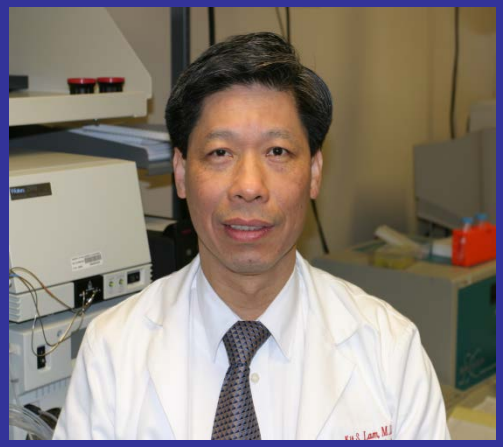
Cancer Therapeutics Program

Kit S. Lam, MD, PhD
Professor and Chair
Department of
Biochemistry & Molecular Medicine



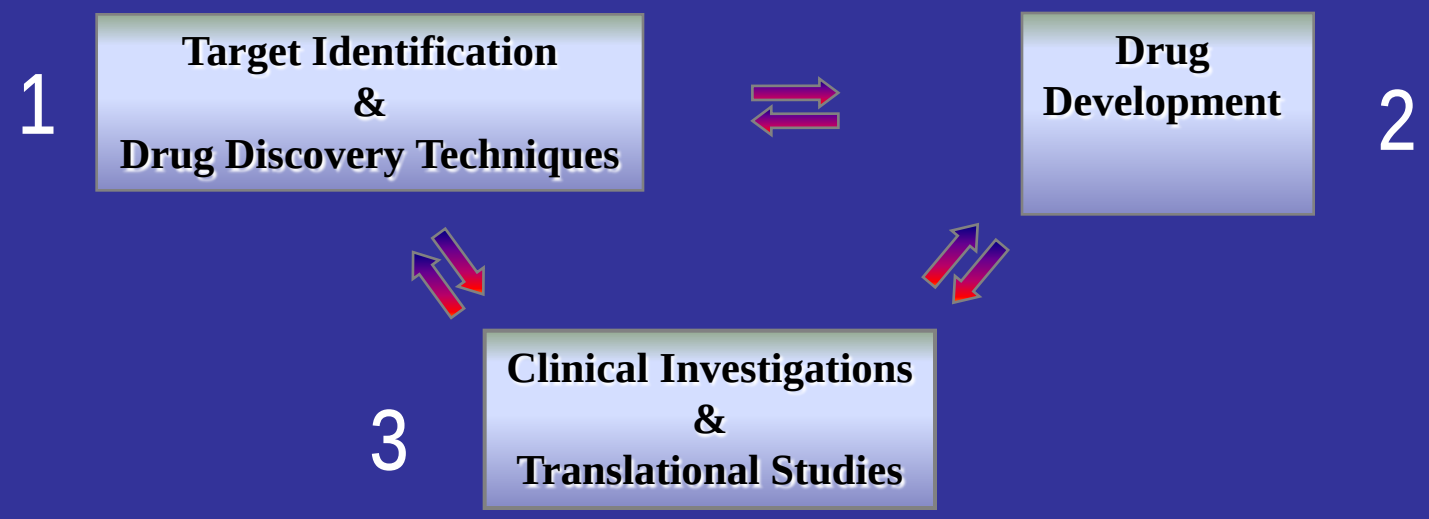
Primo "Lucky" Lara, Jr., MD
Professor of Medicine
Associate Director, Translational Research

Cancer Therapeutics Program:
Specific Aims and Research Themes

Aims:

- Facilitate collaboration between **basic scientists** and **clinical investigators**
- Promote **discovery, development,** and **clinical application** of novel therapeutic approaches
- Develop **translational** and **laboratory-based** clinical investigations

Themes:



Cancer Therapeutics: from Bench to Bedside

Theme 1

Target Identification & Drug Discovery Techniques

- Combi-chem, Med-chem
- Computational Biology
- High-throughput assays
- Structural Biol, cryoEM, AFM, X-ray crystallography, NMR
- Proteomics, glycomics, metabolomics, tumor markers
- Nanotechnology
- Cancer stem cell
- miRNA targeting

Theme 2

Drug Development Projects

- Peptide-targeting
- Mab-targeting
- Protein Kinase inhibitors
- Nanotherapeutics
- FGF, IGF inhibitors
- ImmunoRx
- Arginine Deaminase
- Wheat Germ Extract

Theme 3

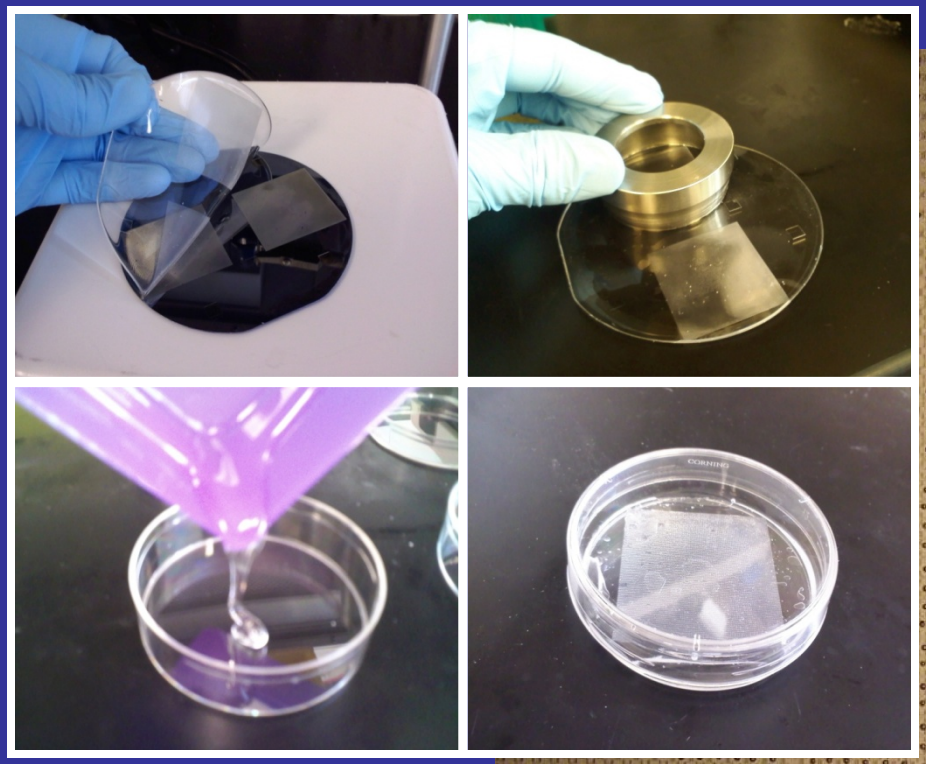
Clinical Investigations & Translational Studies

