Proteins seldom act alone; they usually interact with other molecules to accomplish their biological function. It is becoming increasingly clear that this also holds true for membrane proteins, which interact with intracellular macromolecules such as the cytoskeleton or signal transduction proteins, but also with other membrane components. During recent years, much attention has been paid to the role of the transmembrane (TM) domains in the dynamic assembly and regulation of functional complexes varying in size from homo- or heterodimers to much larger oligomers comprising many different molecular entities. These intramembrane molecular interactions are certainly of major importance for our understanding of the molecular and cellular mechanisms controlling cell adhesion and migration.

This special focus issue aims to cover the latest aspects of the molecular mechanisms and functional consequences of these TM peptide-mediated interactions. Papers in this issue provide authoritative overviews covering a broad range of methodologies from structural studies to functional assays in cells and animal models, and consider several biological systems of relevance to both during physiological and pathological processes.

The first review by Dr. Ulmer presents very recent results which elucidate the structural basis for integrin αIIbβ3 TM association. This complex represents the first experimental structure of a heterodimeric TM receptor. These results are certainly a major advance in the understanding of the integrin "allosteric machine," especially in view of its inside-out signaling properties. Because of their importance in pathological conditions such as cancer and developmental disorders, and of the existence of disease-causing mutations in their TM domains, receptor tyrosine kinases have been at the forefront of studies concerning structure-function relationships in receptor signaling. Drs. Li and Hristova discuss the functional role of receptor tyrosine kinase receptors TM domains, from a structural and thermodynamic point of view. They stress the needs for more quantitative informations about these TM-TM interactions, as well as for full-length receptor structures. The structure elucidation of dimeric TM domains, using different approaches, is discussed in detail by Dr. Bocharov et al. These authors are pioneers in the field, having solved 3 out of 7 such available structures to date, with more certainly to come. Receptor tyrosine kinases TM domains are also discussed by Drs. Cymer and Schneider, focusing on the best studied subgroup of these receptors (the ErbB/EGF receptor family). They show that TM domain interactions do play a role in activation of these receptors, in conjunction with other subdomains of these complex proteins. They also stress the importance of receptor organization in lipid microdomains at the cell surface.

Three other contributions discuss the physiopathological implications and therapeutic perspectives of these TM-TM interactions. A first example is the dimerization of the amyloid precursor protein (APP) reviewed by Dr. Kienlen-Campard and collaborators. APP shares many properties with bitopic...
membrane receptors, including its ability to form homo- or heterocomplexes through motifs in its TM domain. Importance of these interactions for processing of APP and their potential interest as therapeutics targets are discussed. Two papers deal with the role of TM interactions in the immune synapse, where many receptor systems organize into activating clusters allowing for the integration of different signals. Dr. Sigalov describes his model of immune signaling which holds to the role of the association of cytoplasmic domains of multichain receptors. He discusses how inter- and intrareceptor TM interactions could be used as therapeutic targets. Likewise, Dr. Manolios and his collaborators present their work on the small TM inhibitory peptide called Core Peptide. This peptide has demonstrated therapeutic activity in animal models of inflammation. Both papers insist on the potential of interfering with signal transduction using TM peptides as drug templates in a number of pathologies.

Finally, a review by me and my collaborators from Marseille and Strasbourg presents an overview of many different aspects of TM-TM domains interactions in cell adhesion molecules and other membrane proteins playing roles in cell migration and proliferation.

It is perhaps too early to coin the term “New Double Helix” to describe the association of two helical transmembrane domains. Nevertheless, this focus issue demonstrates that many new discoveries pertaining to fundamental and clinical issues in the mechanism of activation of adhesion molecules and receptors lie ahead for researchers interested in small transmembrane helices. Clearly, future developments will address the resolution of more structures of TM dimers and hopefully full length complex receptors such as integrins or tyrosine kinase receptors. The development of more small peptides or other molecules able to modulate TM signaling is also to be expected.