

Handbook of Experimental Pharmacology

Volume 185/II

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Molecular Imaging II

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ISBN: 978-3-540-77449-5

e-ISBN: 978-3-540-77496-9

Handbook of Experimental Pharmacology ISSN 0171-2004

Library of Congress Control Number: 2007943479

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Cover Design: WMXDesign GmbH, Heidelberg

Printed on acid-free paper

9 8 7 6 5 4 3 2 1

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Foreword

Bayer Schering Pharma welcomes Springer Verlag's endeavor to open its well-known Handbook of Pharmacology to the exciting field of molecular imaging and we are pleased to contribute to the printing costs of this volume.

In principle, noninvasive diagnostic imaging can be divided into morphological/anatomical imaging on the one hand, with CT/MRI the most important imaging technologies, and molecular imaging on the other. In CT/MRI procedures, contrast agents are injected at millimolar blood concentrations, while today's molecular imaging technologies such as PET/SPECT use tracers at nanomolar blood concentrations. Morphological imaging technologies such as X-ray/CT/MRI achieve very high spatial resolution. However, they share the limitation of not being able to detect lesions until the structural changes in the tissue (e.g., caused by cancer growth) are large enough to be seen by the imaging technology. Molecular imaging offers the potential of detecting the molecular and cellular changes caused by the disease process before the lesion (e.g., a tumor) is large enough to cause the kind of structural changes that can be detected by other imaging modalities. On the other hand, molecular imaging methods suffer from a rather poor level of spatial resolution, although current PET machines are better than SPECT devices.

The current diagnostic imaging revolution of fusing conventional diagnostic imaging (CT, MRT) with molecular imaging technologies (PET, SPECT) combines the strength of molecular imaging — i.e., detecting pathophysiological changes at the onset of the disease — with the strength of morphological imaging — i.e., high structural resolution. Today, already more than 95% of new PET scanners installed are PET/CT scanners. PET/CT fusion imaging is currently the fastest-growing imaging technology. And PET/MRI fusion scanners are also on the horizon. The trend toward specialized imaging centers, where all the required equipment is available in one facility, is expected to continue. The former technology-driven focus in diagnostic imaging research looks set to change into a more disease-oriented one.

Fusion imaging will make it possible to detect the occurrence of a disease earlier than is possible today. This is significant, because the likelihood of successful therapeutic interventions increases the earlier diseases are diagnosed. Furthermore, because a disease can be characterized at the molecular level, patients can be

stratified for a given therapy and therapeutic responses monitored early on and in a quantitative manner. The growing pressure for selection, early therapy monitoring and justification (outcome) of a specific treatment will have a significant impact on molecular imaging procedures. Hence, molecular imaging technologies are now an integral part of both research and development (early clinical prediction of drug distribution and efficiency) at most pharmaceutical companies.

Bayer Schering Pharma (BSP) has always been a pioneer in the research and development of new imaging agents for “classic” modalities like CT and MRI. In line with this history and BSP’s focus on innovation, we are now fully committed to breaking new ground in molecular imaging, especially in research and development of radio-tracers like PET imaging agents.

A strong and active partnership with academia is essential in order to be successful in the exciting new field of molecular imaging. We want to help make innovative imaging solutions invented in university research labs available to the patients. Furthermore, the low doses of “tracers” injected make it possible to perform clinical research studies under the microdosing/exploratory IND regulations. This will help molecular imaging move into the hospital and, hopefully, also generate early and fruitful collaborations between academia, clinic, regulatory authorities and the pharmaceutical industry.