- Investigator-initiated Trials
- NSG mouse xenotransplant co-clinical trials

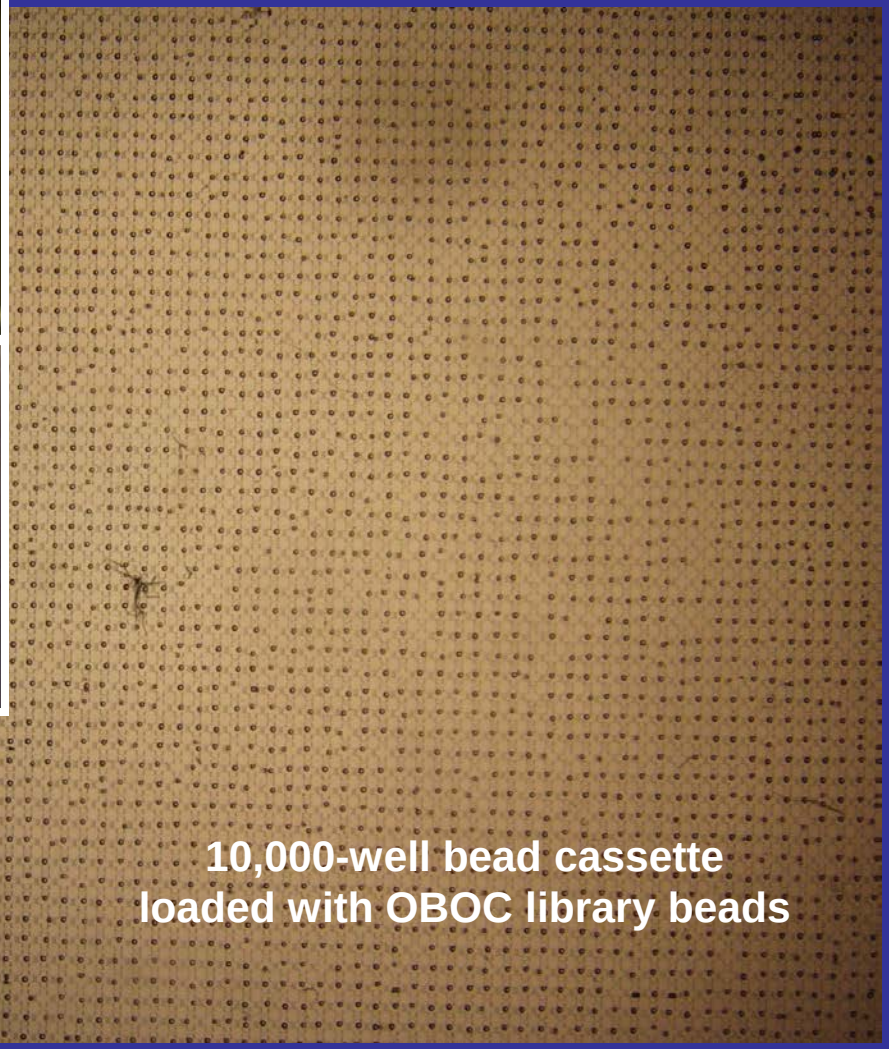
Projects have or will soon proceed to clinical development (highlighted in yellow)

Ultra-high throughput screening

Fabrication of 10,000-well PDMS bead cassette for OBOC solution-phase releasable assay



3.5 cm Petri dish

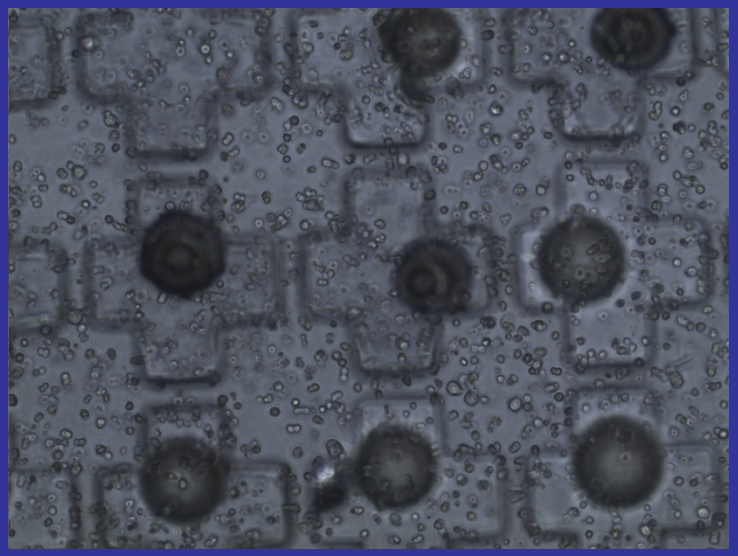


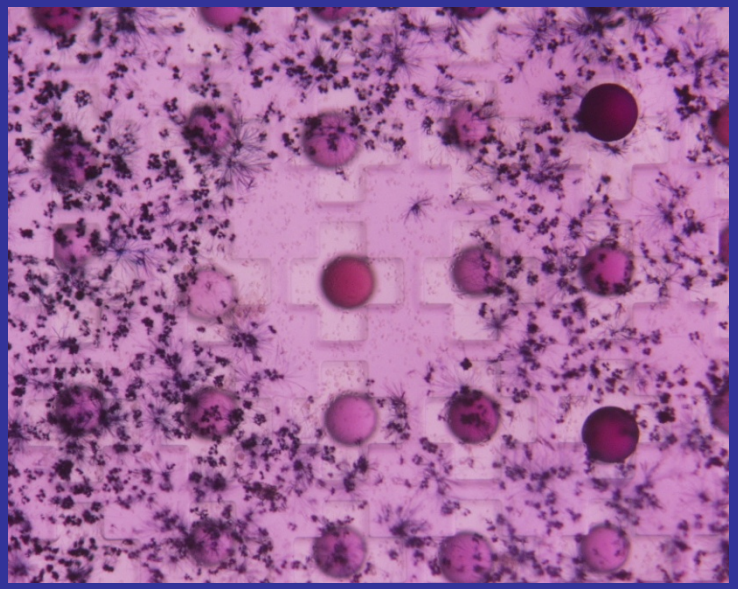
10,000-well bead cassette loaded with OBOC library beads

