Treating Peritoneal Metastasis: Moving Beyond HIPEC

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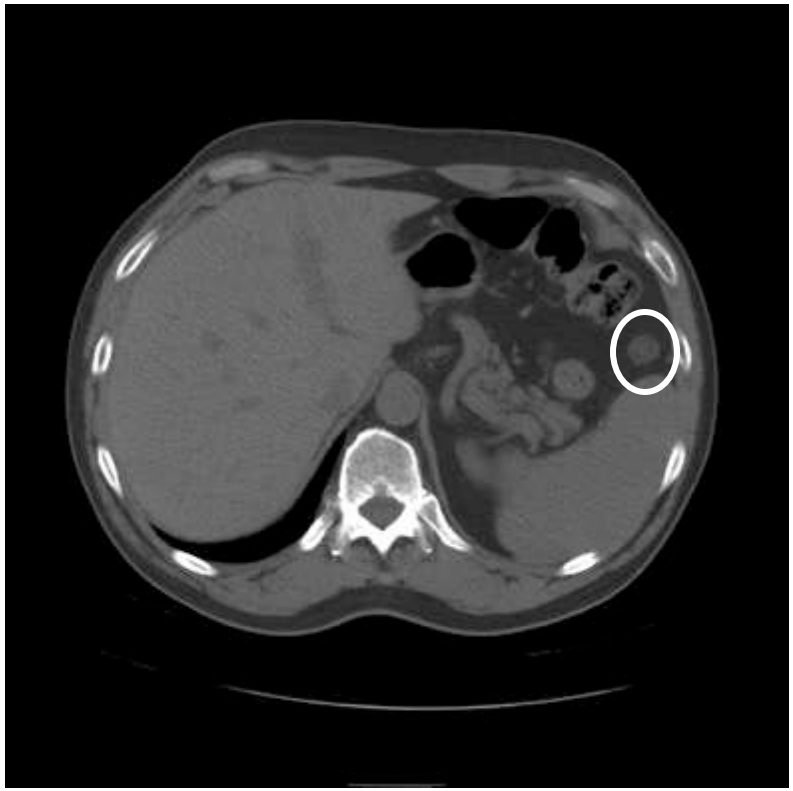
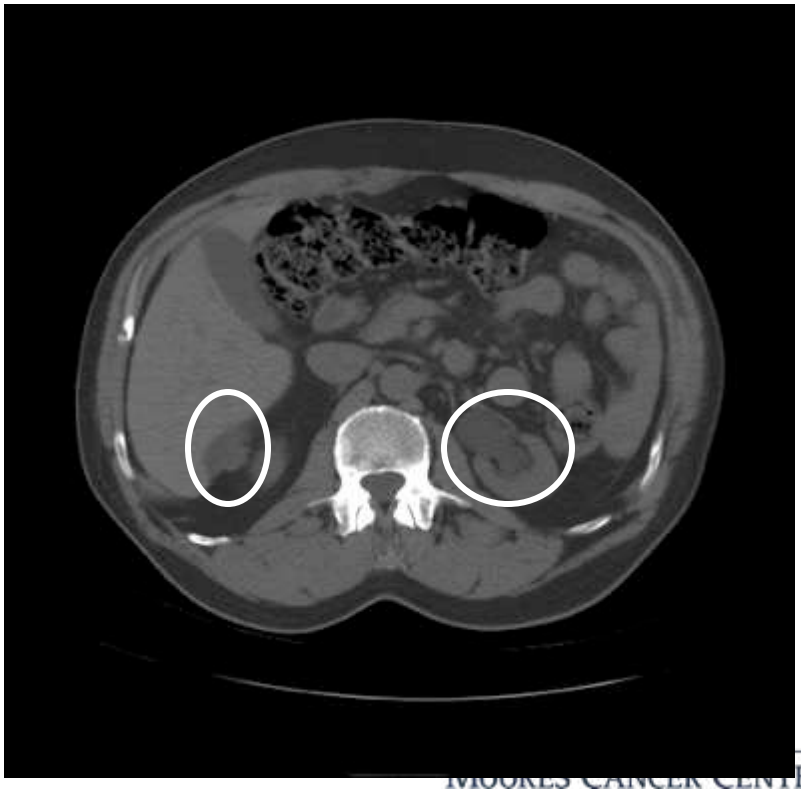
November 2006- 57 yo WM presents with change in stool caliber. Colonoscopy reveals rectal cancer at 10 cm from the anal verge and synchronous cancer of the cecum. CT scan reveals mild L hydroureter and associated multiple peritoneal metastases. Tumor moderately differentiated, CEA 22.4. Management?





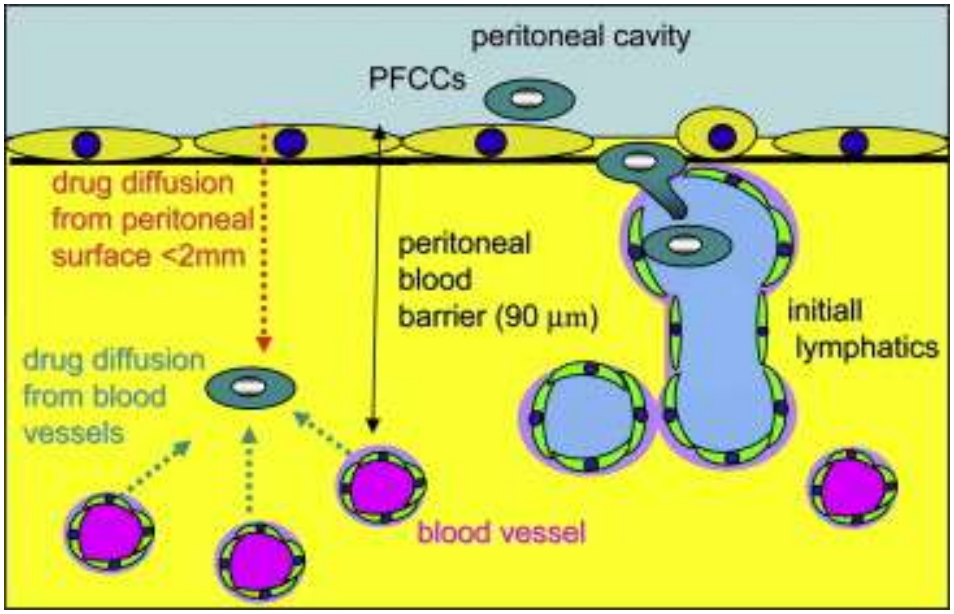
Outline

- Rationale for cytoreductive surgery (CRS) and and hyperthermic intraperitoneal chemotherapy (HIPEC)
- Outcomes of cytoreductive surgery CRS and HIPEC for colorectal peritoneal metastases
- UC San Diego experience
- Tumor penetrating peptides to enhance intraperitoneal therapy
- Other future directions

Central hypothesis: In selected patients and tumor types, peritoneal metastases represent the sole site of metastatic disease and therefore may be amenable to aggressive locoregional therapy.

Peritoneal Metastasis
Rationale for Intraperitoneal Chemotherapy

- Peritoneal/Plasma barrier allows for high dose
- Peritoneal clearance is less than systemic clearance
- Systemic toxicities may be reduced because of poor systemic absorption



Yonemura Y. Eur J Surg Oncol 2010;36(12):1131

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Priority Report

Cancer Research

Hyperthermia Synergizes with Chemotherapy by Inhibiting PARP1-Dependent DNA Replication Arrest

Lea Schaaf[1], Matthias Schwab[1,2], Christoph Ulmer[3], Simon Heine[1], Thomas E. Mürdter[1], Jens O. Schmid[1], Georg Sauer[4], Walter E. Aulitzky[5], and Heiko van der Kuip[1]

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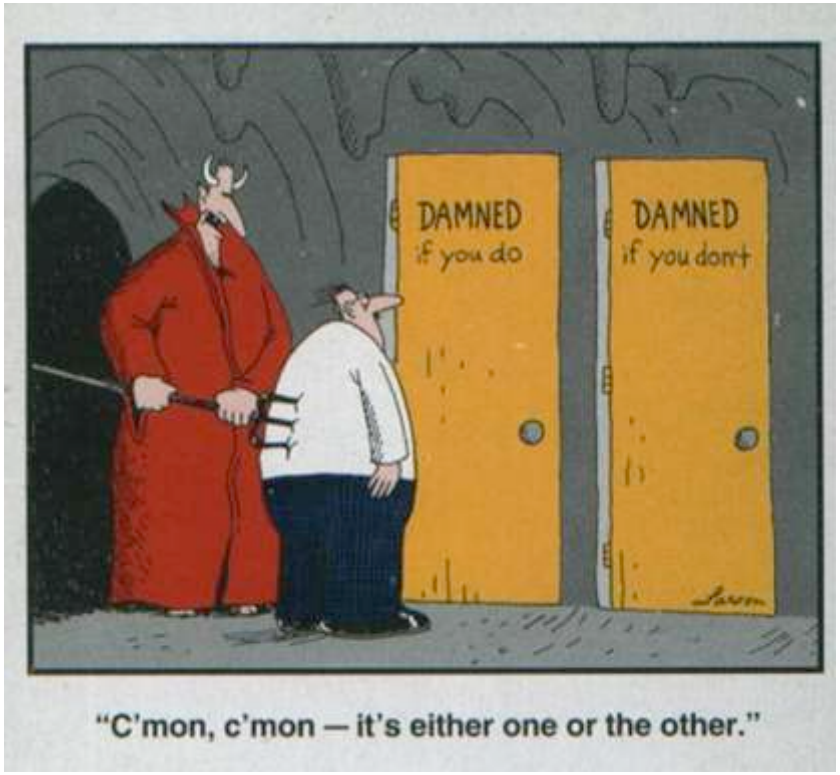
Peritoneal Metastasis
Evidence for HIPEC

- Is HIPEC beneficial in patients with peritoneal metastasis, or just another bad option?



