposition of intra-nuclear accumulated activity using transmission electron microscopy (TEM) images to inform the spatial distribution.
Materials and methods
Q620B head and neck cancer cells were treated with ^{111}In-DTPA-hEGF (8 MBq, 40 nM) for 24 h before microautoradiography (MAR) and TEM preparation and analysis. The complete radiation spectra of ^{111}In was generated using the BrIccEmis code [1], which implements a stochastic model for the atomic relaxation assuming a condensed-phase approach. Dose-point kernels (DPKs) in 1 nm radial bins were calculated using event-by-event simulations with the general-purpose Monte Carlo (MC) code PENELOPE [2]. The simulated DPKs were then overlaid on the TEM images to form a dosemap.
Results
Quantitative analysis of TEM images noted 44 ± 23.85 and 19.96 ± 13.69 grains per cell in the cytoplasm and nucleus respectively. Energy deposition in the first 1 nm radial bin representing a DNA double helix was 176.6 eV with a corresponding DPK of 6.75 MGy. The dose decreased to 6.85 mGy over the scale of an entire mitotic chromosome (1400 nm).
Conclusion
TEM-MAR is a viable method for looking at the spatial distribution of radioisotopes in single cells. The heterogeneity in spatial distribution resulted in a large variation in dose over the nucleus.

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OC47

Noninvasive imaging of multiple Myeloma with ^{68}Ga-DOTA-PEG$_4$-LLP2A via targeting VLA-4

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Multiple myeloma (MM) is a B-cell tumor of monoclonal plasma cells in the bone marrow and is the second most common age-related hematologic malignancy reported in the United States. Very late antigen-4 (VLA-4, $\alpha_4\beta_1$ integrin, CD49d/CD29) is overexpressed on MM. LLP2A is a highly specific peptidomimetic ligand that targets activated VLA-4 with high affinity. In this study, we evaluated ^{68}Ga radiolabeled-DOTA-PEG$_4$-LLP2A tracer as a PET agent for of MM.

The stability of the radiolabeled complex was evaluated with in vitro human serum and found to be >98% intact up to 3 h. Imaging studies were conducted in C57BL6/KaLwRij mice bearing 5TGM1-GFP tumors with i.v., intratibial and xenograft models. Ex vivo autoradiography and histology analysis were conducted on tumor sections to evaluate intra-tumoral distribution. Logan analysis of ^{68}Ga-LLP2A uptake in intra-tibia region was performed using 0-60 minute dynamic imaging data. ^{68}Ga-LLP2A exhibited clear saturable binding to target receptors with distribution volume (DV) indicated on the plot for tumor (T) and muscle (M) (Figure 1). The calculated binding potential ($BP = B_{max}/K_d$) based on this data is $BP = 6.04$.

Human organ radiation dose estimates were calculated by extrapolating biodistribution data from normal C57BL6 mice. The bladder was the dose limiting organ for both male and female mice (1.08 and 1.46 rad/mCi respectively). Toxicity studies will be completed in near future. Overall, ^{68}Ga-DOTA-PEG$_4$-LLP2A displayed good tumor targeting and favorable dosimetry. Thus, we plan to carry this agent forward in future human studies as a noninvasive imaging agent for overexpressed VLA-4 in MM.
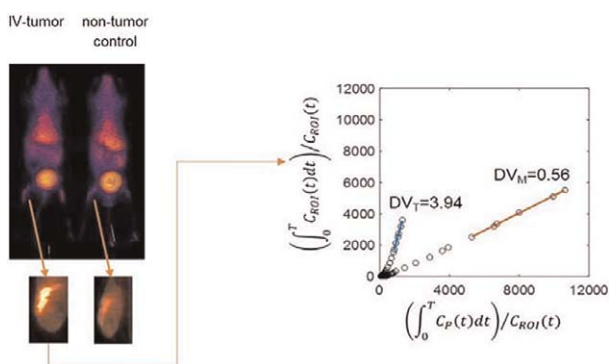
Figure 1. Mouse on left iv tumor bearing and the mouse on right is non-tumor control. Both mice were injected with 150 uCi of ^{68}Ga-LLP2A. Logan analysis of intra-tibia uptake of ^{68}Ga-LLP2A was performed using 0-60 minute dynamic imaging data.

OC48

Theranostics at its best: clinical breast cancer imaging and quantification targeting HER2 receptors

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The currently best known example of a commercialized theranostics is the combination of HercepTest and Herceptin wherein the former is used for HER2 expression assessment and selection of patients that might benefit from the treatment with the latter. However, HercepTest requires biopsy which is an invasive procedure, not sufficiently accurate, and very difficult to perform on several lesions and repeatedly in order to monitor the treatment response. While positron emission tomography (PET) in combination with HER2 targeting radiopharmaceutical provides quantitative whole body examination which accuracy is high and independent on heterogeneity of receptor expression.

PET imaging agent, [^{68}Ga]Ga-ABY-025, was produced in compliance with GMP and GRPP in two peptide doses. The peptide Affibody molecule, ABY-025, was provided by Affibody AB. [68]Ga was obtained from a [68]Ge/^{68}Ga-generator (IGG100, Eckert & Ziegler). Patients with diagnosed metastatic breast cancer

were enrolled. Two PET/CT examinations with low and high peptide content radiopharmaceuticals were performed for each patient. The examination started with dynamic acquisition (0–45 min) followed by three static runs at 1, 2 and 4 h post injection. Immunohistochemistry (IHC) on the metastasis biopsies were performed for HER2 expression verification. The study was approved by the Swedish Medical Products Agency (EudraCT 2012-005228-14, NCT01858116) and the Regional Board of Medical Ethics.