Lam and Liu

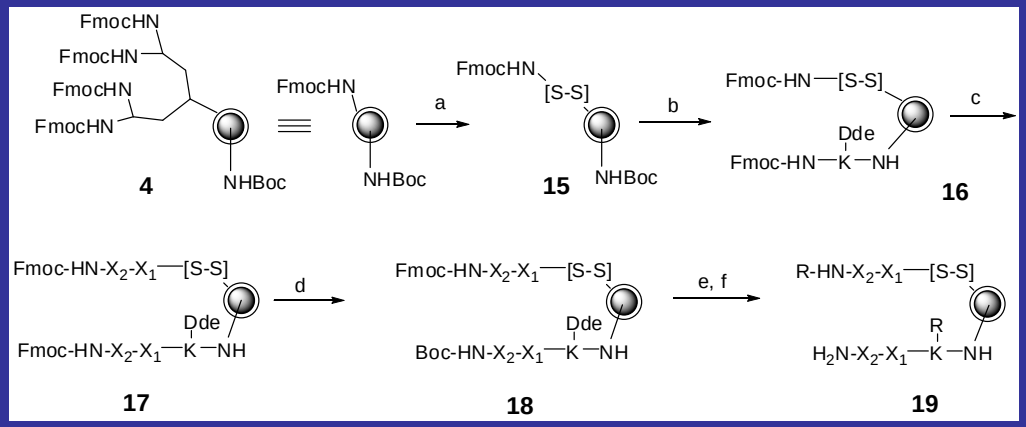
(Journal Combi Chem 2010)

In situ-releasable solution phase cytotoxic assay of OBOC combinatorial small molecule libary





Library synthesis

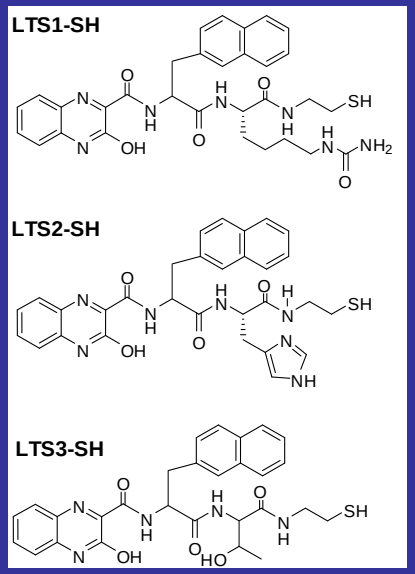


Ultra-high throughput screening for cytotoxic agents:

24 hr: add DTT
48 hr: add MTT

Lam and R. Liu

(Journal Combi Chem 2010)



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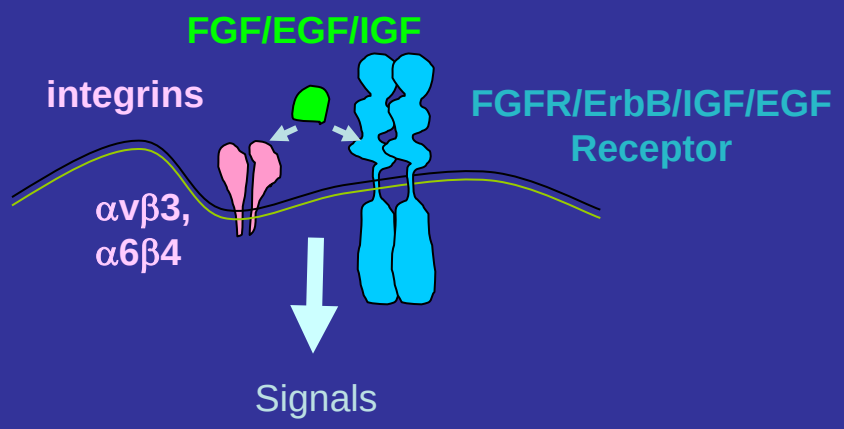
Dominant-negative mutants of growth factors as potential therapeutics in cancer

New Model:

Crosstalk between growth factor receptor & integrin via direct contact



Growth factor mutants that are defective in integrin binding (e.g. R50E)

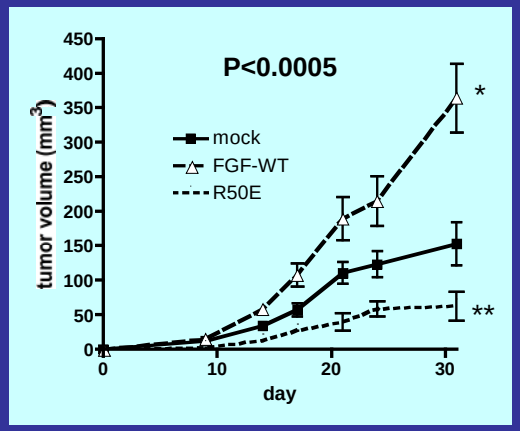
- **defective** in signaling
- **antagonists** of signaling
- **inhibit** tumor growth and angiogenesis