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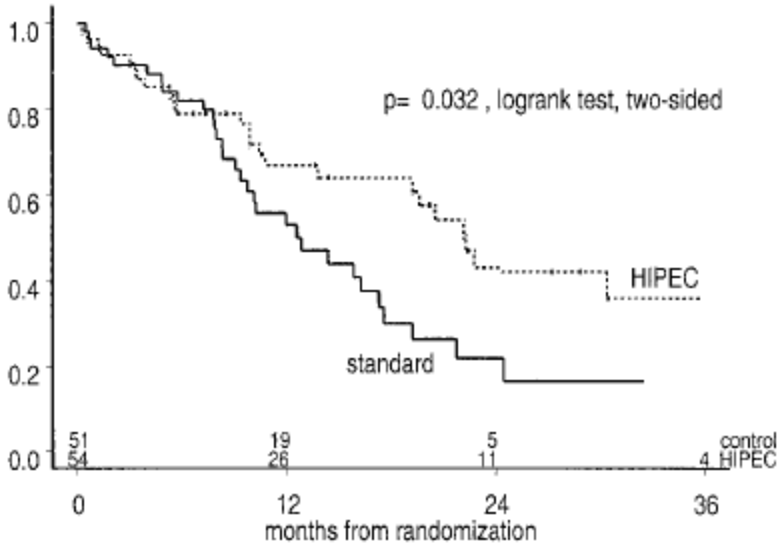
Colorectal Peritoneal Metastasis
Evidence for HIPEC

- RCT of 105 pts with peritoneal carcinomatosis from colorectal CA to systemic 5-FU vs. HIPEC
  - Control arm: 5-FU x 6 mos, palliative surgery for obstruction allowed
  - HIPEC arm: cytoreductive surgery (CRS), then 90 min HIPEC with MMC, then given adjuvant systemic 5-FU 6-12 wks after surgery x 6 mos
  - 8% mortality in HIPEC arm
  - Only 37% with complete/R1 CRS
  - 12.6 vs. 22.3 mo median OS
- Criticisms
  - Antiquated chemo regimen
  - Included 17% appendix primaries



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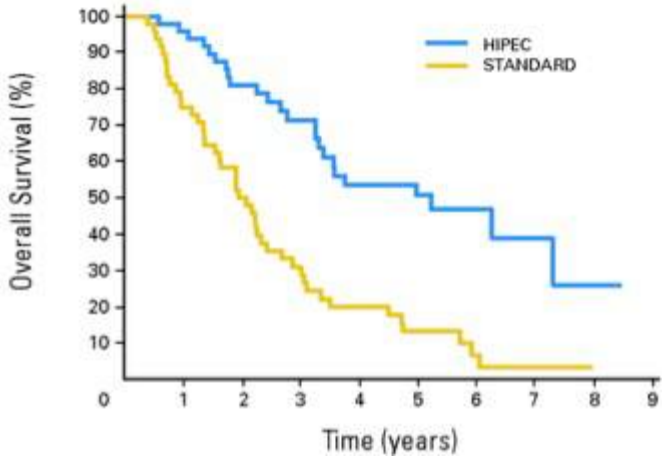
Verwaal VJ. J Clin Oncol 2003;21(20):3737

Colorectal Peritoneal Metastasis
Evidence for HIPEC

- French cohort study
  - 48 pts underwent CRS/HIPEC
    - oxaliplatin x 30 min ± irinotecan, with IV 5-FU (bidirectional), after neoadjuvant chemotherapy
  - Compared to 48 pts with isolated PC who underwent systemic chemotherapy at centers where HIPEC not available
    - Received FOLFIRI, FOLFOX, capecitabine, or others
  - 23.9 month survival in control arm, 62.7 months in HIPEC arm



Elias D. J Clin Oncol 2009;27(5):681-5

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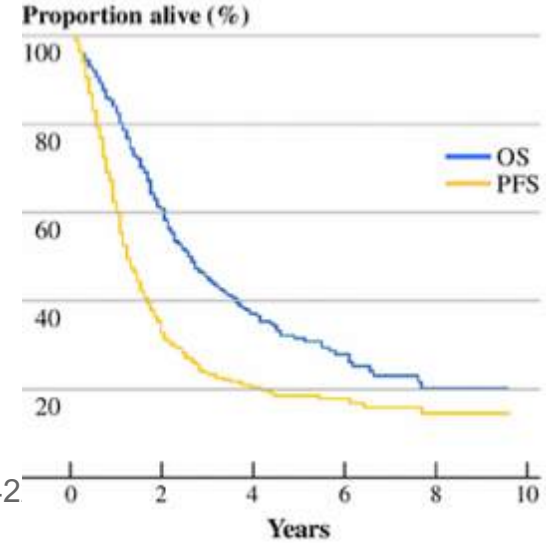
Colorectal Peritoneal Metastasis
Evidence for HIPEC

- Largest published series
  - Nationwide Dutch series of 960 HIPECs over 17 yrs, including 660 CRC pts
  - MMC x 90 min
  - 80% with complete/R1 cytoreduction
  - 34% grade III-IV complications, 3% mortality
  - 15 mo progression-free survival (PFS)
  - 33 mo median and 31% 5yr overall survival (OS)



Kuijpers AM. Ann Surg Oncol 2013;20(13):42

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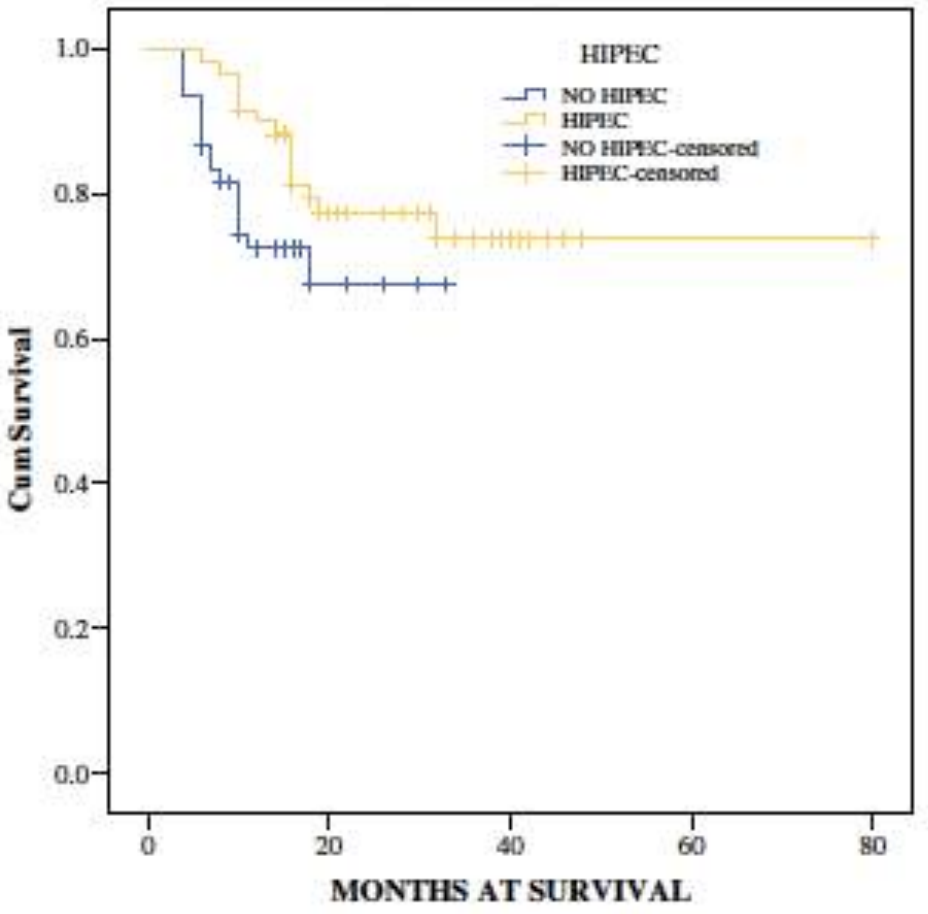
Does HIPEC Actually Matter?

- Randomized trial in recurrent ovarian ca – CRS +/- HIPEC plus systemic therapy n= 120
- HIPEC improved survival in both platinum sensitive and platinum resistant disease
- (26.4 vs. 13.4 mos) No difference in survival in HIPEC arm based on platinum sensitivity



Spillotis et al. Ann Surg Oncol 22:1570-5, 2015.

