Molecular Imaging in Cancer Therapies of the Future

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Synopsis
The objective of Molecular Imaging (MI) is the multi-modality mapping of (patho)physiological and biochemical processes at the cellular and molecular level for diagnostics and therapy. MI will shift the emphasis of oncology towards prevention, early diagnostics and (minimally-invasive) molecular therapies. MRI requires amplification strategies to reach the sensitivity of optical and Nuclear Medicine techniques, but a large role in translational research can be envisaged. Challenges remain for future developments of MI in oncology research: 1) surrogate imaging markers; 2) specific contrast agents; 3) combined diagnostic/therapeutic agents; 4) image-guided technologies for local drug delivery and gene therapy.

Introduction
Molecular Imaging (MI) is a rapidly developing research concept. Its basic definition (Weissleder, Boston) has been evolving to "the mapping of (patho)physiological and biochemical processes at the cellular and molecular level for diagnostics and therapy". Molecular Imaging is a field that builds on the full deciphering of the human genome by looking at local gene expression levels and its consequences. The long-term vision of the role of MI in medicine is that it will shift the current emphasis of health care towards prevention, early diagnostics and (minimally-invasive) molecular therapies. MI includes all imaging modalities, as shown by examples from optical techniques, nuclear medicine approaches, CT, ultrasound imaging and MRI. MI is expected to play an important role in cardiovascular, neurodegenerative diseases, and cancer. This presentation is focused on the oncology field but some concepts of MI will be demonstrated in a more general context.

Some specific objectives of Molecular Imaging in Cancer
1) Early detection and characterization of disease via its "molecular signature"
2) Understanding of (patho)physiology of different types of cancer
3) Selection and evaluation of specific treatment
4) Development of image-guided molecular therapies

Selected examples of Molecular Imaging:
1) Tumor growth and formation of metastasis can be followed in vivo using optical imaging methods based on modified cell lines expressing constitutively the luciferase gene. In preclinical cancer research, these tools lead to a reduction of the use of animals for drug development and an acceleration of the drug evaluation process.
2) Mapping of inflammatory activity has been demonstrated by imaging macrophage activity using USPIO contrast agents. This development may become important in the clinic for detection of lymph node metastasis.
3) Tumor activity can be visualized by targeting angiogenesis either directly by mapping altered gene expression levels or indirectly using biomarkers such as the quantification of perfusion or other physiological parameters (e.g. glycolyis using FDG PET). Also, processes related to apoptosis and degradation of the extracellular matrix can be mapped based on specific contrast agents targeting annexin V and Matrix Metalloproteases, respectively. Once specific markers are found, radiopharmaceuticals, and/or drugs can be attached to locally deliver therapy.
4) (Gene) therapy can be guided by MI. The delivery of a gene can be targeted using real-time image guidance. Biodistribution can be evaluated using MRI using co-released contrast agents. In addition, expression of a marker gene can be quantified using PET, MRI or other imaging modalities using labeled ligands. Spatial and temporal control of transgene expression can be achieved based on a combination of MRI-guided local hyperthermia and a heat-sensitive promoter.
5) Stem cells may be used as gene therapy vectors and for tissue repair. Stem cells have been isolated, and labeled with MR contrast agents, then re-injected and tracked towards their target using serial MRI. Such methods are promising in clarifying the homing of stem cells and may allow image-guided stem cell therapy.

Discussion
Recent advances have demonstrated the large potential of multi-modality Molecular Imaging. MRI requires amplification strategies to reach the specific sensitivity of optical and Nuclear Medicine techniques, but its role in translational MI research and development of biomarkers will probably be significant. Further challenges remain for MI in future cancer diagnosis and treatment:
1) development of clinically relevant imaging biomarkers for cancer treatment,
2) specific contrast agent design for cancer related processes,
3) development of combined diagnostic/therapeutic agents,
4) development of image-guided technologies for molecular therapy (local drug delivery, local gene therapy).