Bayer Schering Pharma, Berlin

Matthias Bräutigam and Ludger Dinkelborg

Preface

“Molecular imaging (MI) is the *in vivo* characterization and measurement of biologic processes on the cellular and molecular level. In contradistinction to ‘classical’ diagnostic imaging, it sets forth to probe such molecular abnormalities that are the basis of disease rather than to image the end results of these molecular alterations” (Weissleder and Mahmood 2001).^a

Imaging has witnessed a rapid growth in recent decades. This successful development was primarily driven by impressive technical advances in structural imaging; i.e., fast computer tomography (CT) and magnetic resonance imaging (MRI). In parallel, functional imaging emerged as an important step in the diagnostic and prognostic assessment of patients addressing physiological functions such as organ blood flow, cardiac pump function and neuronal activity using nuclear, magnetic resonance and ultrasonic techniques. More recently the importance of molecular targets for diagnosis and therapy has been recognized and imaging procedures introduced to visualize and quantify these target structures. Based on the hypothesis that molecular imaging provides both a research tool in the laboratory and a translational technology in the clinical arena, considerable funding efforts in the US and Europe were directed to accelerate the development of this imaging technology. In addition, the industry responded to the new demand with the introduction of dedicated imaging equipment for animal research as well as multimodality imaging (PET/CT), used to combine high-resolution imaging with the high sensitivity of tracer techniques.

Molecular imaging has been applied academically in neuroscience with emphasis on cognition, neurotransmission and neurodegeneration. Besides this established area, cardiology and oncology are currently the fastest growing applications. Vascular biology provides new targets to visualize atherosclerotic plaques, which may lead to earlier diagnosis as well as better monitoring of preventive therapies. Labeling of cells allows localization of inflammation or tumors and labeled stem-cell tracking of these cells *in vivo*. The noninvasive biologic characterization of tumor tissue in animals and humans opens not only exciting new research strategies but also appears

^a Weissleder R, Mahmood U (2001) Molecular imaging. *Radiology* 219:316–333

promising for personalized management of cancer patients, which may alter the diagnostic and therapeutic processes.

Detection and characterization of lesions, especially tumors, remains challenging, and can be only achieved by using specific tracers and/or contrast media. The past decade has seen the development of specific approaches that use labeled antibodies and fragments thereof. However, in general only a relatively low target-to-background ratio has been attained due to the slow clearance of unbound antibody. Other target-specific approaches include labeled proteins, peptides, oligonucleotides, etc. Due to the low concentration of proteins, such as receptors in the target (e.g., tumors, cells), imaging requires highly sensitive probes addressing these structures. Whereas this challenge does not affect the use of positron emission tomography (PET) nor single photon emission tomography (SPECT) because of their high physical sensitivity, optical imaging methods (OT) as well as magnetic resonance imaging (MRI) have limitations: low penetration depth (OT) and inherent low physical sensitivity (MRI prevents straightforward imaging strategies for both latter modalities). PET and SPECT have been successfully used in the past for molecular imaging, employing imaging probes such as monoclonal antibodies, labeled peptides [i.e., somatostatin analogues (Octreotide)], and labeled proteins such as ^{99m}Tc -AnnexinV, etc. Specific imaging probes for OT and MR are under development. However, OT is likely to remain an experimental tool for investigations in small animals, and will be used in humans only for special indications, where close access to targets can be achieved by special imaging devices such as endoscopy or intraoperative probes. In recent years, molecular imaging with ultrasound devices has developed quickly and the visualization of targeted microbubbles offers not only identification of specific binding but also the regional delivery of therapeutics after local destruction of the bubbles by ultrasound.

Achieving disease-specific imaging requires passive, or better yet, active accumulation of specific molecules to increase the concentration of the imaging agent in the region of interest. Marker substrates as well as reporter agents can be used to visualize enzyme activity, receptor or transporter expression. The introduction of new imaging agents requires a multistep approach, involving the target selection, synthetic chemistry and preclinical testing, before clinical translation can be considered. Target identification is supported by molecular tissue analysis or by screening methods, such as phage display. Subsequently, further development requires methods to synthesize macromolecules, minibodies, nanoparticles, peptide conjugates and other conjugates, employing innovative biotechnology tools for specific imaging with high accumulation in the target area. This process involves optimization of the target affinity and pharmacokinetics before in-vivo application can be considered. Amplification of the imaging signal can be enhanced by targeted processes which involve internalization of receptors, transport mechanisms or enzymatic interaction with build-up of labeled products. (i.e., phosphorylated deoxyglucose). Reporter gene imaging provides not only high biological contrast if a protein, which does not occur naturally, is expressed after gene transfer but also leads to signal amplification if tissue-specific promoters in combination with enzymatic or transporter activity are used.