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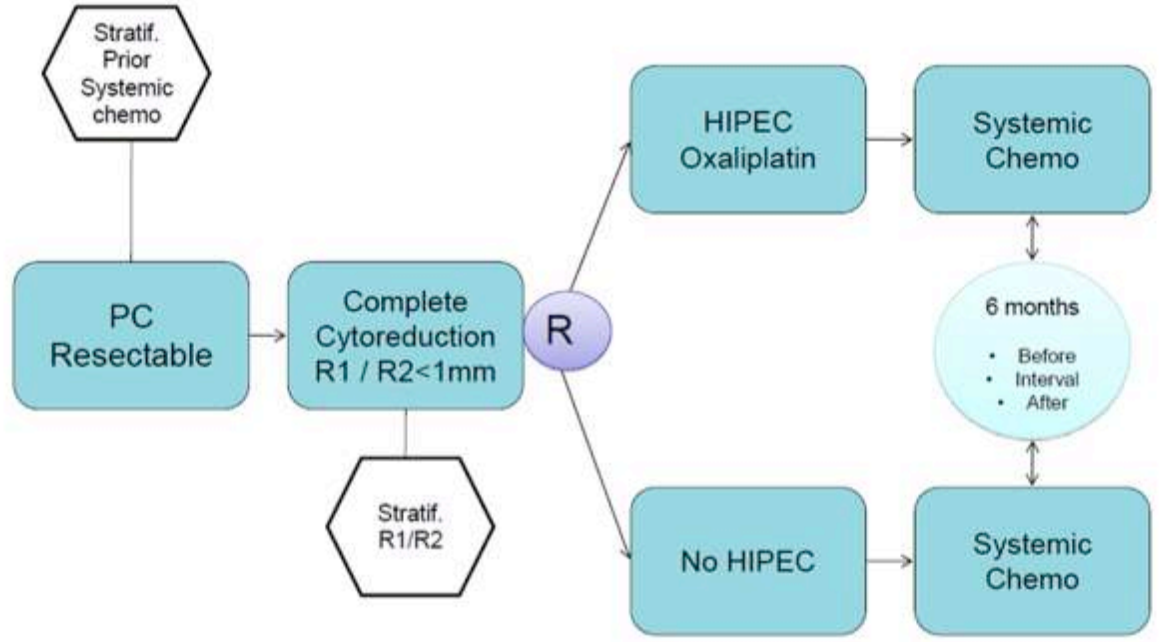
Colorectal Peritoneal Metastasis
French Prodige 7 RCT

- RCT of CRS vs. CRS/HIPEC with 30 min oxaliplatin (bidirectional), with intraoperative IV 5-FU and systemic chemo in both arms



- Eligibility
  - Isolated PC without liver or lung mets
  - Appendix CA excluded
- Opened 12/2007
- 200 enrolled as of 10/2012
- **264 estimated SS for 80% power to improve OS from 30 to 48 months**
- Primary endpoint: OS

Quénet F, Elias D, Glehen O; NCT00769405

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Peritoneal Metastasis
UCSD Approach

- UCSD HIPEC Experience
  - >500 performed since 8/2007
  - 25% for colorectal cancer
  - Median operative time: 7 hrs (3.3-12.5 hrs)
  - Median EBL: 300 cc (50-4000 cc)
  - Median PCI: 13 (2-26)
  - Median PCI of CRC: 8.5 (3-17)
  - 80% CC-0 (84% in CRC), 12% CC-1
  - Median LOS: 10 days (4-36 days)
  - 60 day mortality 1.2%
  - Morbidity $\geq$ Clavien 3 16%
  - Readmission rate 15%

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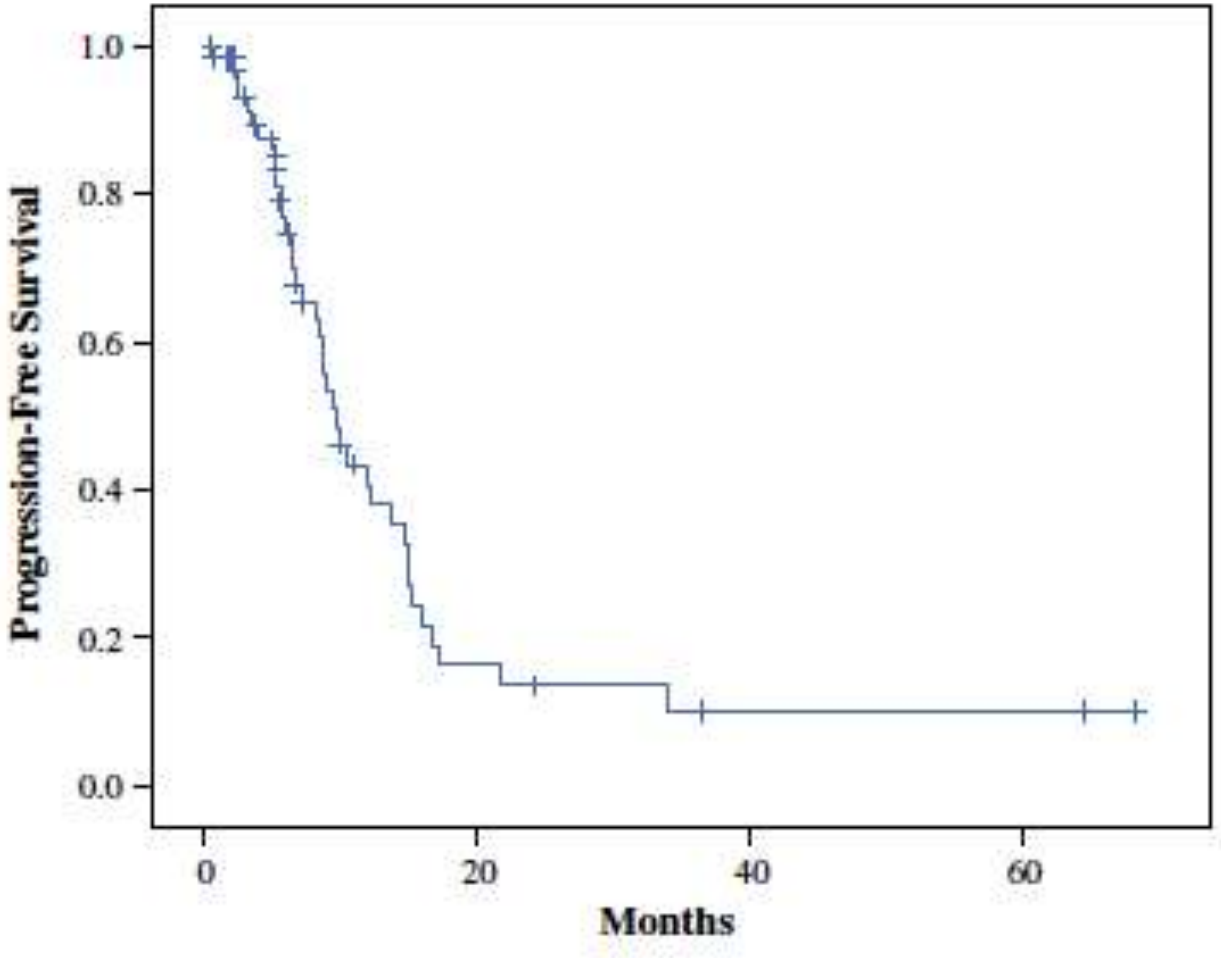
UCSD Cohort of Patients With Colon and High Grade Appendiceal Cancer s/p CRS/HIPEC



Baumgartner et al. Annals Surgl Oncol. 22:1722-25, 2015

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New Approaches to the Treatment of Peritoneal Metastases

- Enhancing drug delivery
  - **Tumor penetrating peptides**
  - Stromal disruption
- Targeted delivery of radiopharmaceuticals
- Immunotherapy

