Editorial

Personalized Medicine in Oncology, the Potential Role of Nuclear Medicine Imaging

The customization of healthcare or "personalized medicine" aimed at providing each patient with an individualized treatment plan is of major clinical interest in oncology given the heterogeneity seen in both the disease course and response to treatment of patients suffering from the same histological type of cancer and presenting with the same disease stage.

The underlying causes for the differences observed in behavior and response of tumors with the same histology and stage reside in the difference in cell populations contained by tumor deposits, both tumor and non-tumor cells, that form ecosystems that steer invasion and metastasis [1-3]. Currently identified ecosystems in this regard include cellular ecosystems comprising molecular pathways, subpopulations of cancer cells interacting with each other, cancer cells and stromal compartments interacting with each other and distant ecosystems that interact through the circulation comprising primary tumors, endocrine organs, bone marrow and distant metastases. The unraveling of the underlying relevant biological networks between these various ecosystems through genomics, proteomics, single cell analysis and high-throughput phenotypic assays has led to a better characterization of the molecular pathways that drive tumor progression and metastases as well as to a better understanding of the underlying causes of multidrug resistance. As a result, targeted drugs that either selectively inhibit specific molecular signaling pathways or that have multi-target activity aimed at overcoming the diverse an compensatory signaling pathways which cancer cells use to survive and evade treatment have been and are being developed [4-6]. As cancer is a potentially life-threatening disease and overall response rates to these highly costly and potentially toxic, novel treatment options will be limited to subgroups of patients only, appropriate biomarkers that help guide the selection of those patients that are likely to benefit from these novel treatment modalities are of major interest. Given the diagnosis of cancer is almost always based on a biopsy and subsequent examination of cells or tumor tissue, pharmacodiagnostic testing through the use of immunohistochemistry, ISH and RT-PCR is currently most commonly used for predictive purposes for targeted therapies [7,8]. However, semi-quantitative analysis of IHC stained tissue sections is operator dependent, requiring both judgment and experience of the observer, resulting in suboptimal reproducibility and most antibodies recognise more than one epitope. Whereas RT-PCR may lack specificity due to false priming, ISH is labour intensive and requires high sensitivity of the probes used. Most importantly, the biopsy material may not be representative for the bulk of the tumor due to errors of sampling. Finally, no functional assessment is made.

As only a limited number of cancer patients are candidates for targeted therapies, the majority of cancer patients are still being treated by non-targeted cancer treatments. For these patients few evidence-based predictive biomarkers of response are currently available. Furthermore, assessment of response to treatment is based on clinical- and morphological-imaging criteria (response evaluation criteria in solid tumors, RECIST-criteria) with CT and/or MRI usually being performed at 3-6 months post-treatment instigation, the minimum time required for tumor tissue to significantly shrink in size [9-11]. As a consequence, using the RECIST criteria and taking into consideration the overall low rate of response to treatment of cancer patients, a significant number of patients will receive an expensive, toxic, inefficient therapy whilst being deprived of a potentially beneficial other treatment option over a longer period of time.

As opposed to morphological imaging, nuclear medicine allows imaging of biological and functional characteristics of tumors. To this purpose, specific radiolabelled probes are designed that are either labelled with single photon emitters (single photon emission computerized tomography or SPECT) or with positron emitters (positron emission tomography or PET). Both PET and SPECT imaging allow full body assessment and thus also assessment of intra-tumor and inter-tumor heterogeneity whilst avoiding the potential of sampling error [12-15]. Several of the aforementioned tumor characteristics are associated with poor outcome e.g. hypoxia and neo-angiogenesis. Furthermore, changes in these biological characteristics following effective treatment by far precede volumetric changes as derived from morphological imaging, e.g. programmed cell death and metabolism. Accordingly, PET or SPECT imaging with radiolabelled probes have the potential to play a key role in personalized patient management of the cancer patient either through visualization of specific, single disease control points e.g. specific receptor or transport linked mechanistic activity of a drug or via visualization of general disease control points (e.g. proliferation, angiogenesis, tumor inflammation) [16-19].

In this issue of current pharmaceutical design, data on the development of and on the potential of currently available radiolabbeled probes for in-vivo tumor characterization and of inflammation, given the relevance of the tumor stroma and the inflammatory cells present, and the related potential for personalized medicine are reviewed and discussed. Kruse *et al*. provide an update on the current existing guidelines on diagnosis, targets and treatments, molecular imaging and response evaluation for a variety of solid tumors. Aside from the potential to predict or more rapidly assess response to treatment, when compared to morphological imaging, various large and small-scale studies using e.g. 18-FDG PET imaging suggest that PET imaging using radiolabelled probes may also impact patient management and treatment decisions during therapy, or after therapy [20]. On the other hand, in patients suffering from adenocarcinoma of the esophagogastric junction, available trials suggest that assessment of early metabolic response via FDG PET imaging to neo-adjuvant chemotherapy may reduce the risk of tumor progression under chemotherapy and of toxic death by de-routing non-responders to surgery. Finally, available data further suggest that PET-guided radiotherapy may increase the precision and accuracy of radiation delivery whilst reducing toxicity [21,22]. Suggestions on how to implement PET and SPECT imaging in clinical practice in oncology for the purpose of "personalized medicine". Finally a reflection on the future role of imaging in oncology and to which degree imaging will be able to accomplish or maybe even replace histological diagnosis is presented.