The examination using radiopharmaceutical with high peptide content resulted in higher contrast images with lower uptake in healthy organs such as liver. The contrast increased with the time however already 2 h post injection was found optimum for routine use. SUVs correlated with IHC HER2-scores. Based on [^{68}Ga]Ga-ABY-025/PET-CT, the treatment was changed in 19% of the patients. [^{68}Ga]Ga-ABY-025/PET-CT demonstrated strong potential to improve patient management efficacy by providing pre-therapeutic accurate whole body determination of HER2 expression extent and treatment response monitoring with minimal patient discomfort.

OC49

Production of ^{68}Ga in a mid-energy cyclotron: the solution is in the target

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The use of gallium-68 (^{68}Ga) is rapidly expanding with new applications arising almost every week. Therefore, the global availability of this nuclide is a critical issue. [68]Ga is currently sourced from commercial [68]Ge/^{68}Ga generators but their production is limited by the availability of the parent nuclide [68]Ge. Alternatively, the use of a [68]Zn salt solution in a liquid target has been proposed [1] [2]. With this process, ^{68}Ga can be produced in a cyclotron as simply as ^{18}F or [13]N. In this paper, a fully automated and GMP-optimized production of ^{68}Ga with a liquid target on a mid-energy cyclotron is described including purification and final peptide labeling using commercial target and synthesis modules (patent application: EP15170854). A fully automated process was implemented. A minimum of 180 mCi of ^{68}Ga was systematically produced on a 40 min irradiation at 45 uA proton beam using 100 mg of [68]Zn solution using an IBA Cyclone 18/9 cyclotron. Purification was performed in about 30 min with >85% yield (d.c.) using a Synthera Extension module and labeling of the final peptide (^{68}Ga-DOTANOC or ^{68}Ga-PSMA-11) was made on a Synthera synthesizer with >70% yield (d.c.) in less than 25 min. Zn and Fe impurities were all below 5 ppm and radionuclidic purity of the final formulation was >99%.

In summary, a final solution of ^{68}Ga radiopharmaceuticals suitable for human use can be produced, with practical and economical gains compared with the conventional generator method. This process can also be adapt for the cold kit labelling system.

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OC50

Radiolabel results from high specific activity e-LINAC produced [67]Cu

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We developed an improved process for producing high quality [67]Cu using an electron accelerator instead of a high energy proton accelerator. The beta/gamma emitting radioisotope [67]Cu was created using the (g,p) reaction on isotopically enriched [68]Zn target (nominally 40 g, 98% enrichment). The high energy photons were produced by bremsstrahlung conversion of electrons from a 45 MeV electron LINAC. A specially designed water cooled converter, end station and target were built and utilized for the transmutation. An additional system was designed and constructed for remote removal of the activated target.

Following transmutation, the ^{67}Cu was separated from the isotopically enriched ^{68}Zn target using a two-step process: physical separation using low pressure evaporation/sublimation (<0.001 mbar, 600°C) and purification using anion exchange column chromatography (DOWEX 1X8, 200 mesh). The specific activity of the final product was determined using an ICP-MS and an HPGe detector. Radiolabeling was performed using ^{67}Cu produced from the process combined with multi-element standards (to measure sensitivity of chelate bonding to non-copper metals) and DOTA, CoSAR, NOTA and NODAGA chelates. We achieved a production yield >50 uCi g^{-1}.kW^{-1}.hr^{-1} with a ^{67}Cu specific activity >20 Ci/mg. ICP-MS data indicated an average of <10 ng total Cu/mCi consistent with radiolabeled yields of 100% pmole chelate to total moles copper. The product is being produced and shipped to customers on demand, and at lower cost than proton accelerator produced isotope.

OC51

Ga-68 research status in Asia

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Application of Ga-68 for clinical and non-clinical studies are rapidly growing in Asia. In this study, China, India, Japan, and Korea were selected to follow up the current status. In case of clinical trial, India was the most active among the four countries. Most of clinical trials in India were imaging studies of neuroendocrine tumor patients by using somatostatin derivatives such as ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC and ^{68}Ga-DOTA-TATE. Prostate cancer patients imaging by targeting prostate surface membrane antigen (PSMA) also was very active recently. Korea was the second active in clinical research. Angiogenesis imaging studies in breast cancer, glioma, atherosclerosis, and moyamoya disease patients have been reported using ^{68}Ga-RGD derivatives in Korea. In China, angiogenesis imaging in glioma and lung cancer patients have been reported using a derivative of ^{68}Ga-labeled RGD dimer. Clinical study of ^{68}Ga-labeled agents was not very active in Japan. One of the reason might be because ^{18}F is more readily available than other countries due to the extensive distribution of cyclotrons. On the other hand, non-clinical studies such as developing bisphosphonate derivatives for bone imaging, benzofuran derivatives for Alzheimer disease patients' imaging, and ^{68}Ga-Df-anti-HER2-scFv for cancer imaging have been performed in Japan. Development of ^{68}Ga-nitroimidazole derivatives for hypoxia imaging, ^{68}Ga-mannosylated human serum albumin (MSA) for mannose receptor imaging, and ^{68}Ga-labeled nanoparticles for PSMA imaging were reported in Korea. A new RGD derivative NGR for imaging angiogenesis was reported in China. However, non-clinical study such as development of new imaging agents labeled with ^{68}Ga was not very active in India. In conclusion, the clinical application and development of ^{68}Ga-labeled agents is increasing in Asia very rapidly, and would become one of the major places in the near future.

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