Yoshi Takada

**(J Bio Chem 2008,
J Bio Chem 2009,
PLoS one 2010,
J Bio Chem 2010)**

DLD-1 colon carcinoma cells transfected with WT or mutant FGF1

Growth in nude mice

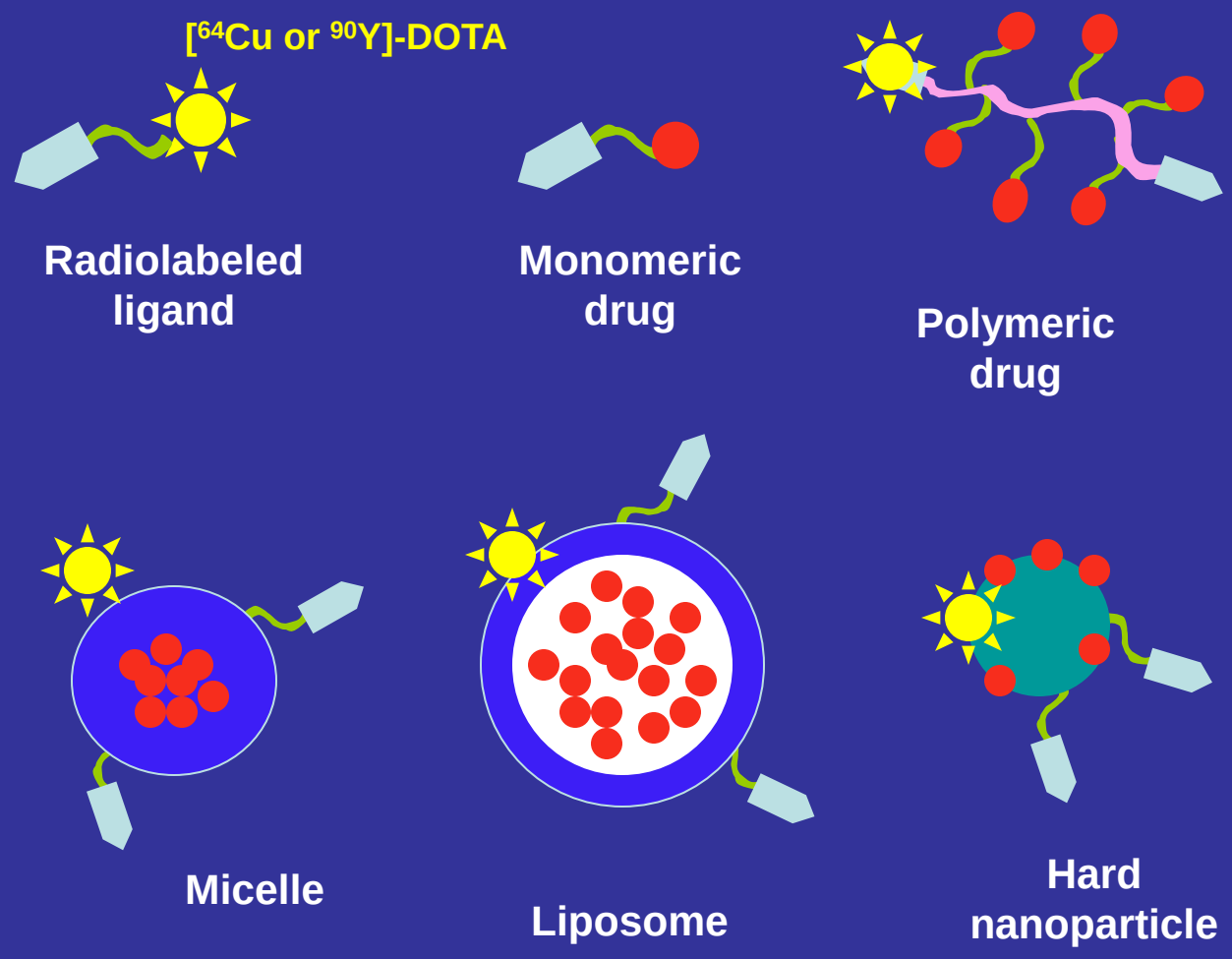


FGF1-WT

Mock

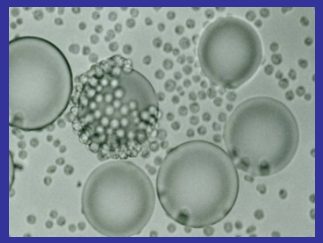
R50E mutant FGF-1

Cancer Targeting Approaches with Cell Surface Targeting Ligands

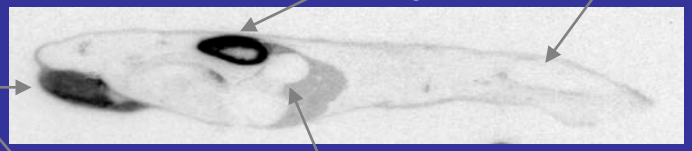


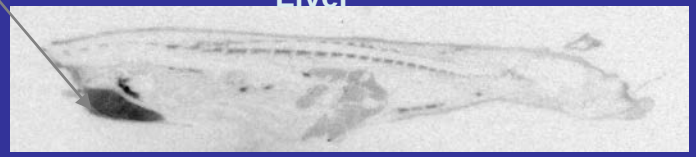
NCDDG (NCI U19)

Targeting agents for human and canine lymphoma



[In-111]-LLP2A





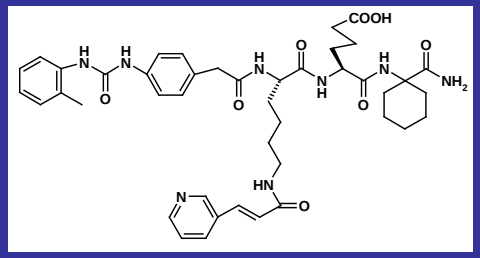
Kidney

Head

Raji B lymphoma

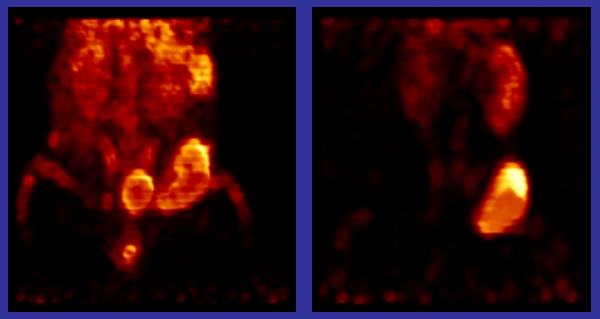
Liver

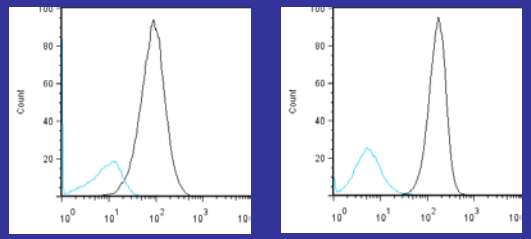
OBOC combinatorial library method



LLP2A
(IC_{50} = 2pM)