The development process usually produces numerous candidates, of which only a few pass preclinical evaluation with the promise of clinical utility. The most suitable substances have to undergo in-depth toxicological evaluation before the regulatory process for clinical use can be started. Currently, this is the major rate-limiting step in the process and requires not only the biological qualification of the compound but also the necessary financial support for the clinical testing required by the regulatory agencies.

With the increasing interest in the experimental and clinical application of molecular imaging, many institutions have created research groups or interdisciplinary centers focusing on the complex development processes of this new methodology. The aim for this textbook of molecular imaging is to provide an up-to-date review of this rapidly growing field and to discuss basic methodological aspects necessary for the interpretation of experimental and clinical results. Emphasis is placed on the interplay of imaging technology and probe development, since the physical properties of the imaging approach need to be closely linked with the biological application of the probe (i.e., nanoparticles and microbubbles). Various chemical strategies are discussed and related to the biological applications. Reporter-gene imaging is being addressed not only in experimental protocols but also first clinical applications are discussed. Finally, strategies of imaging to characterize apoptosis and angiogenesis are described and discussed in the context of possible clinical translation.

The editors thank all the authors for their contributions. We appreciate the extra effort preparing a book chapter during the already busy academic life. We hope this methodological discussion will increase the understanding of the reader with respect to established methods and generate new ideas for further improvement and for the design of new research protocols employing imaging. There is no question that this young field will further expand, stimulated by the rapid growth of biological knowledge and biomedical technologies. It is expected that the experimental work of today will become the clinical routine of tomorrow.

Heidelberg, Germany
Munich, Germany

Wolfhard Semmler
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Glossary

Definition of the terms used in molecular imaging.

Allele The gene regarded as the carrier of either of a pair of alternative hereditary characters.

$\alpha_v\beta_3$ An integrin expressed by activated endothelial cells or tumor cells which plays an important role in angiogenesis and metastatic tumor spread (\Rightarrow Integrins)

Amino acid An organic compound containing an amino and carboxyl group. Amino acids form the basis of protein synthesis.

Angiogenesis Formation of new blood vessels. May be triggered by physiological conditions, like during embryogenesis or certain pathological conditions, such as cancer, where the continuing growth of solid tumors requires nourishment from new blood vessels.

Annexin V A protein in blood which binds to phosphatidyl serine (PS) binding sites exposed on the cell surface by cells undergoing programmed cell death. \Rightarrow Apoptosis.

Antibody A protein with a particular type of structure that binds to antigens in a target-specific manner.

Antigen Any substance which differs from substances normally present in the body, and can induce an immune response.

Antiangiogenesis The inhibition of new blood vessel growth and/or destruction of preformed blood vessels.

Antisense A strategy to block the synthesis of certain proteins by interacting with their messenger RNA (mRNA). A gene whose messenger RNA (mRNA) is complementary to the RNA of the target protein is inserted in the cell genome. The protein synthesis is blocked by interaction of the antisense mRNA and the protein-encoding RNA.

Apoptosis Programmed cell death. A process programmed into all cells as part of the normal life cycle of the cell. It allows the body to dispose of damaged, unwanted or superfluous cells.

Aptamer RNA or DNA-based ligand.

Asialoglycoproteins Endogenous glycoproteins from which sialic acid has been removed by the action of sialidases. They bind tightly to their cell surface receptor, which is located on hepatocyte plasma membranes. After internalization by adsorptive endocytosis, they are delivered to lysosomes for degradation.

Attenuation correction (AC) Methodology which corrects images for the differential absorption of photons in tissues with different densities.

