The alpha(v)beta(3)- and alpha(5)beta(1)-integrins play a key role in angiogenesis, the formation of new vessels in tissues that lack them. By serving as receptors for a variety of extracellular matrix proteins containing an arginine-glycine-aspartic acid (RGD) sequence, these integrins mediate migration of endothelial cells into the basement membrane and regulate their growth, survival, and differentiation. Besides being involved in angiogenesis, the alpha(v)beta(3)-integrin is also presented on tumor cells of various origin, where it is involved in the processes that govern metastasis. Because the alpha(v)beta(3)-integrin is an attractive target for cancer treatment, high-affinity ligands containing the RGD sequence, for example, cyclic pentapeptides, have been developed. They inhibit angiogenesis, induce endothelial apoptosis, decrease tumor growth, and reduce invasiveness and spread of metastasis. This development finally resulted in cyclo(RGDf(NMe)V) (cilengitide), which is a drug for the treatment of glioblastoma (currently in phase III clinical trials). With the growing focus on individualized medicine, clinicians would like to be able to assess the severity of the disease and monitor therapy for each patient. Such measurements would be based on a noninvasive visualization and quantification the alpha(v)beta(3)-integrin expression levels before, during, and after antiangiogenic therapy. A wide
spectrum of in vivo imaging probes for the nuclear imaging modalities positron emission tomography (PET) and single-photon emission computed tomography (SPECT), for optical imaging, and for magnetic resonance imaging (MRI) have been developed with these goals in mind. In this Account, we describe the synthesis and preclinical and clinical assessments of dedicated targeting probes. These molecules ideally accumulate selectively and in high concentrations in alpha(v)beta(3)-integrin-expressing tissues, have low uptake and retention in nontarget tissues, and are highly stable against in vivo degradation. [(123)I]cyclo(RGDyV) was the first radiolabeled "imaging analogue" of cilengitide that we evaluated preclinically in detail. Subsequent studies focused on cyclo(RGDfK) and cyclo(RGDyK), which allowed conjugation with various signaling moieties, such as prosthetic groups, bifunctional chelators (DTPA, DOTA, NOTA, TETA, and TE2A for labeling with (111)In or (177)Lu for SPECT and (86)Y, (68)Ga, or (64)Cu for PET), or fluorescent dyes (Cy5.5, cypate). Furthermore, pharmacokinetic modifiers such as carbohydrates, charged amino acids, or PEG analogues were coupled to the peptide core without significantly affecting the binding affinity. Finally, dimers, tetramers, octamers, and polymers and decorated quantum dots with several dozens of peptide units were constructed and investigated. Some of these multimers demonstrated significantly improved affinity (avidity) and targeting efficiency in vivo. Besides peptidic alpha(v)beta(3)-integrin ligands, researchers have investigated radiolabeled antibodies such as Abeegrin and used molecular modeling to design small peptidomimetics with improved activity, in vivo stability, and subtype selectivity (e.g., (111)In-TA138). Furthermore, there is an increasing interest in nanoparticles such as nanotubes, quantum dots, or paramagnetic particles coated with cyclic RGD analogues as targeting agents. [(18)F]Galacto-RGD, a glycosylated cyclo(RGDfK) analogue, was the first such substance applied in patients and has been successfully assessed in more than 100 patients so far. Because of modification with carbohydrates, rapid renal excretion, and inherently low background activity in most regions of the body, imaging of alpha(v)beta(3) expression with high tumor/background ratios and high specificity is possible. Other (18)F-labeled RGD analogues recently developed by Siemens and GE Healthcare have entered clinical trials.