

A Peptide Targeting Tumor Blood Vessels: From Experimental to Clinical Applications

Chi Hin CHO, B.Pharm., Ph.D.

School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong

Deficiencies of Chemotherapy:

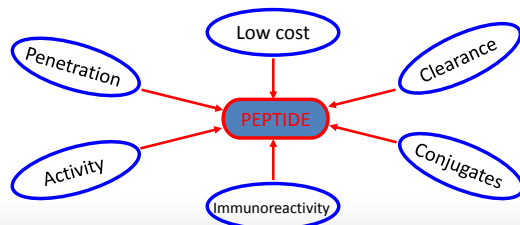
1. Late diagnosis with metastasis
2. Non-selectivity with wide-spread toxicities
3. Multi-drug resistance

Our peptides are dealing with these deficiencies

Background

➤ The development of drug delivery/imaging probe systems represents the ongoing effort to improve the selectivity and efficacy of anti-cancer drugs and diagnosis.

- ✓ Peptides are important for drug delivery/imaging vectors that can target the predefined molecules, cells or tissues.



Background



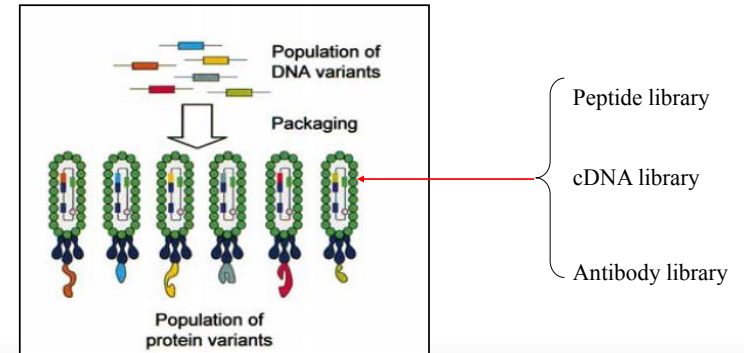
*Kakolyris et al, 2000;
Konerding et al, 2001*

- Tumor blood vessels express a distinct set of molecules on their surface from normal resting blood vessels.
- Peptides bound to a specific site in the tumor vasculature are attractive for delivery of drug and image contrast.

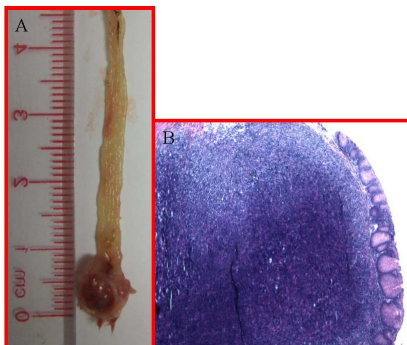
Our studies

- To biopan and identify peptides specifically targeting the vasculature of orthotopic colorectal cancer through *in vivo* phage display technology
- To develop these peptides as vectors for imaging detection and drug delivery for colorectal cancer.

Phage-display library

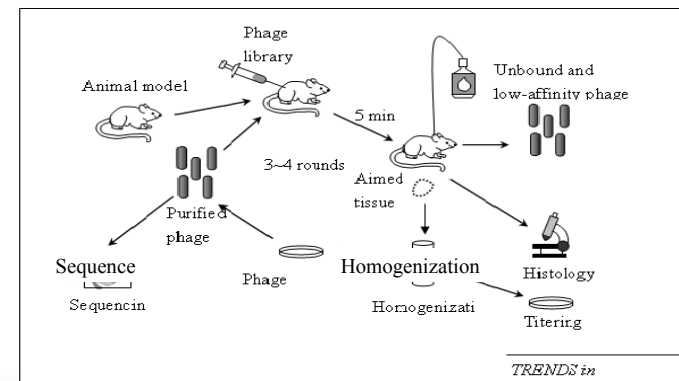


Establishment of orthotopic colorectal cancer

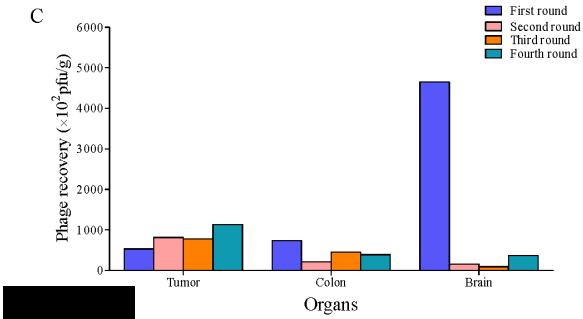


➤ Unlike those subcutaneously transplanted tumor in nude mice, the tumor mass not only locates in the rectal lumen with the same complex interior biological environment but also grows in immunologically intact mice. This provides an opportunity to examine tumor blood vessel changes in a more physiologically relevant microenvironment in the colon.