microPET/CT with [Cu-64]-LLP2A





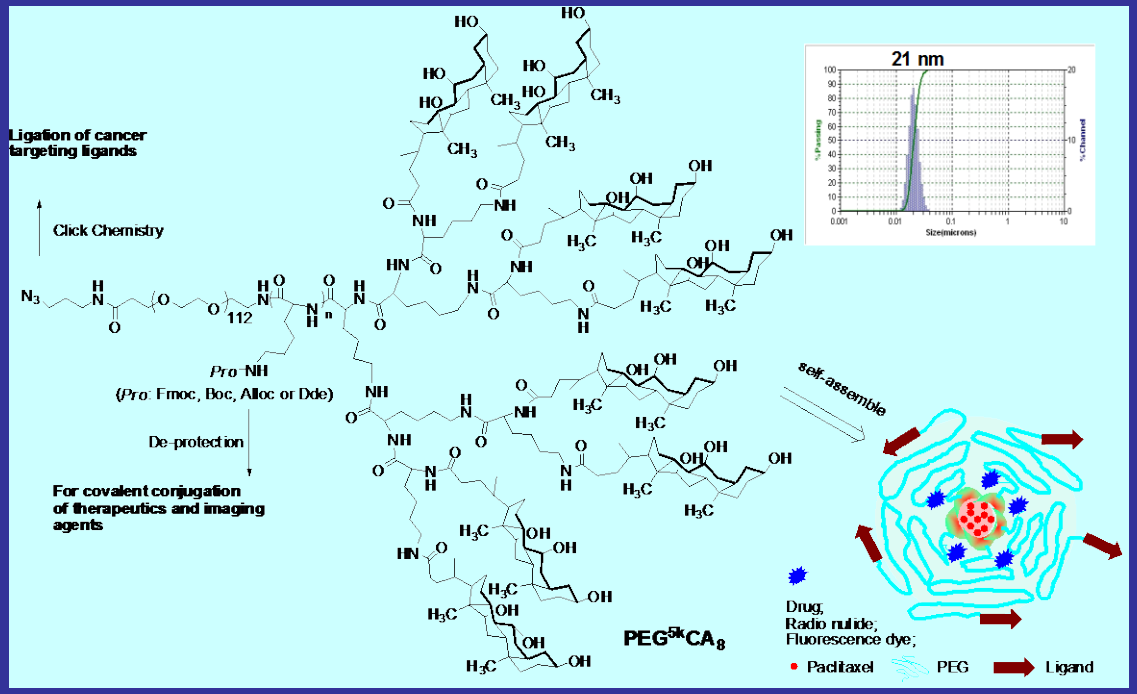
Satake:

LLP2A binds to freshly isolated pediatric ALL cells

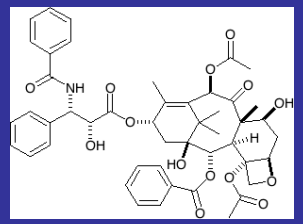
Lam, Takeda, Sutcliff (Prog 6), Cherry (Prog 6), S DeNardo, Wisner, Zwingsonburger, Kurth, Liu, Kumaresan, Tuscano, Lightstone, Lau

(Nature Chemical Biology 2006, Molecular Cancer Therapeutics 2008, J Med Chem 2007 & 2008, J Nuc Med 2009)

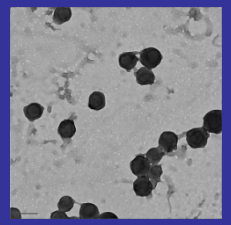
Novel Cancer Nanotherapeutics



Paclitaxel



TEM of nanoparticle drug

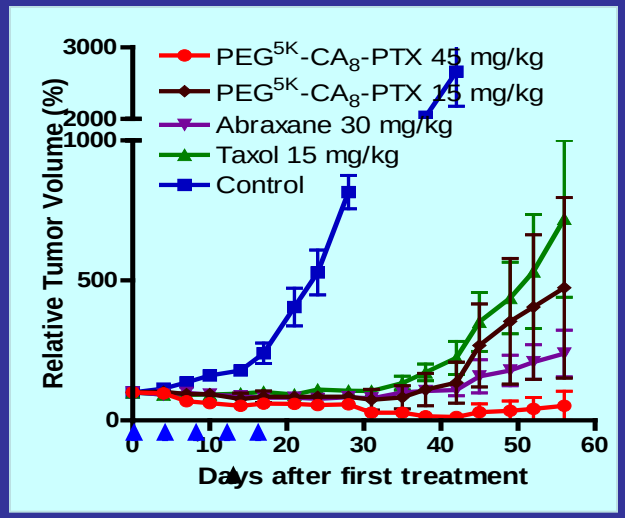


Drugs successfully loaded

- Paclitaxel
- Etoposide
- Doxorubicin
- Vincristine
- SN-38
- BCNU
- Temsirolimus
- Bortezomib
- Lapatinib
- Sorafenib
- Dexamethasone

Phase I & II studies

Ovarian cancer targeting (xenograft)