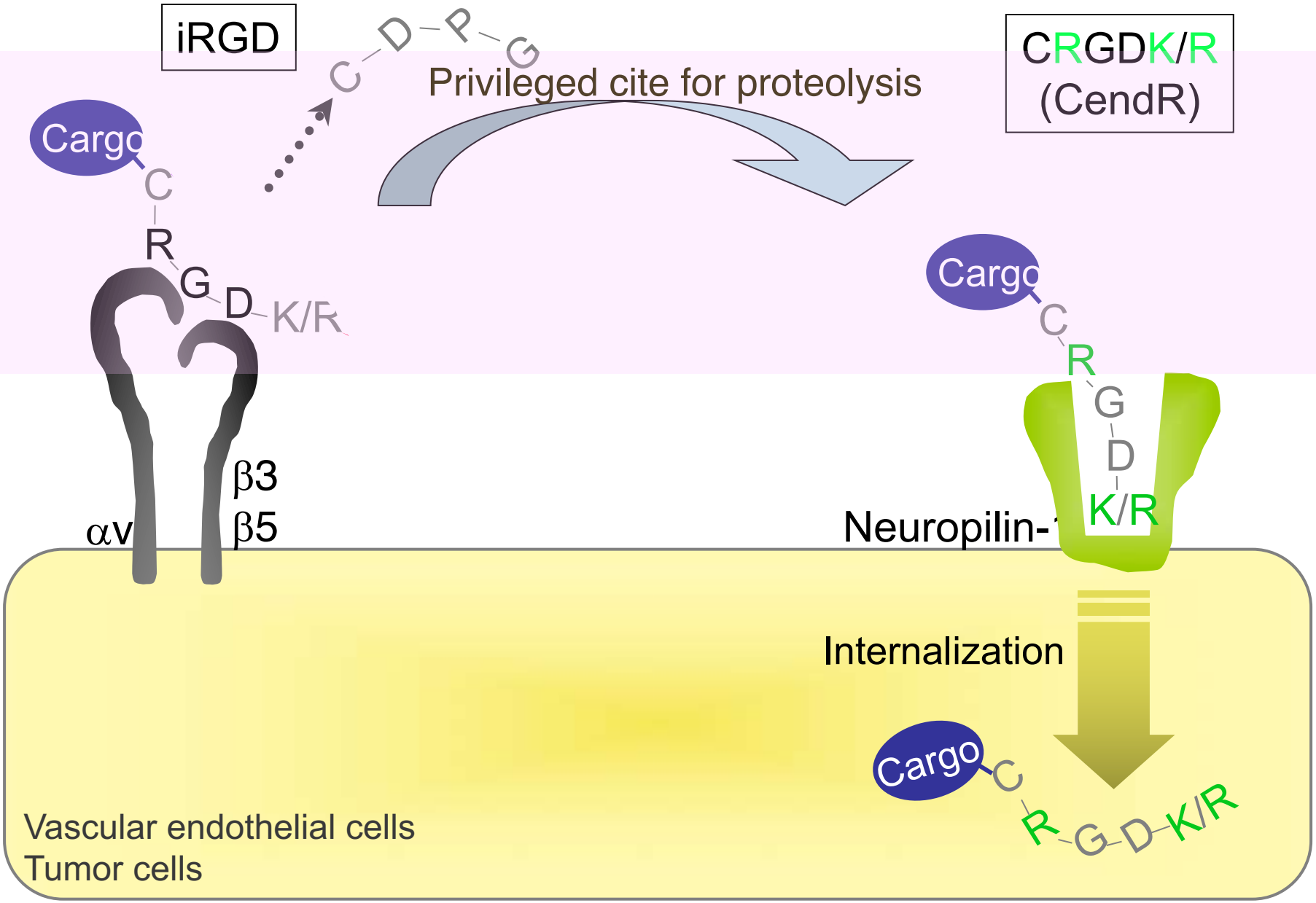
Tumor Penetrating Peptides

- Identified via phage display- searching for peptides that bind to integrin (alpha V, beta-3, 5) and neuropilin (1,2) receptors that are highly expressed on tumor vasculature and tumor tissue

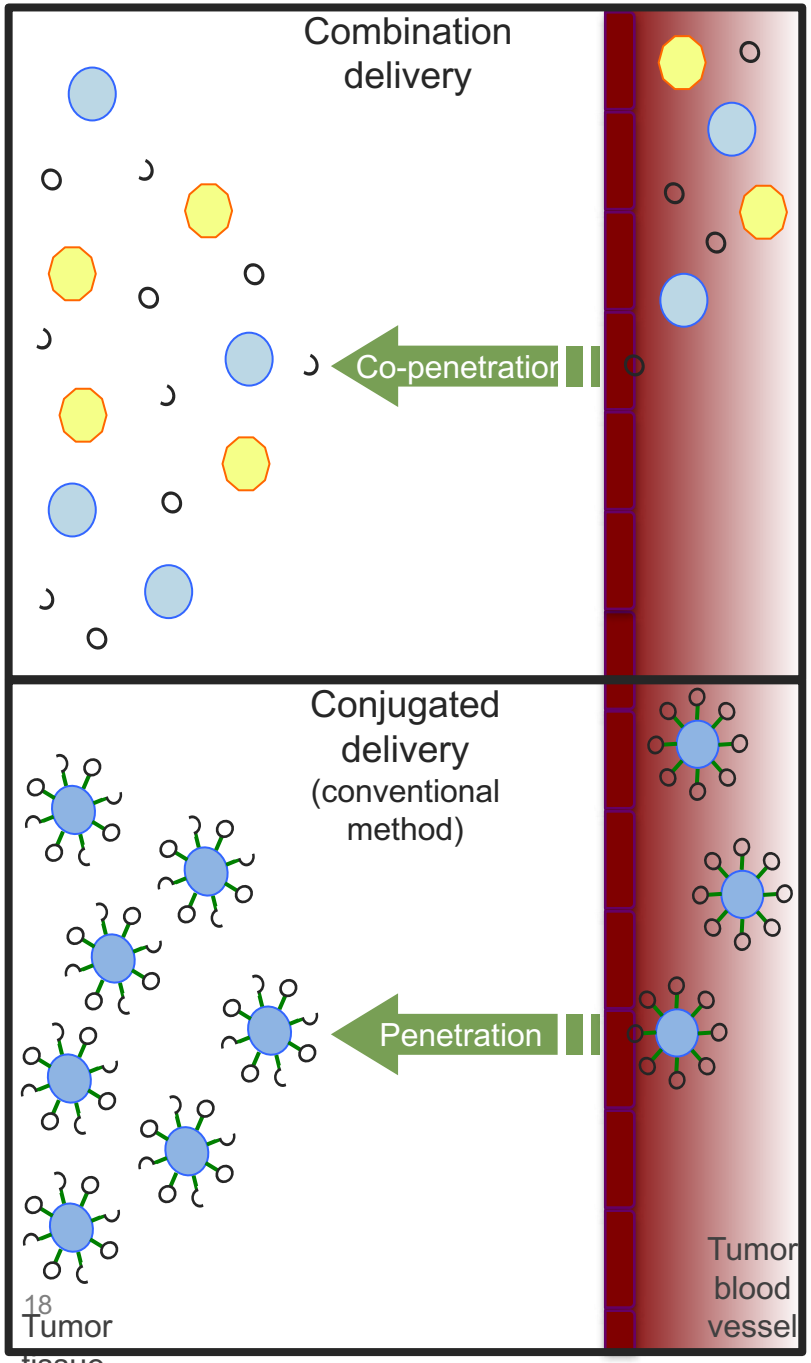
- Co-receptor for NRP-1, 2 is VEGF- they mediate vascular permeability

- Hypothesis that synthetic peptides could deliver cargo via tumor vasculature deep into the tumor microenvironment

The iRGD peptide and C-end Rule (CendR)



Sugahara KN et al, *Cancer Cell* 16:510-20, 2009



Tumor specific drug delivery increases anti-tumor effects, while reducing toxicity to normal organs.

○ : iRGD

ↄ : CRGDK/R (cleaved iRGD)

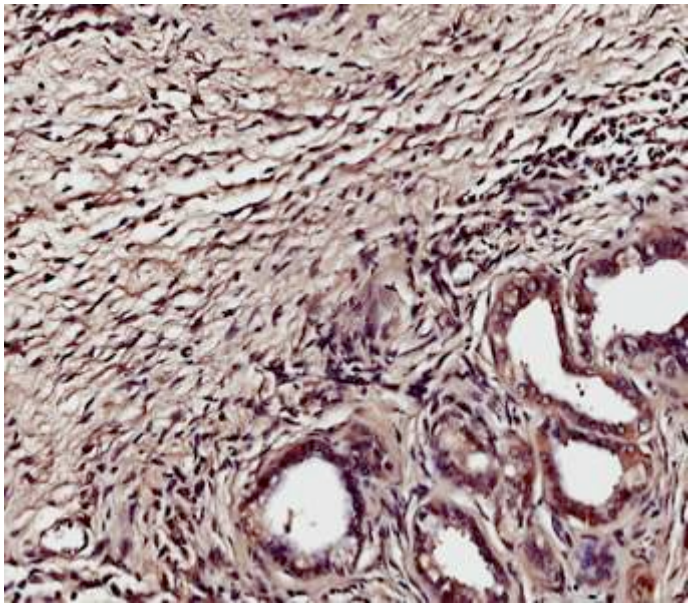
— : Peptide linker

: Drugs and imaging agents

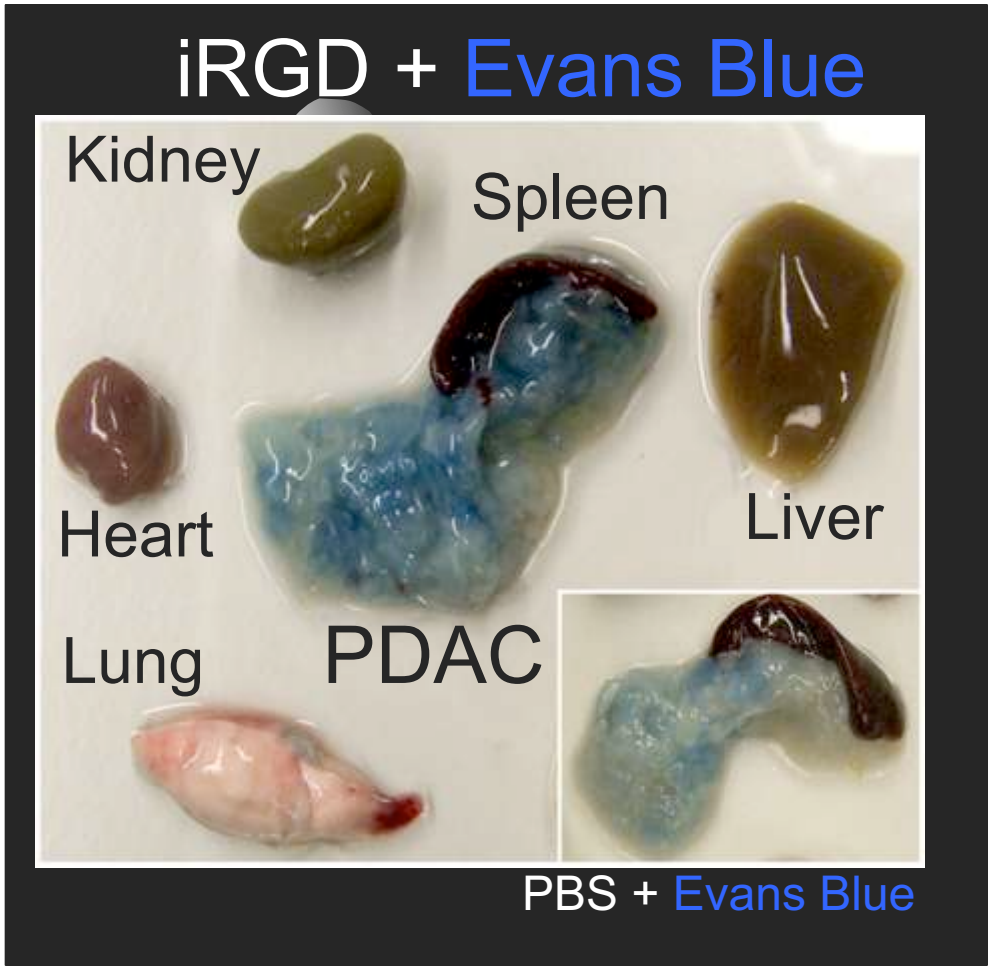
Sugahara KN et al, *Science* 328:1031-5, 2010