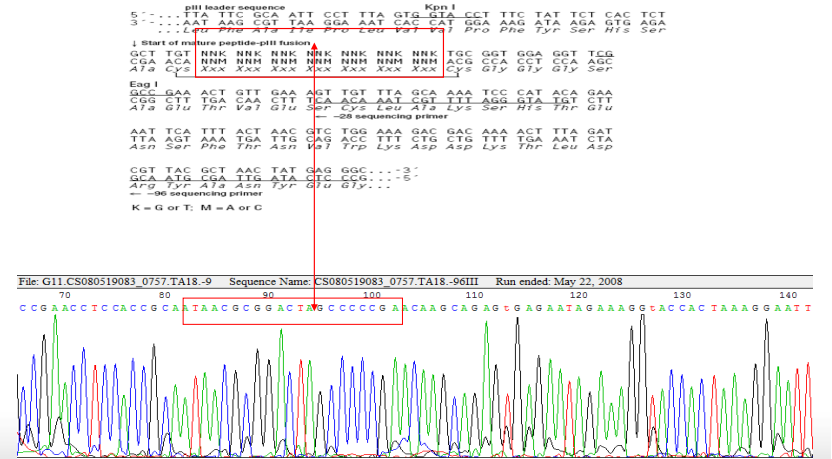
In vivo phage display



Isolation of tumor-targeting phages using an in vivo phage display



Identification of inserted fragments

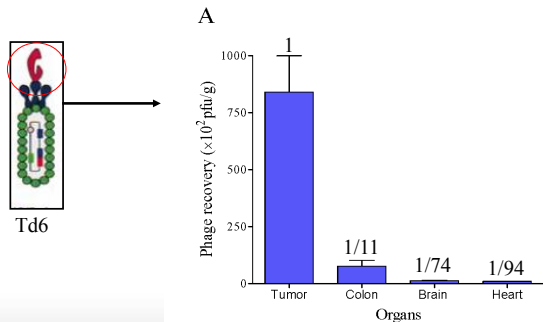


Td6 phage shows a strong homing ability to tumor

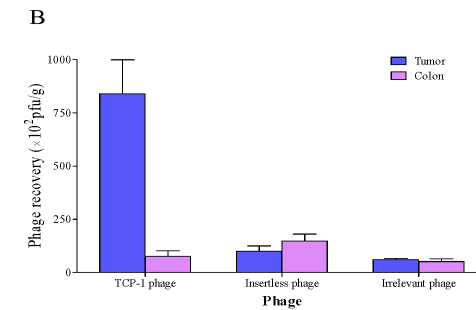
Appeared most frequently

Displayed a peptide consisting of 7 amino acids

Termed **TCP-1**

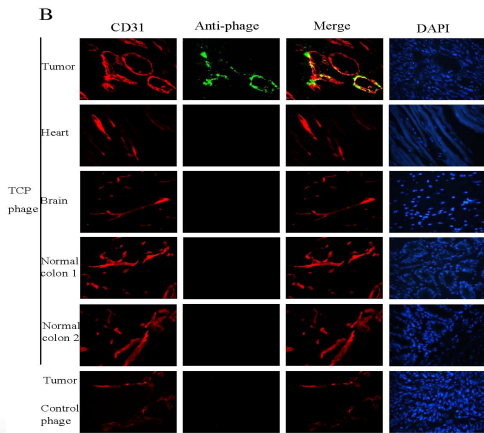


Control phage has no homing ability

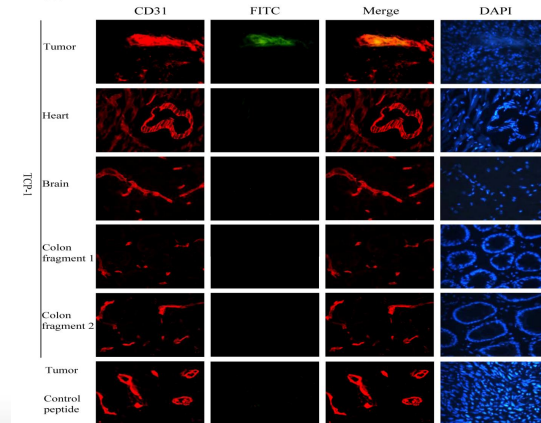




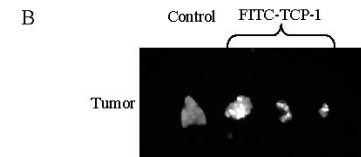
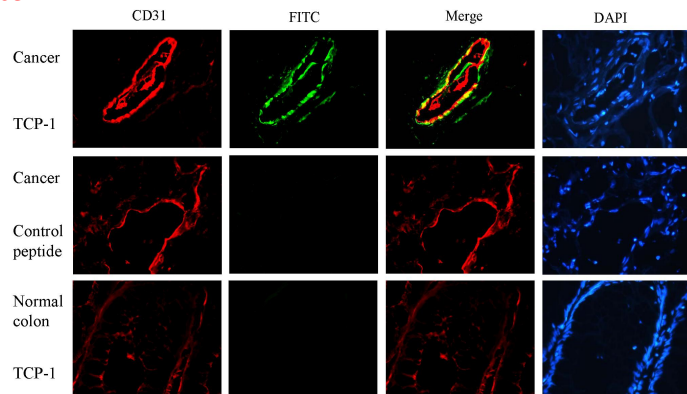
Colocalization of homing phage (TCP-1) with the vasculature in tumors



FITC-labeled TCP-1 colocalizes at the vasculature of tumors



FITC-labeled TCP-1 recognizes the vasculature of human colorectal cancer



TCP-1 peptide can be used as a potential tool for imaging detection of colorectal cancer.



TCP-1 for drug delivery