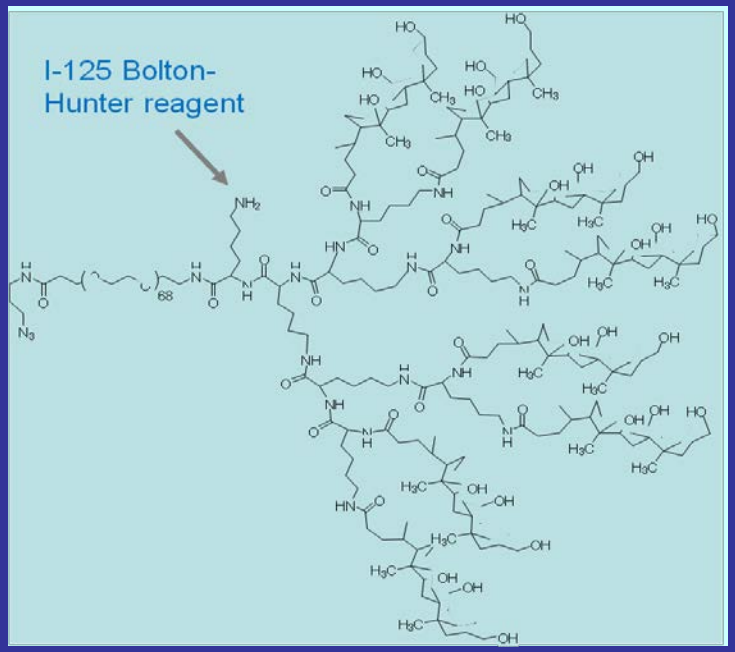


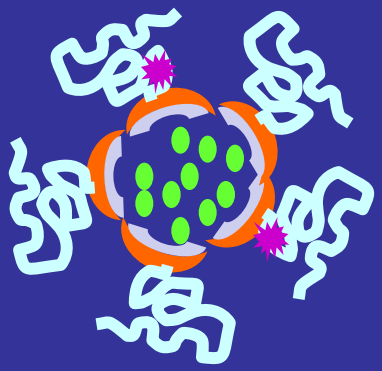
Lam, Luo, Liu G, Cheng (Prog 3)

Kent, Skorupski, Rodriguez (Prog 2)

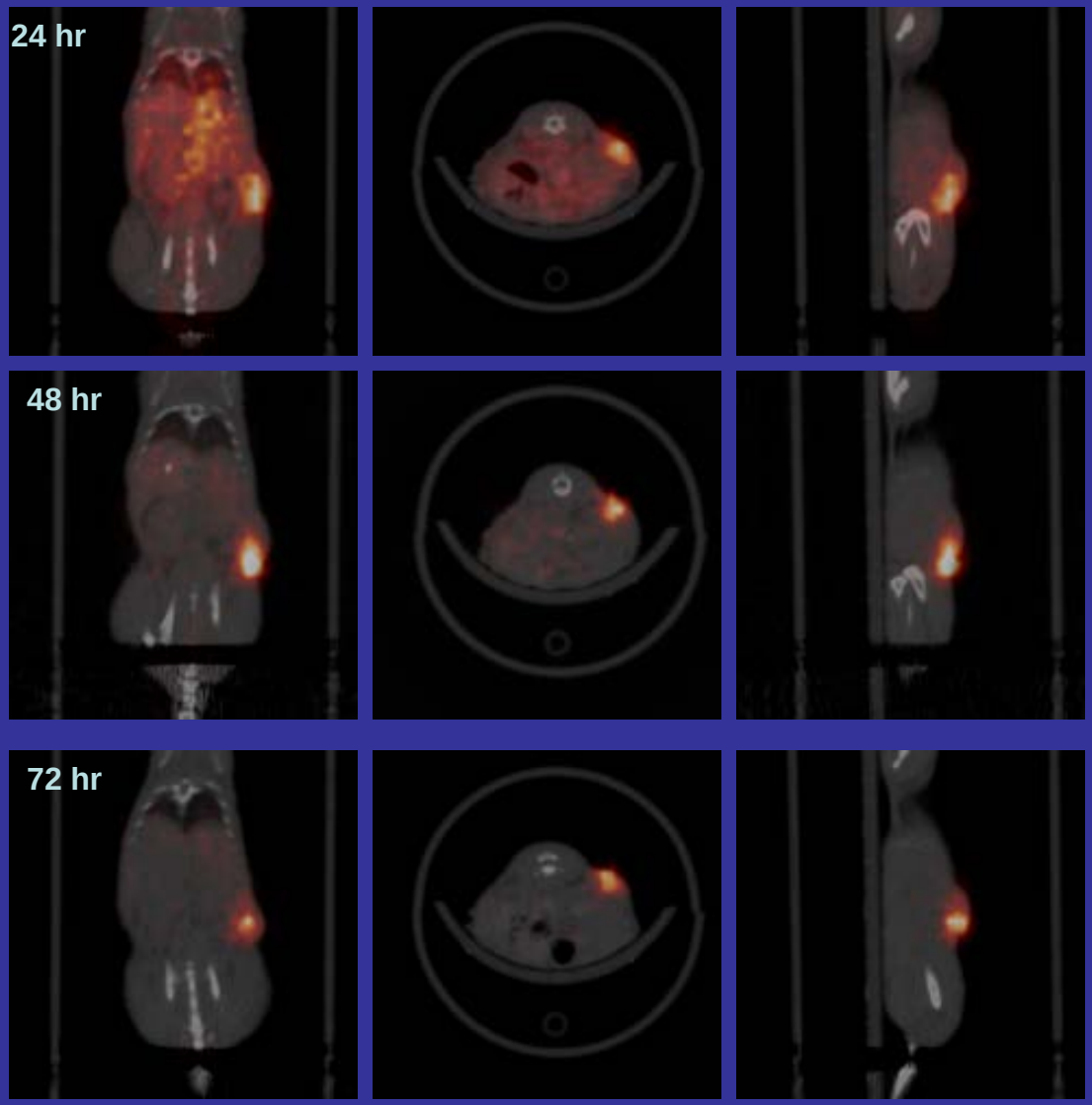
(Biomaterial 2008, J Control Drug Release 2009, Bioconjugate Chemistry 2010, Biomaterial 2011)

microSPECT/CT imaging of SKOV3 ovarian cancer xenograft in nude mice using I-125 labeled paclitaxel-loaded nanoparticle





microSPECT/CT

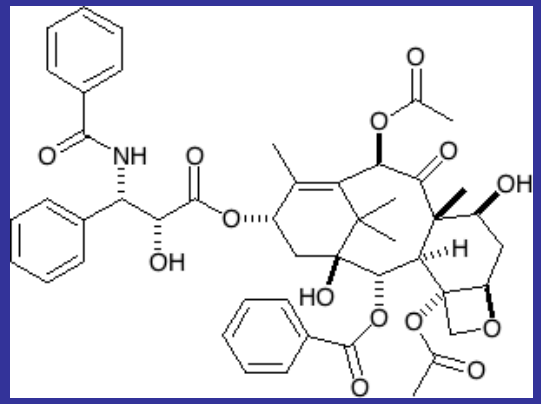


Coronal Transverse Sagittal

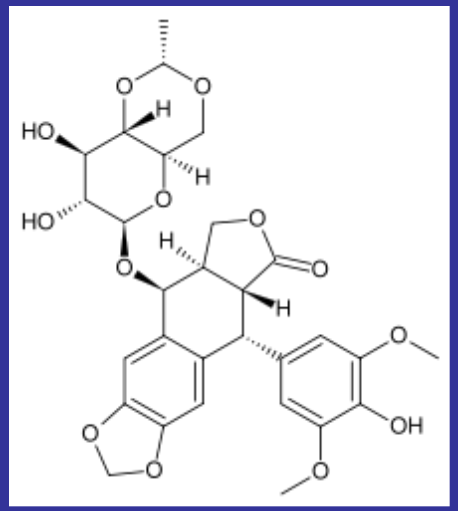
Lam, Luo (Prog 3)