iRGD delivers Evans Blue into PDAC in KPC mice

Strong NRP-1 expression in KPC tumors



KPC mice: KrasG12D/+;LSL-Trp53R172H/+;Pdx-1-Cre

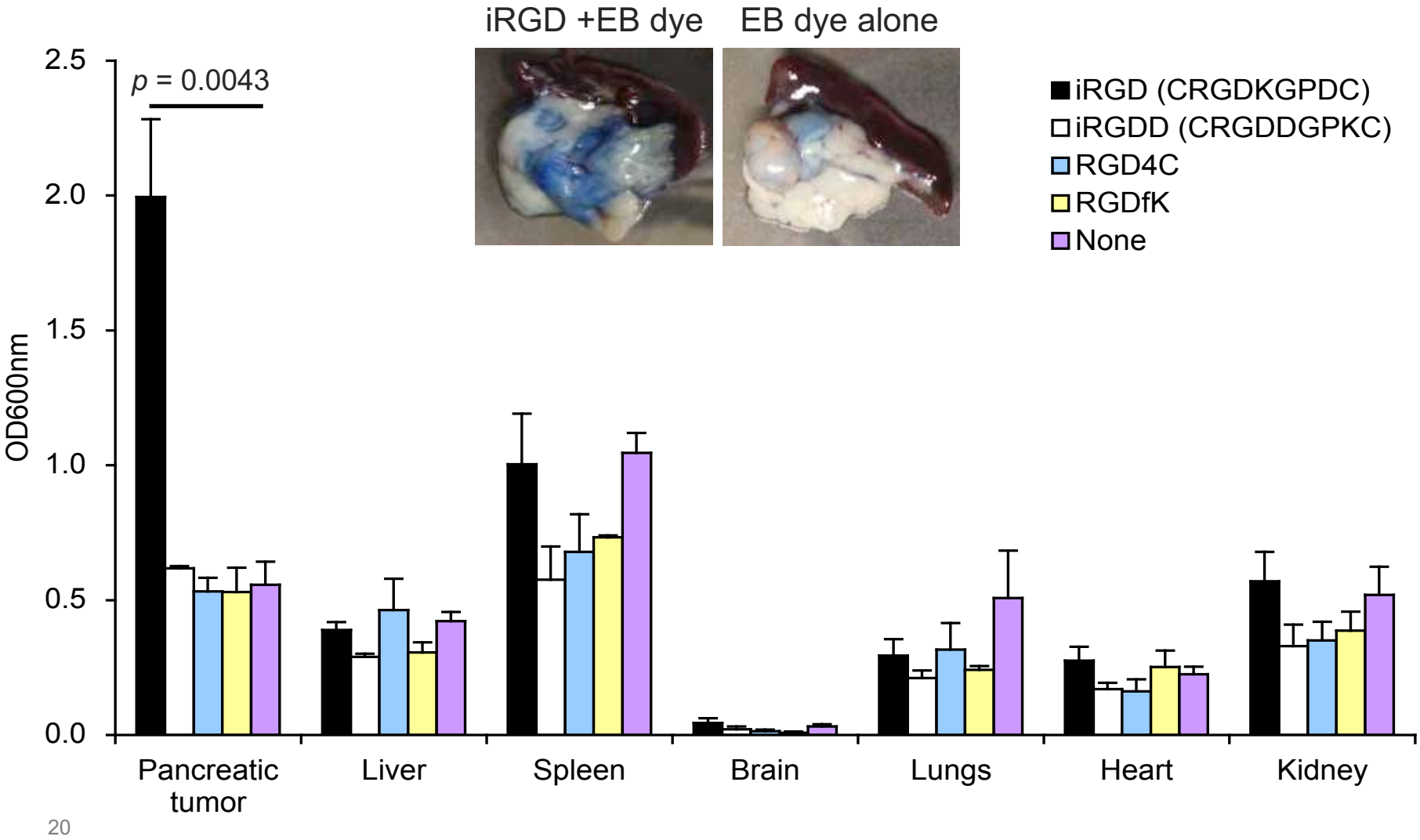


Lung metastasis

Mose et al. unpublished data

iRGD peptide induces a tumor-specific entry of co-injected Evans blue

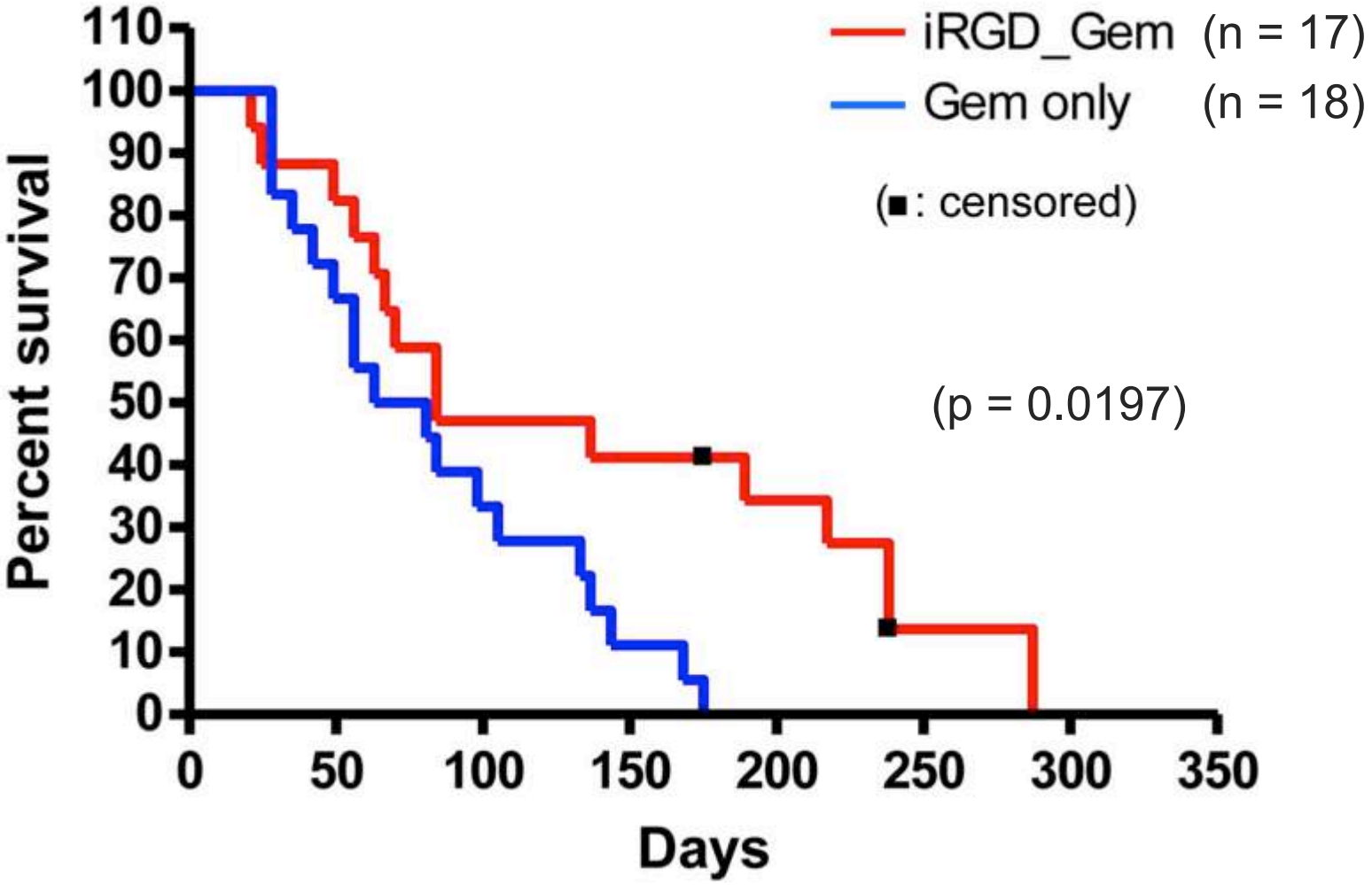
Evans Blue (EB; an albumin-binding dye) was co-injected with various peptides into mice bearing orthotopic pancreatic xenograft tumors. The amount of EB in the tissues was quantified.



Sugahara KN et al, *Science* 328:1031-5, 2010

iRGD-gemcitabine combination therapy in KPC mice

KPC mice bearing PDAC were treated with 100 mg/kg Gemcitabine with or without 100 μg iRGD twice a week.
The treatment started when tumors became palpable (14-18 week of age).