- ✓ The sequence (KLAKLAK)₂ is a synthetic peptide leading to cell death by disrupting mitochondrial membranes and convert pro-caspase 3 to cleaved caspase 3, a hallmark of apoptosis.
- ✓ Peptide coupled with this pro-apoptotic peptide has been successfully employed to target angiogenic endothelial cells and the vasculature of arthritis and white fat.



Targeted proapoptotic peptide treatment of tumor-bearing mice

- I : PBS
- II : DKK (TCP/ proapoptotic peptide)
- III : CDK (TCP conjugated proapoptotic peptide)

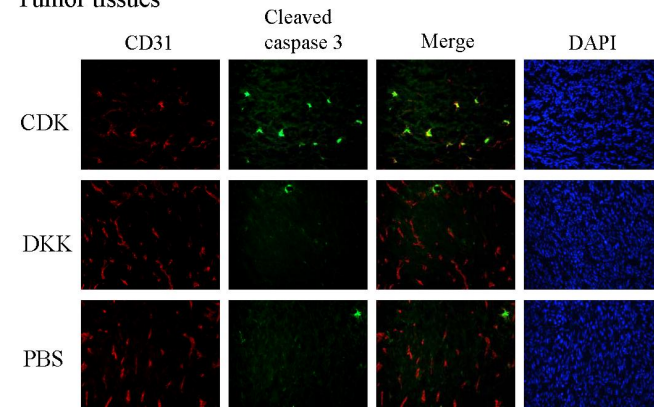
Mice(n=5) were i.v. injected with CDK, DKK (an equimolar mixture of TCP/proapoptotic peptide) or PBS

Dose: 100 nmol/mouse every three days

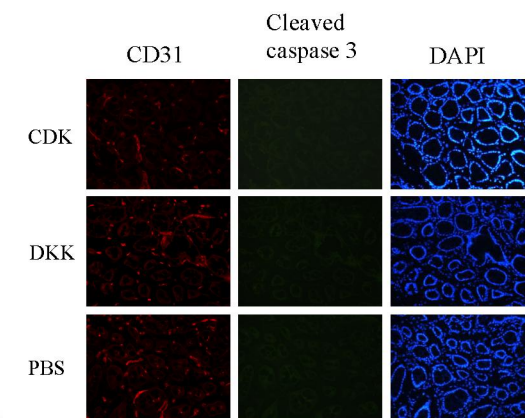
Treatment was terminated 7 days after the first peptide administration



Tumor tissues



Colon tissue





TCP-1 peptide mediates drug and fluorescein delivery to the vasculature of orthotopic colorectal cancer