Cherry (Prog 6)

Loading other drugs

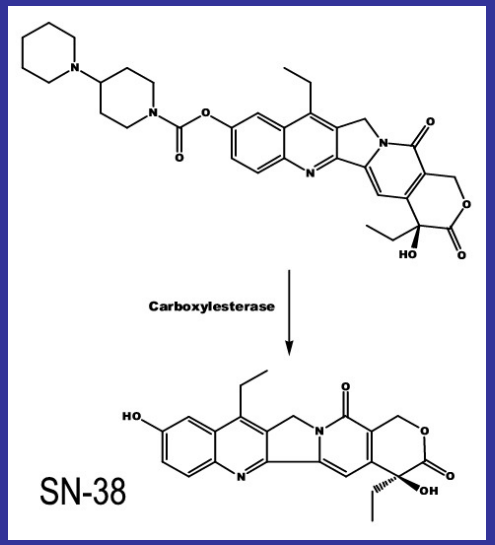


Paclitaxol
(6-12 mg/mL)



Etoposide
(4.5-6 mg/mL)

Irinotecan



SN-38
(2.4 mg/mL)

Paclitaxel
Etoposide
Doxorubicin
Vincristine
SN-38
BCNU

Temsirolimus
Bortezomib
Lapatinib
Sorafenib
Dexamethasone

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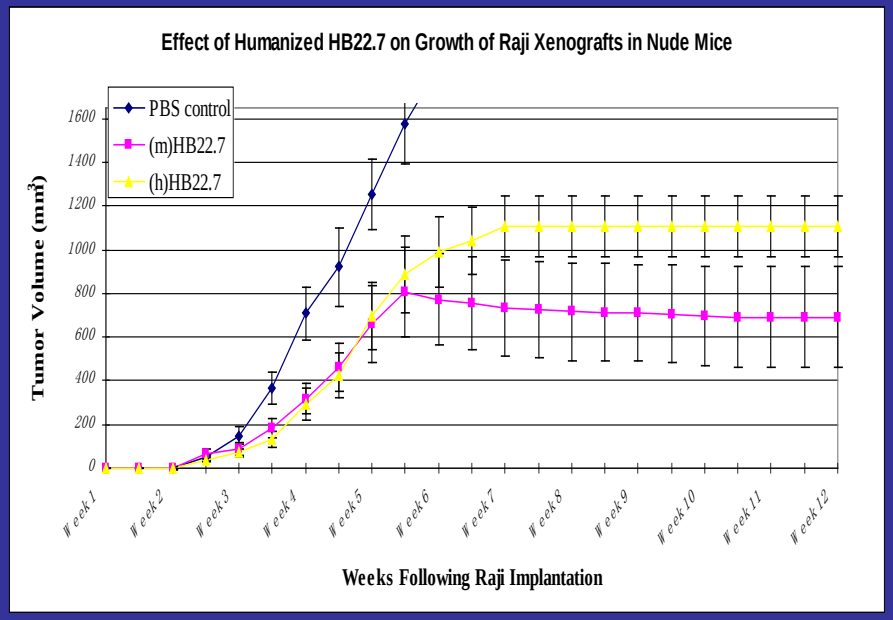
- Investigator-initiated Trials
- NSG mouse xenotransplant co-clinical trials

Projects have or will soon proceed to clinical development (highlighted in yellow)

Anti-CD22 HB22.7 in Lymphoma

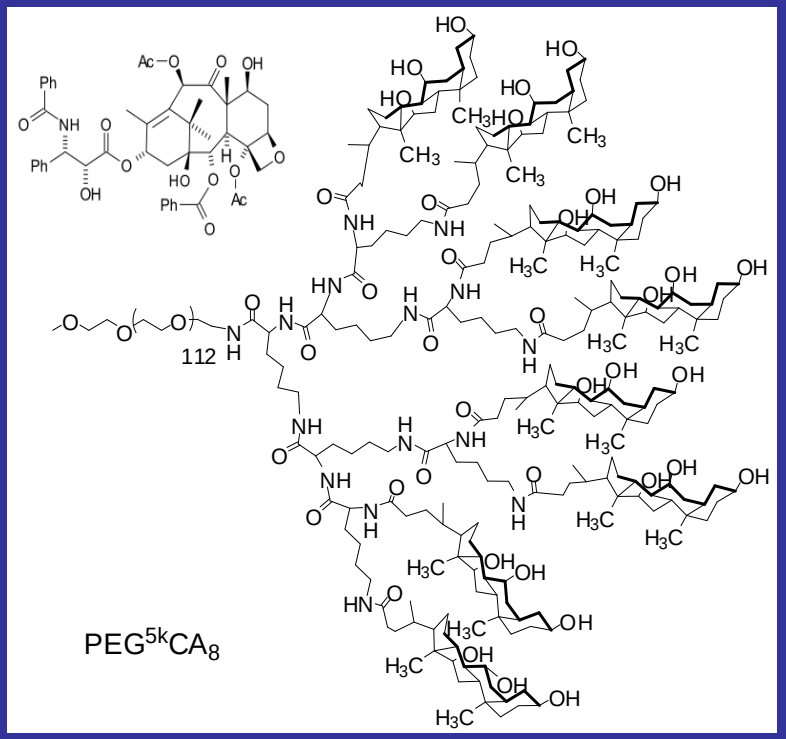


HB22.7 in Raji Xenograft Model

NCI RAID Approved Production of HB22.7
GMP in progress at Aragen Biosciences (NCI subcontract)
NCI R21 hHB22.7 Phase I/II clinical trial planned

Tuscano, O'Donnell, Beckett (Cancer Immunol Immunother 2009, Clin Cancer Res 2010)

