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**Small Molecules Target Carcinogenic Proteins** CLAUDIU GRADINARU, University of Toronto — An ingenious cellular mechanism of effecting protein localization is prenylation: the covalent attachment of a hydrophobic prenyl group to a protein that facilitates protein association with cell membranes. Fluorescence microscopy was used to investigate whether the oncogenic Stat3 protein can undergo artificial prenylation via high-affinity prenylated small-molecule binding agents and thus be rendered inactive by localization at the plasma membrane instead of nucleus. The measurements were performed on a home-built instrument capable of recording simultaneously several optical parameters (lifetime, polarization, color, etc) and with single-molecule sensitivity. A pH-invariant fluorescein derivative with double moiety was designed to bridge a prenyl group and a small peptide that binds Stat3 with high affinity. Confocal fluorescence images show effective localization of the ligand to the membrane of liposomes. Stat3 predominantly localizes at the membrane only in the presence of the prenylated ligand. Single-molecule FRET (fluorescence resonance energy transfer) between donor-labeled prenylated agents and acceptor-labeled, surface tethered Stat3 protein is used to determine the dynamic heterogeneity of the protein-ligand interaction and follow individual binding-unbinding events in real time. The data indicates that molecules can effect protein localization, validating a therapeutic design that influences protein activity via induced localization.

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