Avidin A biotin-binding protein (68 kDa) obtained from egg white. Binding is so strong as to be effectively irreversible.

Bioinformatics The science of managing and analyzing biological data using advanced computing techniques. Especially important in analyzing genomic research data.

Biotechnology A set of biological techniques developed through basic research and now applied to research and product development. In particular, biotechnology refers to the industrial use of recombinant DNA, cell fusion, and new bioprocessing techniques.

Biotin A prosthetic group for carboxylase enzyme. Important in fatty acid biosynthesis and catabolism, biotin has found widespread use as a covalent label for macromolecules, which may then be detected by high-affinity binding of labeled avidin or streptavidin. Biotin is an essential growth factor for many cells.

Cancer Diseases in which abnormal cells divide and grow unchecked. Cancer can spread from its original site to other parts of the body and is often fatal.

Carrier An individual who carries the abnormal gene for a specific condition but has no symptoms.

Cavitation The sudden formation and collapse of low-pressure bubbles in liquids as a result of mechanical forces.

cDNA ⇒ Complementary DNA.

Cell The basic structural unit of all living organisms and the smallest structural unit of living tissue capable of functioning as an independent entity. It is surrounded by a membrane and contains a nucleus which carries genetic material.

Chromosome A rod-like structure present in the nucleus of all body cells (with the exception of the red blood cells) which stores genetic information. Normally, humans have 23 pairs, giving a total of 46 chromosomes.

Coincidence detection A process used to detect emissions from positron-emitting radioisotopes. The technology utilizes opposing detectors that simultaneously detect

two 511 keV photons which are emitted at an angle of 180 degrees from one another as a result of the annihilation of the positron when it combines with an electron.

Complementary DNA (cDNA) DNA synthesized in the laboratory from a messenger RNA template by the action of RNA-dependent DNA polymerase.

Cytogenetics The study of the structure and physical appearance of chromosome material. It includes routine analysis of G-banded chromosomes, other cytogenetic banding techniques, as well as molecular cytogenetics such as fluorescent in situ hybridization (FISH) and comparative genomic hybridization (CGH).

Deoxyglucose \Rightarrow 18 F-deoxyglucose.

DNA Deoxyribonucleic acid: the molecule or 'building block' that encodes genetic information.

DNA repair genes Genes encoding proteins that correct errors in DNA sequencing.

Enzyme A protein that acts as a catalyst to speed the rate at which a biochemical reaction proceeds.

Epistasis A gene that interferes with or prevents the expression of another gene located at a different locus.

Epitope The specific binding site for an antibody.

Expression \Rightarrow Gene expression.

¹⁸F-deoxyglucose The predominant PET imaging agent used in oncology. The deoxyglucose is 'trapped' in cells which have increased metabolic activity as a result of phosphorylation. The process results in an accumulation of fluorine-18 (¹⁸F) in the cells, allowing the location of the cells and intensity of tumor metabolism to be determined using PET imaging.

Fluorine-18 (¹⁸F) A positron-emitting radioisotope used to label deoxyglucose or other molecular probes for use as radiopharmaceuticals.

F(ab) fragment The shape of an antibody resembles the letter 'Y'. Antigen binding properties are on both short arms. Digestion by various enzymes yields different fragments. Fragments with one binding site are called F(ab).

F(ab')₂ fragment Antibody fragment with two binding sites (\Rightarrow also F(ab) fragment).

Fc fragment (Crystallizable) antibody fragment which has no binding properties (\Rightarrow also F(ab) fragment). The Fc fragment is used by the body's immune system to clear the antibody from the circulation.

Fibrin Fibrous protein that forms the meshwork necessary for forming of blood clots.

Fibroblast growth factor Acidic fibroblast growth factor (alpha-FGF, HBGF 1) and basic FGF (beta-FGF, HBGF-2) are the two founder members of a family of structurally related growth factors for mesodermal or neuroectodermal cells.

Fingerprinting In genetics, the identification of multiple specific alleles on a person's DNA to produce a unique identifier for that person.