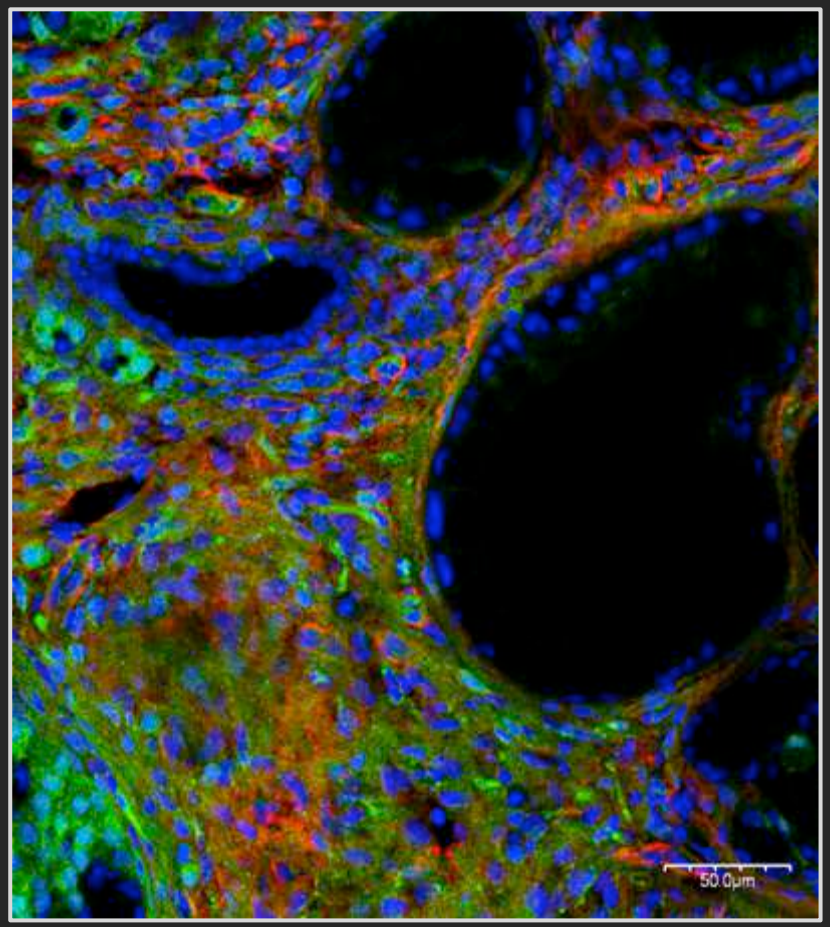


Mose et al. unpublished data

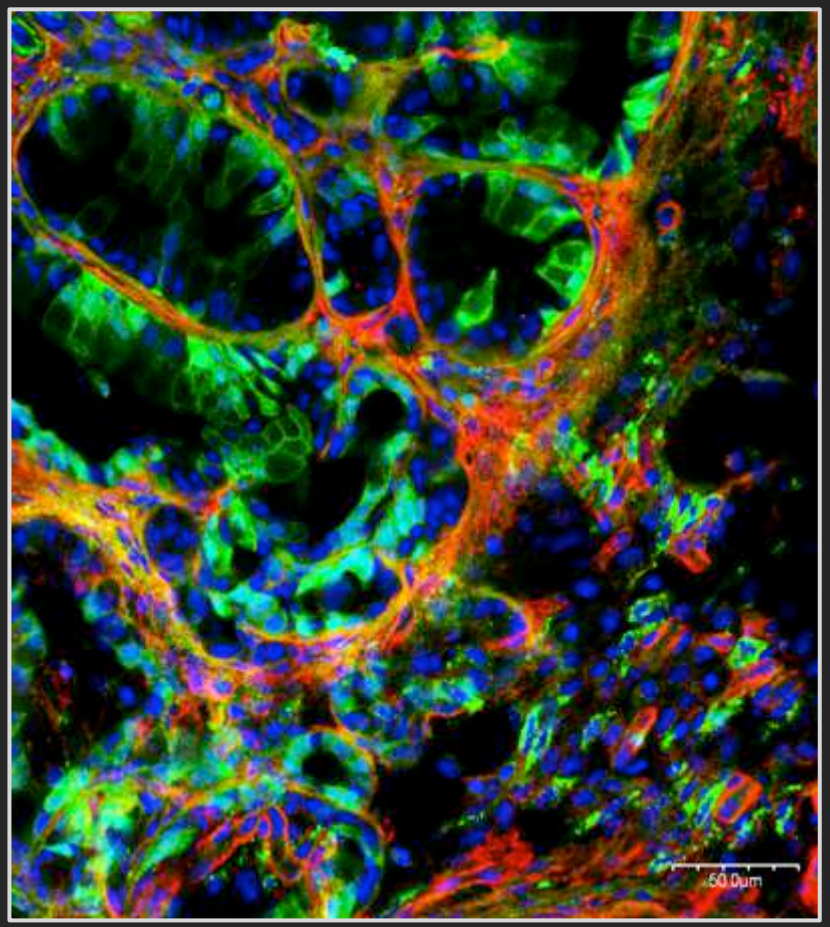
Stroma-dependent iRGD penetration into PDAC tissue

IV injection of FAM-iRGD into PDAC mice

15 min



30 min



Stromal fibers, FAM-iRGD, Nuclei

de Mendoza TH et al, unpublished data

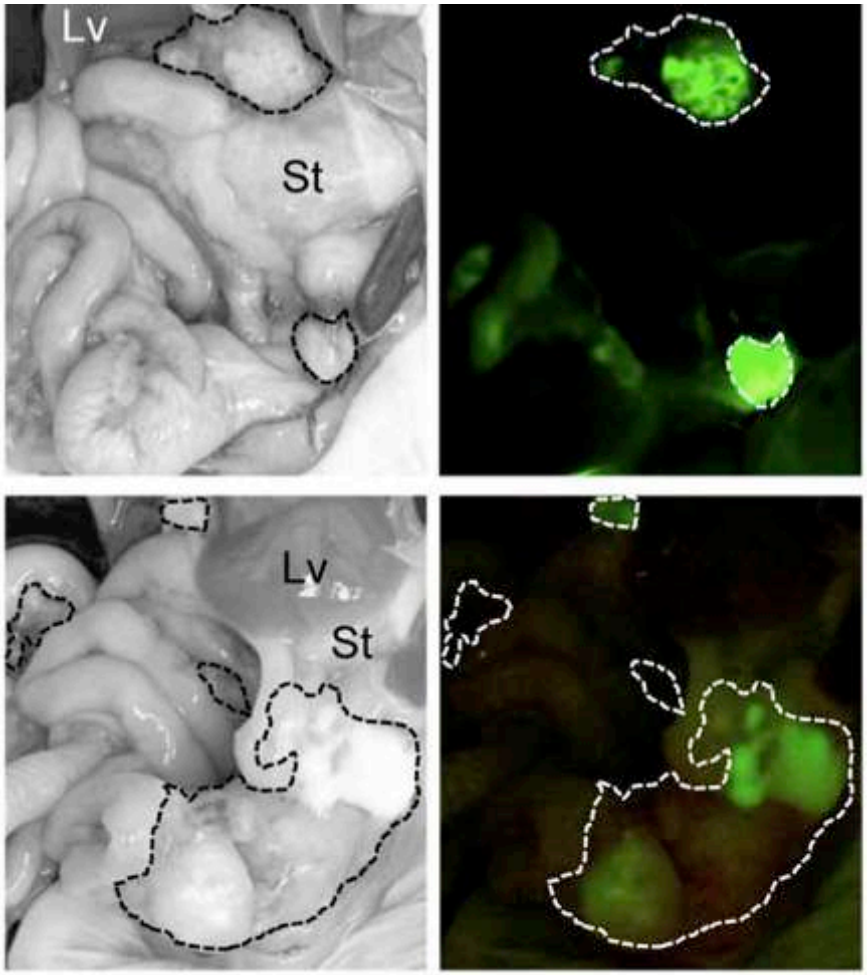
The Journal of Clinical Investigation RESEARCH ARTICLE

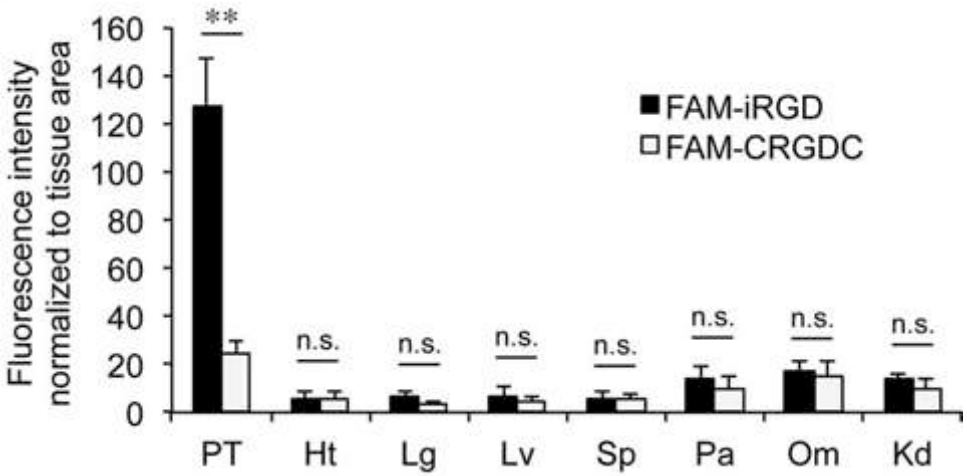
Tumor-penetrating peptide enhances transcytosis of silicasome-based chemotherapy for pancreatic cancer

