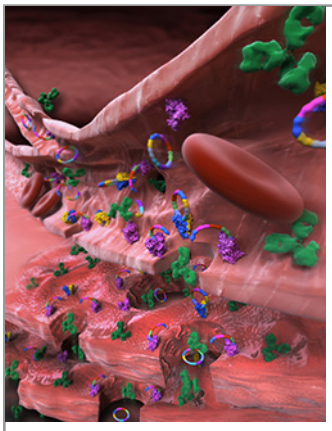
April 7, 2010

Cancer Drug Effectiveness Substantially Advanced

Co-administered peptide directs medicines to tumors and deep into tumor tissue, increasing drug efficacy and reducing side effects



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A tumor-penetrating peptide allows co-injected drugs to penetrate into tumor tissue.
Intravenously injected iRGD, a cyclic tumor-penetrating peptide (colorful ring), binds to angiogenesis-associated integrins (blue and yellow receptor) in a tumor blood vessel. The peptide is then cleaved to become an active CendR peptide (colorful half ring) that binds to neuropilin-1 (purple receptor). The CendR/neuropilin-1 binding mediates an active transport system that allows co-injected drugs such as antibodies (green molecules) to extravasate. The cascade continues within the extravascular tumor tissue such that the drugs penetrate deeper and deeper into the tumor.
(Image created by Peter Allen, UCSB).

Santa Barbara, Calif., April 8, 2010
? Researchers have shown that a peptide (a chain of amino acids) called iRGD helps co-administered drugs penetrate deeply into tumor tissue. The peptide has been shown to substantially increase treatment efficacy against human breast, prostate and pancreatic cancers in mice, achieving the same therapeutic effect as a normal dose with one-third as much of the drug. In a transformative paper published today in the online edition of the journal *Science*, Erkki Ruoslahti, M.D., Ph.D., distinguished professor at Sanford-Burnham Medical Research Institute and founding member of the UC Santa Barbara-Sanford|Burnham Center for Nanomedicine,

Kazuki N. Sugahara, M.D., Ph.D., Tambet Teesalu, Ph.D., and fellow researchers at the Center for Nanomedicine and the Cancer Center of Santa Barbara, announced this significant advance in cancer therapy.

?Drugs generally have difficulty penetrating tumors beyond a few cell diameters from a blood vessel,? said Dr. Ruos lahti. ?This leaves some tumor cells with a suboptimal dose, increasing the risk of both recurrence and drug re sistance. The iRGD peptide solves this problem by activating a transport system in tumors that distributes co-injected drugs into the entire tumor and increases drug accumulation in the tumor.?

Dr. Ruoslahti showed in the 1980s that a 3 amino-acid peptide motif (RGD?Arginine-Glycine-Aspartic Acid) se rves as a highly selective identifier of malignant tissue, binding to unique re-ceptors in the vasculature of cancers. The RGD peptide?s ability to home to tumors has been used to design new compounds for cancer di agnosis and treatment.

The new variant of RGD (iRGD?internalizing RGD) combines the RGD motif with a tissue penetration el ement called CendR. Like the earlier RGD peptides, iRGD homes to tumors, but exposure of the CendR motif when the iRGD is enzymatically cleaved activates a transport system through tumor blood vessel walls into the tumor core. In a paper published in *Cancer Cell* late last year, the research team showed that coupling iRGD to anti-cancer drugs allowed them to penetrate deep into tumors, effectively increasing the activity of the drugs.

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The research reported in this latest *Science* paper adds a new and important twist to the story: The researchers made the unanticipated discovery that anti-cancer drugs do not need to be chemically attached to the iRGD peptide for iRGD to boost their efficacy. Simply co-administering iRGD with a drug enhances the drug?s anti-ca ncer properties. Co-administration could be even more effective at delivering therapeutic agents inside tumors than conjugating the agents with the peptide. This new paradigm means that iRGD has the potential to enhance the efficacy of already approved drugs without creating new chemical entities, which would complicate the path to approval for clinical use.

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In addition to being effective against human breast, prostate and pancreatic cancers grown in mice, iRGD can penetrate other tumor types, and could possibly be used to treat most, if not all, solid tumors. The iRGD peptide was also shown to enhance the therapeutic effects of multiple types of anti-cancer drugs, including a small molecule drug, a monoclonal antibody and two nanoparticle drugs. Tumors essentially resistant to a particular drug showed good responses when the drug was combined with iRGD, and tumors partially responsive to another drug were eradicated by the combination.

?We are really excited about the potential of iRGD, and I?d like to thank my colleagues, Kazuki Sugahara and Tamb et Teesalu in particular, who made this all happen,? said Dr. Ruoslahti. ?These results with human tumors in mice are very promising, but we still have to demonstrate the value of iRGD in treating cancers in humans.?

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Related Links

- New Peptide Helps Cancer Drugs Break Into Tumors - AAAS Science Now

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