Gadolinium A paramagnetic ion which changes the relaxivity of adjacent protons. It affects signal intensity in MR images (\Rightarrow garmagnetism).

Ganciclovir An antiviral agent which is phosphorylated by thymidine kinase. As a phosphorylated substance it stops cell division by inhibiting DNA synthesis.

Gene The fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product (i.e., a protein or RNA molecule). The totality of genes present in an organism determines its characteristics.

Gene expression The process by which a gene's coded information is converted into the structures present and operating in the cell. Expressed genes include those that are transcribed into mRNAs and then translated into proteins, and those that are transcribed into RNAs but not translated into proteins (e.g., transfer and ribosomal RNAs).

Gene mapping Determination of the relative positions of genes on a DNA molecule (chromosome or plasmid) and of the distance, in linkage units or physical units, between them.

Gene prediction Predictions of possible genes made by a computer program based on how well a stretch of DNA sequence matches known gene sequences.

Gene sequence (full) The complete order of bases in a gene. This order determines which protein a gene will produce.

Gene, suicide \Rightarrow Suicide gene.

Gene therapy An experimental procedure aimed at replacing, manipulating, or supplementing nonfunctional or malfunctioning genes with therapeutic genes.

Genetic code The sequence of nucleotides, coded in triplets (codons) along the mRNA, that determines the sequence of amino acids in protein synthesis. A gene's DNA sequence can be used to predict the mRNA sequence, and the genetic code can, in turn, be used to predict the amino acid sequence.

Genetic marker A gene or other identifiable portion of DNA whose inheritance can be followed.

Genetic susceptibility Susceptibility to a genetic disease. May or may not result in actual development of the disease.

Genome All the genetic material in the chromosomes of a particular organism; its size is generally given as its total number of base pairs.

Genomics The science aimed at sequencing and mapping the genetic code of a given organism.

Genotype The genetic constitution of an organism, as distinguished from its physical appearance (its phenotype).

ICAM Intercellular adhesion molecules: glycoproteins that are present on a wide range of human cells, essential to the mechanism by which cells recognize each other, and thus important in inflammatory responses.

Indium-111 (¹¹¹In) A single-photon-emitting radioisotope used to label various molecular probes for SPECT imaging.

Integrins A specific group of transmembrane proteins that act as receptor proteins. Different integrins consist of different numbers of alpha and beta subunits. Over 20 different integrin receptors are known.

Lectin Sugar-binding proteins which are highly specific for their sugar moieties. They bind to glycoproteins on the cell surface or to soluble glycoproteins and play a role in biological recognition phenomena involving cells and proteins, e.g., during the immune response.

Liposome A spherical particle in an aqueous medium, formed by a lipid bilayer enclosing an aqueous compartment.

Locus The relative position of a gene on a chromosome.

Lysosome A minute intracellular body involved in intracellular digestion.

Messenger RNA (mRNA) RNA that serves as a template for protein synthesis.

Microarray Sets of miniaturized chemical reaction areas that may also be used to test DNA fragments, antibodies, or proteins.

Micronuclei Chromosome fragments that are not incorporated into the nucleus at cell division.

MID Molecular imaging and diagnostics.

Molecular biology The study of the structure, function, and makeup of biologically important molecules.

Molecular genetics The study of macromolecules important in biological inheritance.

Molecular medicine The treatment of injury or disease at the molecular level. Examples include the use of DNA-based diagnostic tests or medicine derived from a DNA sequence. It includes molecular diagnostics, molecular imaging and molecular therapy.

Monoclonal antibodies Antibodies made in cell cultures; these antibodies are all identical.

Monosaccharide A simple sugar that cannot be decomposed by hydrolysis.

Nucleic acid A nucleotide polymer. There are two types: DNA and RNA.

Nucleotide A subunit of DNA or RNA consisting of a nitrogenous molecule, a phosphate molecule, and a sugar molecule. Thousands of nucleotides are linked to form a DNA or RNA molecule.