Because of the over-expression of different peptide-receptors in various tumors, radiolabelled proteins and peptides are currently being developed as theranostics as evidence by the various ongoing clinical phase I/II and III trials using these compounds in oncology. For the purpose of theranosis, quality control and subsequent in vitro biomedical and in vivo pharmacokinetic analyses are of increasing importance to enhance the success rate of the preclinical-to-clinical transfer of these radiopharmaceuticals. A detailed overview on the various available radiolabelling procedures, quality control analyses, stability characteristics, in-vitro biomedical characterization and assessment of in-vivo biodistribution for and of radiolabelled proteins and peptides is provided by Wynendaele *et al*. A complementary paper on the subject, dedicated to the development of small-molecule PET-probes is further provided by Elsinga *et al*. Both radiolabelled peptides and proteins as well as small molecule PET tracers, when developed in concert with drug development, will have a built in synergy that will accelerate the drug development process, targeted imaging and personalized medicine. While the simultaneous development of these probes with the clinical therapeutic agent will add to the complexity of the drug development and costs, its appropriate use will increase return on the research and development costs by improving early decision making to reduce new drug attrition in later stages. Of interest, competition studies with these probes e.g. a receptor binding probe will enable direct assessment of the relationship between drug plasma concentration and target occupancy as well as

target delivery e.g. brain metastasis. Also, provided "dual purpose" radionuclides or radionuclide pairs with emissions suitable for both imaging and therapy are available, these probes may allow for pre-therapy low-dose imaging and high-dose therapy in the same patient, a concept referred to as "theragnostics" [23,24]. A major problem that yet remains to be resolved in this regard is the lack of availability, in sufficient quantities of a majority of the best candidate theragnostic radionuclides in a carrier-added form.

The G-protein coupled heptaspanning receptor system is widely distributed throughout the body and common hallmarks of malignant tumors, e.g. the ability to sustain proliferative signaling, evade growth suppression, resist cell death, are connected with the malfunctioning of these receptor systems. As such, various of these receptor systems have been exploited for the purpose of nuclear medicine imaging. The most well studied and exploited system, providing the proof of concept for "personalized" medicine by means of nuclear medicine imaging is the somatostatin system. In this issue of CPD, Buscombe provides an historical overview of the development of radiolabelled agents targeting this receptor system both for diagnosis and treatment, highlighting the various pitfalls and difficulties, amongst others receptor expression heterogeneity, encountered in the development of these agents. In addition, other G-protein coupled receptor systems of potential interest for "personalized medicine" by means of nuclear medicine imaging are described. Similar to G-protein coupled receptor systems, tyrosine kinase receptor systems are involved in several circuits essential for cancer cell function, viability, cytostasis, differentiation proliferation and motility. As indicated by Altai *et al*. intra- and inter-patient expression heterogeneity and alteration of tyrosine kinase receptor expression during therapy indicate the need for "personalization" of tyrosine kinase receptor-targeting treatment. Available data suggest that radionuclide molecular imaging of tyrosine kinase receptors is a feasible way to stratify patients and to monitor treatment response. While several classes of imaging agents are under active pre-clinical and clinical development, intensive work is required for determining the most suitable agent for each particular application and for developing the optimal clinical protocols. Receptor signaling, in addition to cell-matrix interactions, also play a key role in neo-angiogenesis which is essential for tumor growth. With a lack of validated genetic or molecular biomarkers for anti-angiogenic responsiveness, novel methods to identify responsive patients are required. In this regard, nuclear medicine imaging might help in the elucidation of the basic drug mechanisms as well as resistance routes and aid in the "personalization" of anti-angiogenic treatment by enabling target expression quantification prior and during treatment. Terry *et al*. provide a comprehensive overview of the development of radiolabeled probes targeting four key proteins expressed during angiogenesis, namely αvascular endothelial growth factor and its receptor, the integrin receptor $_{v}\beta_{3}$, the extracellular domain of fibronectin and matrix metalloproteinases and how these probes can be used for personalized anti-angiogenic treatment. The vascular network induced via neo-angiogenesis is not optimal and associated with both structural and functional deficiencies. Newly formed vessels are characteristically leaky, tortuous and irregular and constantly altered resulting in tumor hypoxia, the presence of which impairs the effectiveness of both chemotherapy and especially radiotherapy. Accordingly, a non-invasive method identifying those patients that would benefit from appropriate treatments circumventing hypoxia is of major clinical interest. As described by Mees *et al*. in this issue, to this purpose, several potential candidate molecules have been labeled for PET and SPECT. However, none of these is currently used in routine clinical practice due to a number of practical difficulties encountered that need to be resolved by further studies.

Any effective treatment of cancer primarily attempts to induce cell death through apoptosis. To date, the evaluation of the degree of success of treatment is largely defined by the level of tumour shrinkage derived from morphological imaging at well-defined time points following treatment initiation. As overall tumour shrinkage occurs relatively late following effective treatment, respectively 3-6 months following treatment initiation, those patients not responding to the treatment are deprived from a potentially more efficient treatment. Accordingly, specific apoptosis targeting probes have been developed of which the most intensely studied ins radiolabelled Annexin A5. As stated by De Saint-Hubert *et al*., this probe has been improved for imaging purposes via site-specific labeling strategies with good results being described in both pre-clinical and clinical studies. Additional probes of interest are also described. Furthermore, the complementary role of apoptosis imaging to currently used methodologies for treatment assessment is highlighted. Finally, due to their genetic instability, tumor cells are a continuous source of new and altered proteins that are recognized by the adaptive immune system as antigens and anti-tumor effector cells, immunosuppressive cytokines as well as FasL and its receptor play a significant role in tumor control and growth. Finally, in the last paper of this issue, the potential role of various probes that are being developed for the purpose of personalized imaging in infection and inflammation is described. In the future, it may be anticipated that several of these probes may also prove of use in the field of oncology.

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