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Will magnetic resonance imaging (MRI)-based contrast agents for molecular receptor imaging make their way into the clinic?

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Recent advances in magnetic resonance (MR) molecular and functional imaging are providing novel insights into several diseases including cancer. The development of contrast agents (CAs) that generate receptor- or molecular-targeted contrast has greatly increased the scope of magnetic resonance imaging (MRI) applications. Because of its high sensitivity, radiopharmaceutical-based nuclear imaging has been the predominant method of choice for receptor imaging. Several receptor-based SPECT tracers for tumour detection are already clinically available and include [^{111}In]OctreoScan® for the detection of somatostatin receptor-expressing tumours [2], [^{111}In] Zevalin for the detection of CD20-positive lymphomas [3], and [^{111}In]ProstaScint for detecting prostate-specific membrane antigen (PSMA)-expressing prostate cancer [4]. Antibody-based probes provide high target receptor affinity, although their biodistribution can include substantial non-targeted uptake in both the liver and spleen. Vascular receptors are more accessible to monoclonal antibodies than receptors on cancer cells in the tumour. Targeting monoclonal antibodies to cancer cell receptors can take 24–48 hrs to generate maximum contrast.

The exquisite spatial resolution of MRI has led to studies exploring its use in imaging receptor expression in pre-clinical studies. In this issue of The *Journal of Cellular and Molecular Medicine,* Towner and colleagues [1] report on the in vivo detection of c-Met receptor expression by molecular MRI. The c-Met receptor is a tyrosine kinase receptor, which is located in the plasma membrane of cancer cells and contains an extracellular domain. The natural substrate of c-Met is the hepatocyte growth factor (HGF). Both the c-Met receptor itself and HGF are associated with poor prognosis in glioblastomas. As demonstrated by Towner and colleagues [1], novel MRI-detectable receptor probes can exploit the advantage of this inherently high resolution of MRI. Contrast enhancement using MRI is typically induced by altering the relaxation rate constants of the abundant water signal in tissue. This is done by employing either chelated Gd^{3+} to create T_1 (spin-lattice relaxation time) positive contrast or superparamagnetic Fe_2O_3 particles to create T_2 (spin-spin relaxation time) negative contrast. Probes that are amenable to labelling with radiometals for SPECT or PET can also be labelled with Gd^{3+}-chelates for use in MRI. Because the sensitivity of detection for MRI is considerably lower than that of either SPECT or PET, MRI probes must either contain many chelated Gd^{3+} ions or the density of receptor targets must be high, usually in the range of 10^6 receptors per cell. An example of successful receptor imaging in preclinical studies using T_1 contrast MRI was reported using a biotinylated Herceptin antibody to target Her2/neu expressing breast cancer tumours [5]. In this approach, once the antibody has had sufficient time to bind and clear from non-specific tissues, a

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Gd^{3+}-chelated avidin probe is injected and binds specifically to the biotin present on the Herceptin antibody [5]. This generates positive contrast, enabling imaging of Her2/neu receptor expression [5].

In addition to radiopharmaceutical and MRI-based receptor imaging, optical and ultrasound receptor imaging are also being explored. Both antibody and small molecule probes have been conjugated to fluorophores emitting from the green through near-infrared (NIR) wavelength range. NIR light passes through tissue with less attenuation than shorter wavelengths and is making these dyes an attractive choice for fluorescence imaging. Attenuation is the critical limitation of this technique and optical receptor imaging is only just emerging as a pre-clinical modality to study cancer and cancer therapy [6]. To generate contrast for receptor imaging in ultrasound applications, microbubbles, which are typically perfluorohydrocarbon gas in hydrophobic vesicles have recently been used [7, 8]. Microbubbles enhance the ultrasound echo by creating backscatter, because they expand and contract when being exposed to ultrasound beams of any frequency [8, 9].

While MRI-based CAs for oncologic receptor imaging, such as those developed by Towner and colleagues for c-Met imaging of malignant gliomas [1] are finding useful applications in pre-clinical studies, limitations imposed by the sensitivity of detection may restrict their clinical translation. Unlike radiopharmaceuticals, MR CAs are not used in tracer quantities and will be subject to stricter evaluation by regulatory bodies such as the Food and Drug Administration (FDA) in the U.S. The critical challenges for the future are to increase sensitivity of detection by designing signal amplification strategies or novel CAs. Such advances will realize the tremendous clinical potential of MRI in molecular and functional imaging applications.

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