

**First Mediterranean Thematic Workshop on Advanced Molecular Brain
Imaging with Compact High Performance MRI-Compatible PET and SPECT
Imagers –Potential for a Paradigm Shift**

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Abstract. The picomolar sensitivity of Positron Emission Tomography (PET) is increasingly recognized in industrial drug development projects aiming for rapid confirmation of new treatment principles in humans. Three major approaches can be identified. Radio-labeling of a new drug to high specific radioactivity allows for a detailed mapping of drug distribution to critical organs in man after administration of a microdose (<1 µg) at which level limited toxicology documentation is required. For CNS-drugs this approach is particularly useful for passage across the BBB and confirmation of brain exposure. A second approach is to develop a suitable radioligand for the targeted protein. The radioligand can then be used to indirectly measure the occupancy of a candidate drug. This approach is widely used for proof of mechanism, for dose finding and to support dose recommendations. A third approach is to develop radioligands that bind to in vivo biomarkers for pathophysiology, such as beta-amyloid in Alzheimer's disease. Research on the pathophysiology of psychiatric disorders has to a significant degree been based on psychopharmacology. For instance, the dopamine hypothesis of schizophrenia is based on the fact that most antipsychotic drugs block D2-dopamine receptors and the serotonin hypothesis of anxiety and depression is based on the effect of antidepressant drugs on serotonin levels. Testing of such hypothesis with PET has demonstrated changes in dopamine transmission among patients with schizophrenia. New radioligands that are sensitive to endogenous serotonin levels are currently implemented. Understanding of brain physiology may serve as another lead to understand the pathophysiology of major psychiatric conditions. A general view is that the phenotypic expression of higher brain functions comes from an interplay between physiology and environment. This reciprocal relationship between biochemistry and behavior has recently been confirmed with PET for central dopamine receptor binding in relation to personality traits and working memory.

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