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Family of pH-Low-Insertion-Peptides (pHLIPs) DHAMMIKA WEERAKKODY, ANNA MOSHNIKOVA, Department of Physics, University of Rhode Island, VALENTINA MOSHNIKOVA, College of William and Mary, MAK THAKUR, BETHANY ROSSI, University of Rhode Island, DONALD ENGELMAN, Department of Molecular Biophysics and Biochemistry,Yale university, OLEG ANDREEV, YANA RESHETNYAK, Department of Physics, University of Rhode Island — pHLIP (pH (Low) Insertion Peptide) is a novel delivery system for targeting of acidic diseased tissue such as solid tumors, sites of inflammation, arthritis and other pathological states. The molecular mechanism of pHLIP action is based on pH-dependent insertion and folding of pHLIP in membrane. We performed sequence variation and investigated 16 pHLIP variants with main goals of understanding the main principles of peptide-lipid interactions and tune delivery capability of pHLIP. The biophysical studies including thermodynamics and kinetics of the peptides interaction with a lipid bilayer of liposomes and cellular membranes were carried out. We found that peptides association to membrane at neutral and low pH could be modulated by 3-4 times. The apparent pK of transition from surface bound to membrane-inserted state could be tuned from 6.5 to 4.5. The rate of peptide's insertion across a bilayer could be enhanced 100 times compared to parent pHLIP. As a result, blood clearance and tumor targeting were modulated in a significant degree. The work is supported by NIH grants CA133890 to OAA, DME, YRK.

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