Oligonucleotides Polymers made up of a few (2-20) nucleotides. In molecular genetics, they refer to a short sequence synthesized to match a region where a mutation is known to occur, and then used as a probe (oligonucleotide probes).

Operon Combination of a set of structural genes and the DNA sequences which control the expression of these genes.

Oncogene A gene, one or more forms of which is associated with cancer. Many oncogenes are directly or indirectly involved in controlling the rate of cell growth.

Paramagnetism Magnetism which occurs in paramagnetic material (e.g. \Rightarrow gadolinium), but only in the presence of an externally applied magnetic field. Even in the presence of the field there is only a small induced magnetization because only a small fraction of the spins will be orientated by the field. This fraction is proportional to the field strength. The attraction experienced by ferromagnets is nonlinear and much stronger.

Peptide A short chain of amino acids. Most peptides act as chemical messengers, i.e., they bind to specific receptors.

Peptidomimetics Engineered compounds that have similar binding characteristics to those of naturally occurring proteins. The advantages are increased stability and prolonged presence in the bloodstream.

Perfluorocarbon A compound containing carbon and fluorine only.

PESDA Perfluorocarbon exposed sonicated dextrose albumin microbubbles.

PET Positron emission tomography. An imaging modality which utilizes opposing sets of detectors to record simultaneous emissions from a positron-emitting radioisotope throughout 360° . The image data are processed using reconstruction algorithms to create tomographic image sets of the distribution of the radioisotope in the patient.

PET/CT A combination technology which creates tomographic image sets of the metabolic activity from PET and the anatomical tomographic image sets from CT. CT \Rightarrow computed tomography: An imaging modality employing a rotating x-ray tube and a detector as well producing numbers of projection imagings during its rotation around the object of interest. Specific reconstruction algorithms are used to generate three-dimensional image of the inside of an object. The two images sets are fused to form a single image, which is used to assign the PET abnormalities to specific anatomical locations.

Phage A virus for which the natural host is a bacterial cell.

Phagocytosis Endocytosis of particulate material, such as microorganisms or cell fragments. The material is taken into the cell in membrane-bound vesicles (phagosomes) that originate as pinched-off invaginations of the plasma membrane. Phagosomes fuse with lysosomes, forming phagolysosomes, in which the engulfed material is killed and digested.

Pharmacodynamics The study of what a drug does to the body and of its mode of action.

Pharmacogenomics The influence of genetic variations on drug response in patients. This is performed by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity during therapy.

Pharmacokinetics The determination of the fate of substances administered externally to a living organism, e.g., the metabolism and half-life of drugs.

Phenotype The physical characteristics of an organism or the presence of a disease that may or may not be genetic.

Phosphorylation A metabolic process in which a phosphate group is introduced into an organic molecule.

Plasmid Autonomously replicating extrachromosomal circular DNA molecules.

Polymerase An enzyme that catalyzes polymerization, especially of nucleotides.

Polysaccharides Any of a class of carbohydrates, such as starch and cellulose, consisting of a number of monosaccharides joined by glycosidic bonds. Polysaccharides can be decomposed into the component monosaccharides by hydrolysis.

Polypeptide A peptide containing more than two amino acids.

Probe Single-stranded DNA or RNA molecules of specific base sequence, labeled either radioactively or immunologically, that are used to detect the complementary base sequence by hybridization.

Promoter A specific DNA sequence to which RNA polymerase binds in order to 'transcribe' the adjacent DNA sequence and produce an RNA copy. The action of RNA polymerase is the first step in the translation of genes, via mRNA, into proteins.

Protein A large molecule comprising one or more chains of amino acids in a specific order that is determined by the base sequence of nucleotides in the gene that codes for the protein. Proteins are required for the structure, function, and regulation of the body's cells, tissues, and organs. Each protein has unique functions. Examples are hormones, enzymes, and antibodies.

Proteomics The global analysis of gene expression in order to identify, quantify, and characterize proteins.