Xiangsheng Liu,[1] Paulina Lin,[1] Ian Perrett,[1] Joshua Lin,[1] Yu-Pei Liao,[1] Chong Hyun Chang,[1] Jinhong Jiang,[1] Nanping Wu,[2] Timothy Donahue,[2] Zev Wainberg,[3] Andre E. Nel,[1,4] and Huan Meng[1,4]

[1]Department of Medicine, Division of NanoMedicine, University of California, [2]Department of Surgery, Division of General Surgery, and Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, [3]Department of Medicine and [4]California NanoSystems Institute, University of California, Los Angeles, California, USA.

iRGD Targets Peritoneal Metastases





Sugahara et al. JCR 232:188-195, 2016

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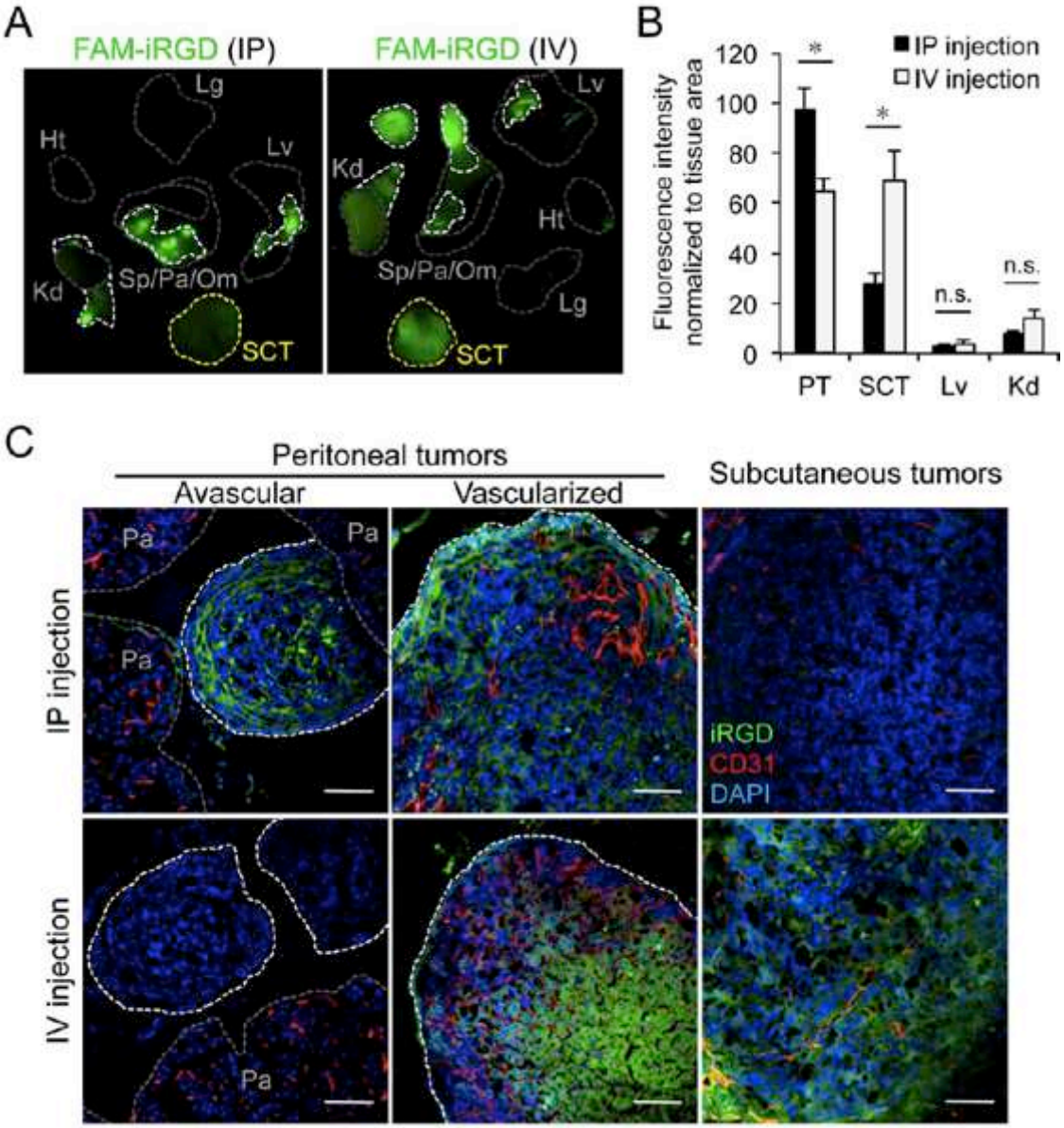
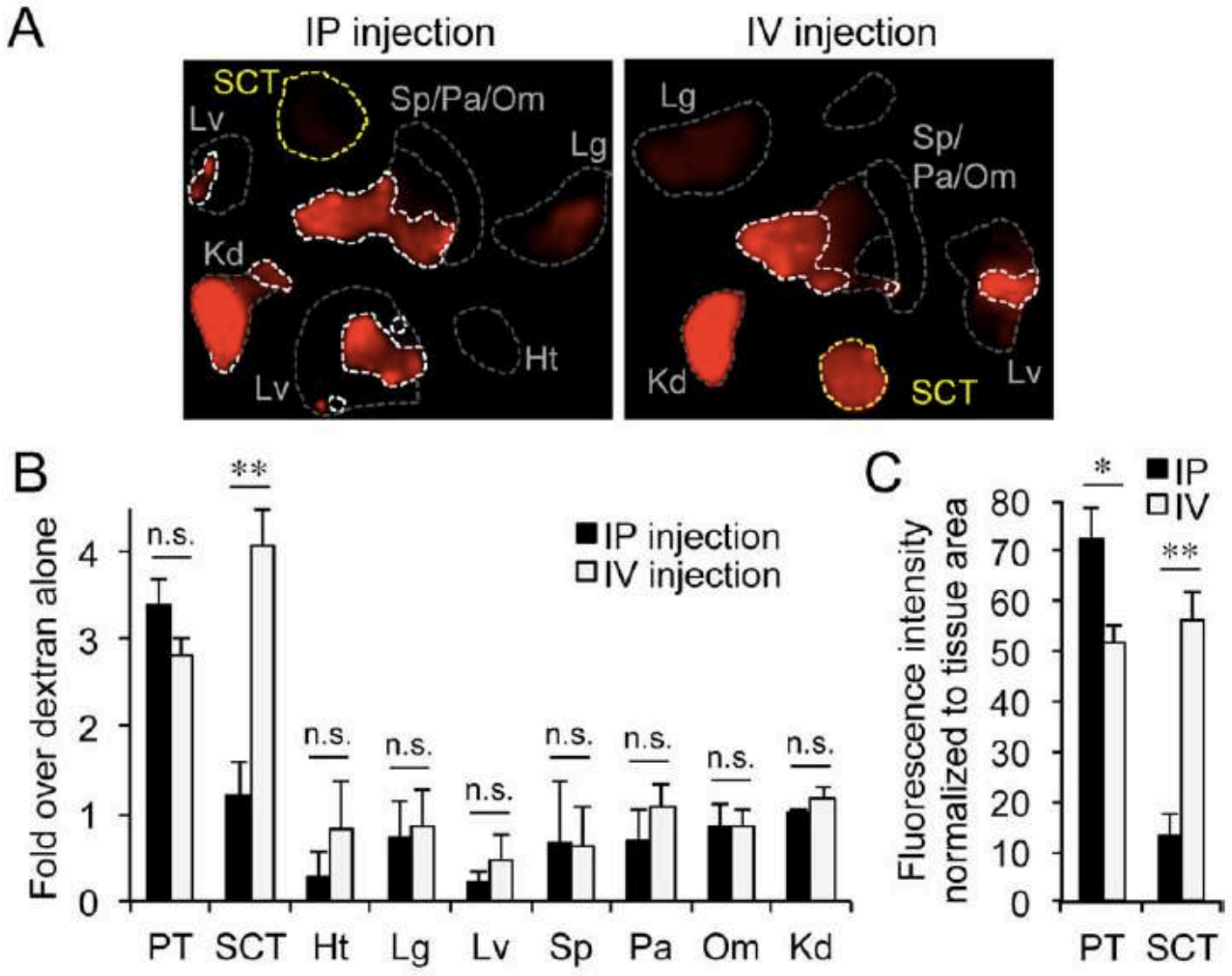
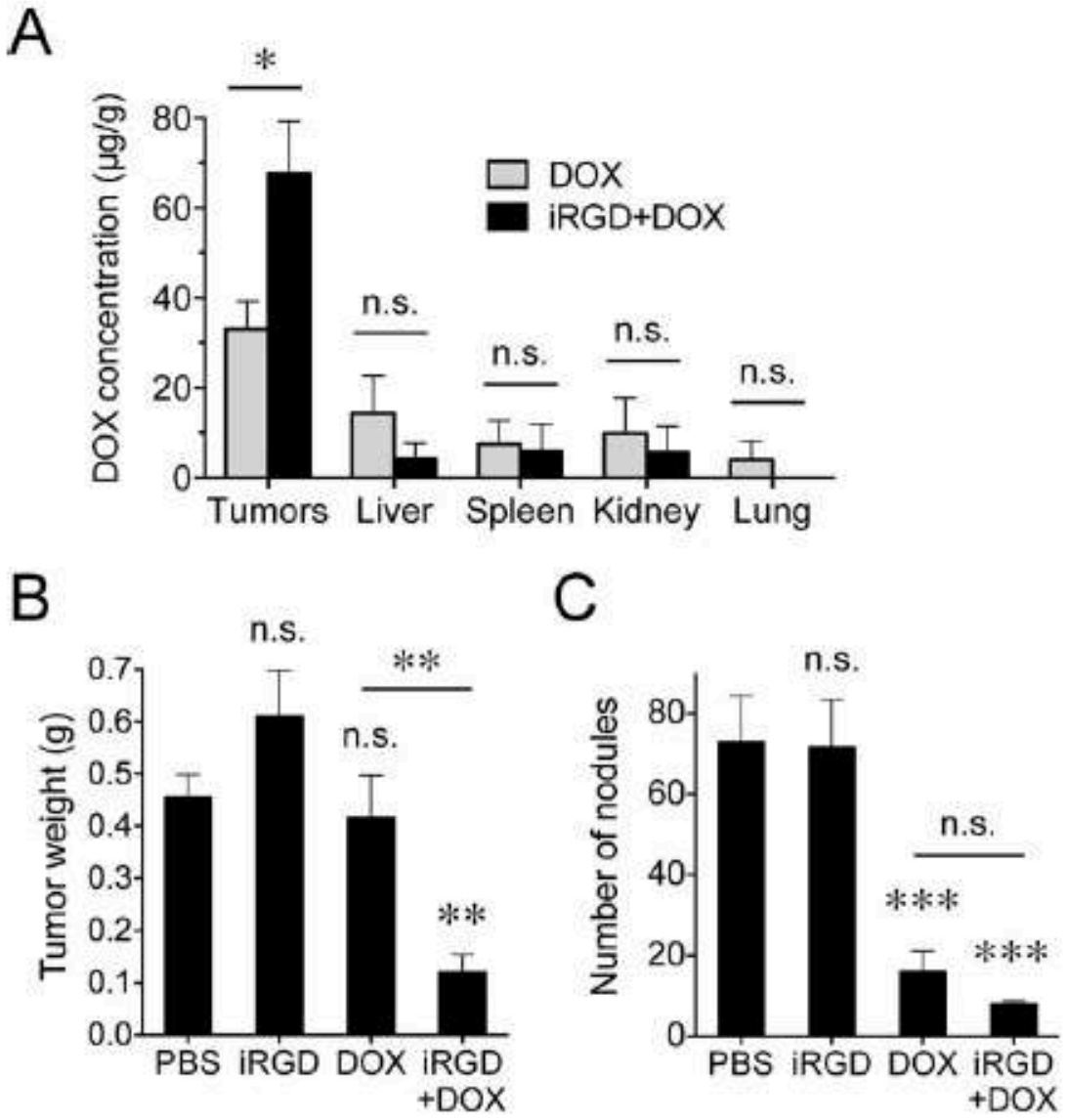
iRGD Penetration of Peritoneal Metastases is Circulation Independent



