

Preclinical Applications of Imaging Biomarkers

Markus von Kienlin, F. Hoffmann-La Roche AG, Basel, Switzerland

Magnetic Resonance Imaging and Spectroscopy (MRI/MRS) in principle should be the ideal, translational modality to diagnose pathologic processes and to predict the clinical effect of medical interventions, because:

- (i) it can measure a large number of relevant anatomical, physiological and functional parameters, hereby providing essential insights into the disease and drug effects,
- (ii) it can measure these parameters non-invasively, repeatedly in the same individual, allowing to monitor disease and treatment effects over time, hereby alleviating inter-individual variability, and
- (iii) it can be applied both in human patients as well as in animal models of disease, hereby bridging bench research to clinical science.

Despite these valuable properties, it also needs to be recognized that for many years to come, MRI/MRS will not qualify as accepted primary endpoint in clinical trials (with possibly few examples from oncology or MS the most notable exceptions confirming the rule): for each indication, the qualification process to become a primary endpoint which is accepted by the authorities requires anew several, independent trials which need to firmly establish the link between a putative imaging marker and the clinical outcome in the patient. But even if MRI/MRS is not (yet) an established surrogate in clinical trials, it has become a critical asset in the preclinical drug discovery process. Preclinical imaging in the pharmaceutical industry creates value in essential phases in the discovery and the early development of new drugs:

- (i) it can elucidate molecular mechanisms in (patho-)physiologic processes and hereby allows the validation of potential targets for pharmacological intervention,
- (ii) it can characterize and validate the physiological and functional properties of animal models of disease,
- (iii) it can characterize and differentiate the actions of new compounds in the living organism,
- (iv) it can elucidate mechanisms which impact the safety of potential new drugs, and
- (v) it can support the discovery and the development of imaging biomarkers for early clinical development.

Preclinical MRI/MRS studies have become a critical element for decision making in many drug discovery projects in the pharmaceutical industry, to ensure that only the best compounds are brought forward in the R&D pipeline and to reduce the attrition rate at advanced stages. In this course, examples will be presented for each of the aforementioned applications of preclinical MRI/MRS, coming from the areas of neuroscience and metabolic diseases.