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New molecular targets for radionuclide therapy

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In gene therapy based on based on the transduction of receptor genes, the recombinant gene expression in tumor cells is monitored using radiolabeled ligands. This may also be used for radiopeptide therapy. Transfer of transporter genes such as the sodium iodide transporter or the norepinephrine transporter permit the visualization of transduction via accumulation of iodide or pertechnetate in the targeted tissue and may be used for genetically modified radioisotope therapies. However, since the efficiency of in vivo gene transfer is very limited using currently available viral vectors these options are not clinically relevant at the present stage.

Pharmacogenomics will identify new surrogate markers for therapy monitoring which may represent potential new tracers for imaging. Also drug distribution studies for new therapeutic biomolecules are needed at least during preclinical stages of drug development. New treatment modalities such as gene therapy with suicide genes will need procedures for therapy planning and monitoring. Finally, new biomolecules will be developed by bioengineering methods which may be used for isotope-based diagnosis and treatment of disease.

The identification of useful new molecules out of huge libraries must be done by use of high throughput methods. Display systems are used for the selection of molecules from libraries in which peptides or proteins are physically linked to their corresponding encoding sequences. In addition these systems can be used to modify the biophysical properties of the displayed molecules by evolution through cycles of mutation, selection and replication.

The principle of phage-displayed peptide libraries is the display of the peptide libraries fused with the carboxy-terminal domain of the minor coat protein, gene III or VII protein fragment, on the surface of a filamentous phage. The relevant molecule is then directly detected and screened using the target molecules and amplificated after infection of E. coli. This allows a rapid selection (within weeks) of particular clones from large pools (> 10^{10} clones), and determination of the amino acid sequence of a peptide displayed on a phage by sequencing the relevant section of the phage genome. Selection is done by exposing the library to proteins, cells or even injecting it into animals (biopanning). The method is used for a couple of applications such as mapping and mimicking of epitopes, identifying new receptors and natural ligands, identifying high-affinity antibodies and analogues, isolating specific antigens that bind to bioactive compounds, producing novel enzyme inhibitors and DNA-binding proteins, probing cellular and tissue-specific processes. Furthermore, the identification of tumor-specific peptides or antibodies offers new targets for radiopeptide based diagnosis and therapy.

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