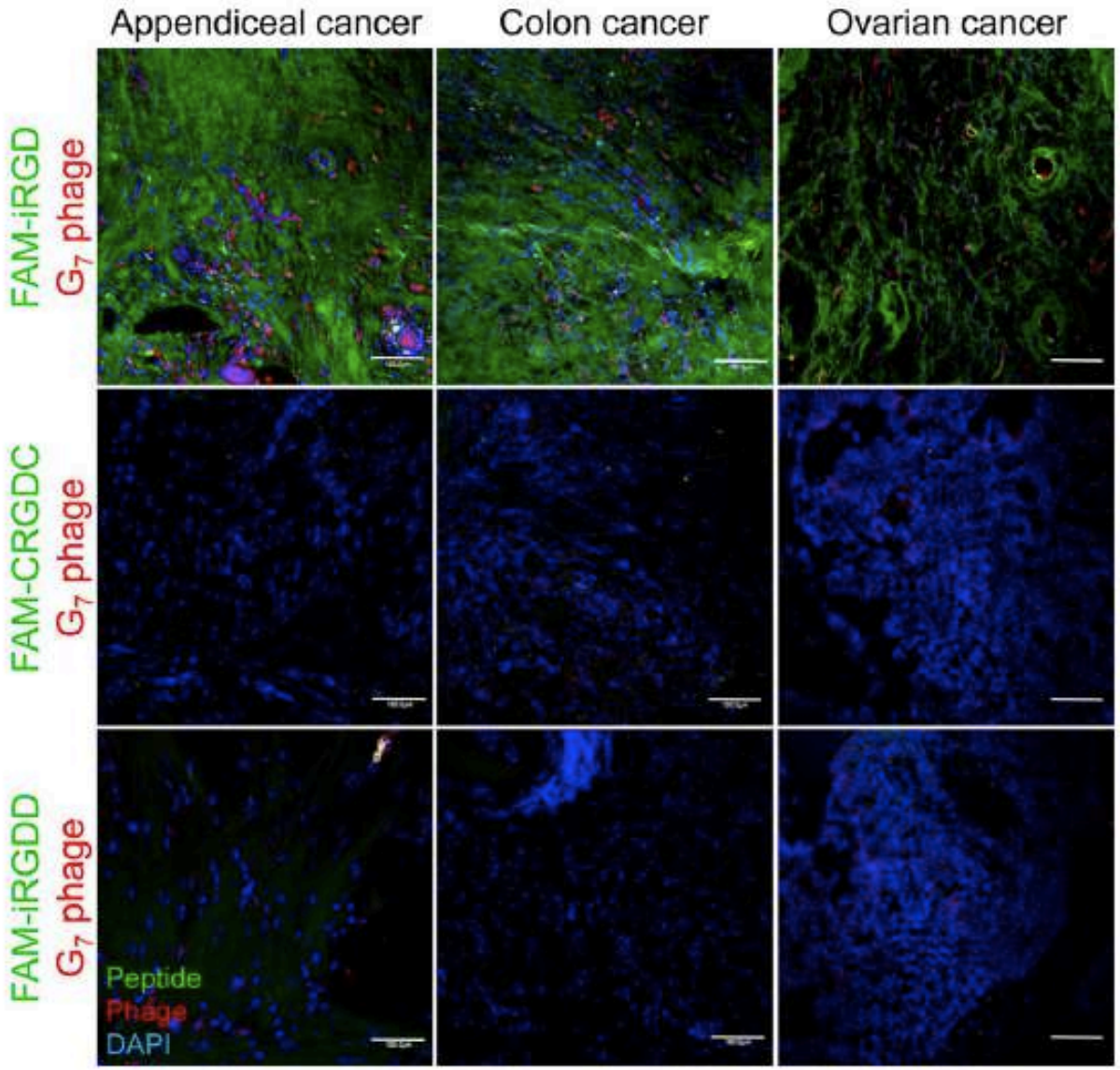
iRGD Dependent Drug Delivery Occurs Independent of Circulation



iRGD Enhanced Delivery of IP Chemotherapy Improves Treatment of Peritoneal Metastases



iRGD Effectively Penetrates Large Peritoneal Metastases from Human Cancers



Conclusions

- iRGD tumor penetrating peptides can enhance drug delivery to peritoneal metastases when delivered IV/IP
- In animal models, iRGD potentiates the effects of chemotherapy in the treatment of peritoneal metastases
- iRGD peptides can effectively penetrate human peritoneal metastases greater than 1 cm in size
- Phase 1 trials of iRGD are in latter stages of development

Original Article

Tumor Biology

Hyaluronan-binding peptide for targeting peritoneal carcinomatosis

Tumor Biology
May 2017: 1–9

DOI: 10.1177/1010428317701628
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Hideki Ikemoto[1], Prakash Lingasamy[1], Anne-Mari Anton Willmore[1], Hedi Hunt[1], Kaarel Kurm[1], Olav Tammik[2], Pablo Scodeller[1], Lorena Simón-Gracia[1], Venkata Ramana Kotamraju[3], Andrew M Lowy[4], Kazuki N Sugahara[3,5] and Tambet Teesalu[1,3,6]

Journal of Controlled Release 232 (2016) 188–195

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Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Urokinase-controlled tumor penetrating peptide

Gary B. Braun [a], Kazuki N. Sugahara [a,b], Olivia M. Yu [a,d], Venkata Ramana Kotamraju [a], Tarmo Mölder [f], Andrew M. Lowy [e], Erkki Ruoslahti [a,c], Tambet Teesalu [a,c,f,*]

ORIGINAL ARTICLE

OPEN

Safety and Outcome Measures of First-in-Human Intraperitoneal α Radioimmunotherapy With ^{212}Pb-TCMC-Trastuzumab

Ruby F. Meredith, MD, PhD, Julien J. Torgue, PhD,† Tania A. Rozgaja, PhD,† Eileen P. Banaga, MS,† Patty W. Bunch, OCN,‡ Ronald D. Alvarez, MD,‡ J. Michael Straughn, Jr, MD,‡ Michael C. Dobelbower, MD, PhD,* and Andrew M. Lowy, MD§*

(*Am J Clin Oncol* 2016;00:000–000)

Purpose: One-year monitoring of patients receiving intraperitoneal

Peritoneal Metastasis
Additional ongoing research

- Ct DNA in patients with peritoneal metastasis
- Oncolytic vaccinia virus Phase 1
- Laparoscopic approach in patients with limited disease
- Randomized trial of Enterg to reducing length of stay following HIPEC
- Systems biology profiling of peritoneal metastases, placement in appropriate trial of targeted therapy
- Immunotherapy- myeloid cell depletion and adjuvant checkpoint studies (collaboration with Novartis)
- Examining outcomes and associated risk factors

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Tambet Teesalu

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Thank You!