Receptor A molecular structure within a cell or on the cell surface that selectively binds a specific substance having a specific physiological effect.

Rhenium-188 (^{188}Re) A beta-emitting radioisotope used to label various molecular probes for targeted radiotherapy applications.

Reporter gene imaging Imaging of genetic or enzymatic products/events initiated by molecular therapies which have assigned specific reporter genes to express specific targets.

Ribosomal RNA (rRNA) A class of RNA found in the ribosomes of cells.

RNA Ribonucleic acid: a chemical found in the nucleus and cytoplasm of cells; it plays an important role in protein synthesis and other chemical activities of the cell. The structure of RNA is similar to that of DNA. There are several classes of RNA molecules, including messenger RNA, transfer RNA, ribosomal RNA, and other small RNAs, each serving a different purpose.

Selectins A family of cell adhesion molecules consisting of a lectin-like domain, an epidermal growth factor-like domain, and a variable number of domains that encode proteins homologous to complement-binding proteins. Selectins mediate the binding of leukocytes to the vascular endothelium.

Sequencing Determination of the order of nucleotides (base sequences) in a DNA or RNA molecule or the order of amino acids in a protein.

Sonothrombolysis Dissolving a thrombus using ultrasound, either alone or in conjunction with microbubbles.

SPECT Single photon emission computerized tomography: an imaging modality in which a detector is rotated about the patient, recording photon emissions throughout 360° . Reconstruction algorithms are used to convert the data into a set of tomographic images.

Stem cell Undifferentiated, primitive cells in the bone marrow that have the ability both to multiply and to differentiate into specific cells for the formation of specific tissues (hematopoietic, mesenchymal and neuronal stem cells).

Streptavidin A biotin-binding protein obtained from bacteria.

Structural genomics The study to determine the 3D structures of large numbers of proteins using both experimental techniques and computer simulation.

Suicide gene A protein-coding sequence that produces an enzyme capable of converting a nontoxic compound to a cytotoxic compound, used in cancer therapy.

Technetium-99m ($^{99\text{m}}\text{Tc}$) A single-photon-emitting radioisotope used to label various molecular probes for scintigraphic imaging, including SPECT imaging.

Theranostics The application of MID for therapy guidance using genomic, proteomic and metabolomic data for predicting and assessing drug response.

Thymidine kinase (tk) The gene coding for the tk from the herpes simplex virus (HSV-tk) can be used as a 'suicide gene' or a reporter gene (\Rightarrow Reporter gene imaging) in cancer therapy. \Rightarrow also Ganciclovir.

Tissue factor An integral membrane glycoprotein of around 250 residues that initiates blood clotting after binding factors VII or VIIa.

Tracer principle The use of molecular probes labelled with radioisotopes to allow for nuclear imaging devices to detect the presence and location of the targeted structures by specific binding (e.g., to receptors, proteins, ...) or trapping in cells.

Transfection The introduction of DNA into a recipient cell and its subsequent integration into the recipient cell's chromosomal DNA.

Transfer RNA Small RNA molecules with a function in translation. They carry specific amino acids to specified sites.

Transgene A gene transferred from one organism to another.

Translation The process by which polypeptide chains are synthesized, forming the structural elements of proteins.

Translational research Applying results obtained by basic research to answer scientific questions concerning human disease processes.

USPIO Ultrasmall particles of iron oxide. These particles have a high magnetic moment causing strong local susceptibility and field inhomogeneities, with strong effects in T2- and T2*-weighted MR imaging.

VEGF Vascular endothelial growth factor. VEGF is a protein secreted by a variety of tissues, when stimulated by triggers like hypoxia. VEGF stimulates endothelial cell growth, angiogenesis, and capillary permeability.

Virus A noncellular biological entity that can only reproduce within a host cell. Viruses consist of nucleic acid (DNA or RNA) covered by protein; some animal viruses are also surrounded by membrane. Inside the infected cell, the virus uses the synthetic capability of the host to produce progeny viruses.