Protease Activated Receptors (PAR) Mimetics for Cancer Treatment. (Hadasit)

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Need:

Target-specific approaches are recognized as the basis for novel cancer therapeutics. Protease-Activated-Receptors (PARs), a G Protein-Coupled Receptor, play central roles in tumor progression. PARs are over-expressed in a wide range of epithelial malignancies relative to normal epithelium, thus offering the opportunity for a tumor-specific drug. The PAR C-terminal PH domain binds to other proteins that have a key role in tumorigenesis, suggesting that this domain might be effectively targeted by a novel therapeutic.

Breast cancer, as the leading indication, is treated with monoclonal antibodies (Herceptin for $Her2^{+}$ tumors), hormone-blocking therapy & chemotherapy. The estimated market is ~$10B (mostly Herceptin) and growing with increased disease incidence. Given PAR expression in epithelial tumors, additional cancer indications include ovary, prostate, colon & melanoma – each a growing >$1B market and in some cases $10B in the future. Since the mechanism of action of the PAR peptide is orthogonal to that of other drugs, the new drug is expected to be used in combination with other available drugs.

Innovation:

Peptides mimicking the primary binding site on the PAR_2 C-terminal PH-domain as a potential therapeutic for epithelial cell tumors.

Findings:

PAR_1 or PAR_2 overexpression enhances breast tumor growth in a mouse xenograft model of breast cancer.

PAR_1 and PAR_2 act as a functional heterodimeric unit during tumor development.

Inhibition of PAR_2 expression or activity either by a non-functional PAR_2 protein or by knocking-down of PAR_2 expression attenuates the activity of both PAR1 and PAR_2.

A peptide from the PAR_2 PH domain inhibits the growth of tumors driven by PAR_1/PAR_2 overexpression.

Indications/Applications:

A novel tumor-specific therapeutic for epithelial malignancies.

Competitive Advantages:

Specific targeting of a biologically key protein for tumor progression as a therapeutic for a wide range of epithelial malignancies.

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