LMN-001: Phase I trial of paclitaxel-loaded nanoparticle in advanced solid tumors



Dose level	LMN001 (mg/m2)	% change from prior dose level
-1*	10	- 50%
1	20	N/A
2	40	100%
3	70	~ 70%
4	100	~ 50%
5	140	40%
6	180	30%
7	230	30%
8	300	30%

	Day 1 Cycle 1	Day 1 Cycle 2	Day 1 Cycle 3	Day 1 Cycle 4	Day 1 Cycle 5
LMN001	x	x	x	x	x

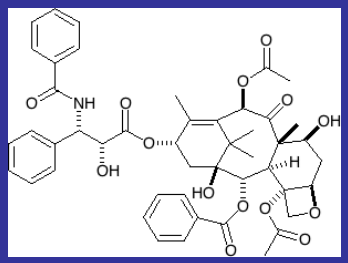
Status:
Protocol completed
GMP in progress
SRC approved
R21 trial submitted
IND to be submitted ….

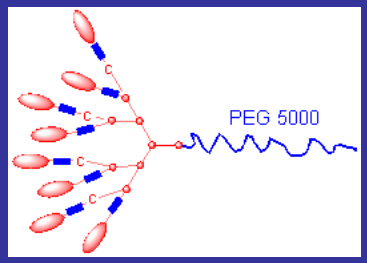
Lam, Lara, Lee, Luo, Beckett

(Biomaterial 2008, J Control Drug Release 2009, Bioconjugate Chemistry 2010, Biomaterial 2011)

Therapeutic Efficacies of Disulfide Cross-linked Micelle (LMN-002)

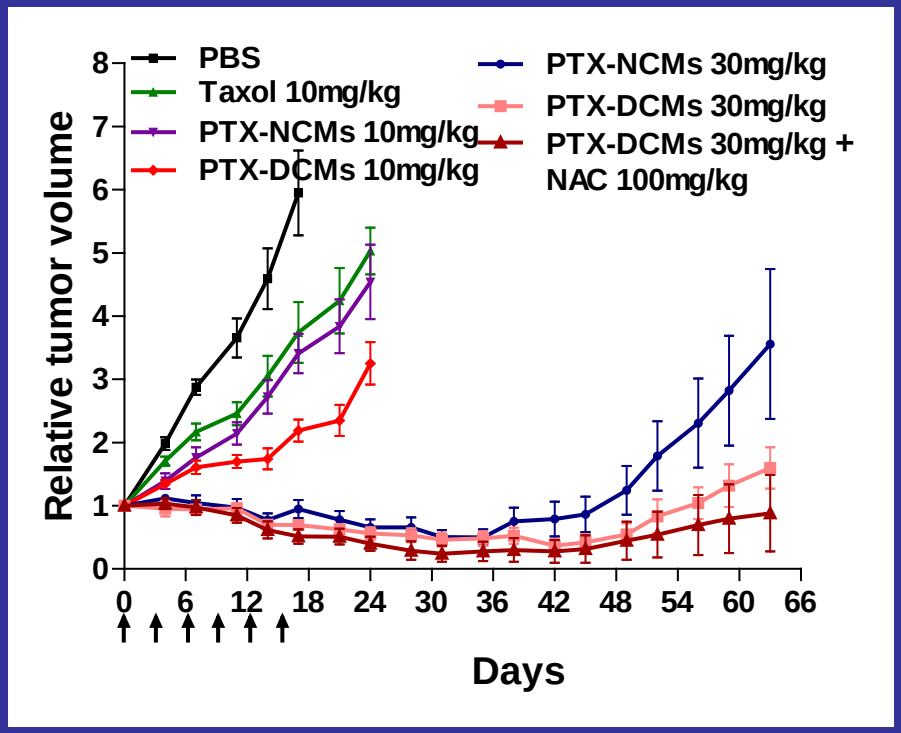
Intracellular cleavage with endogenous glutathion (GSH)

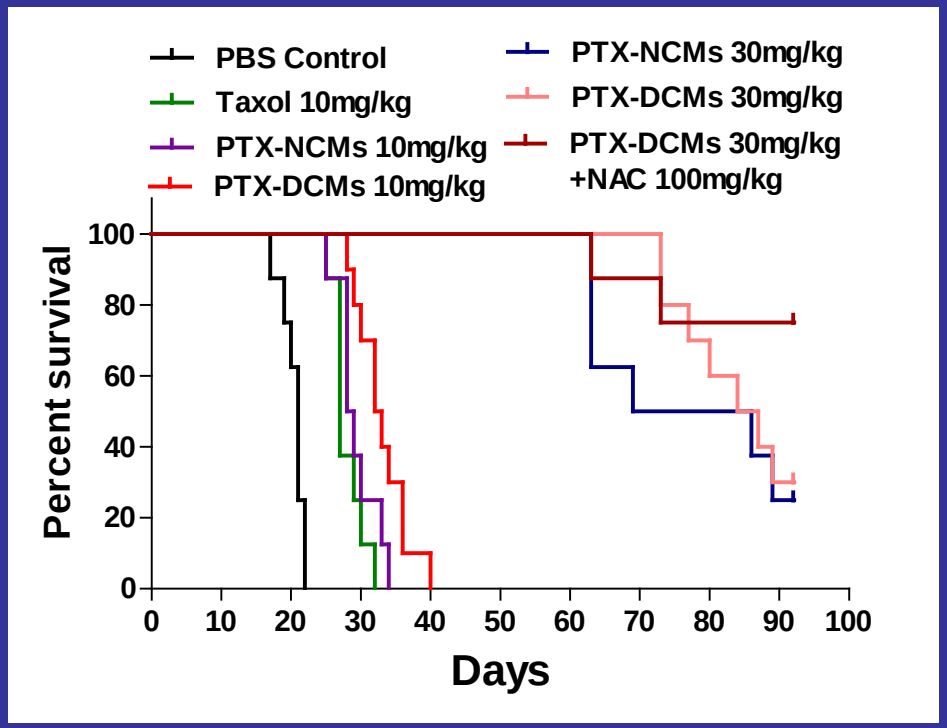




On-demand cleavable with exogenous N-acetyl cysteine (NAC)

NAC is a FDA approved antidote for Tylenol overdose





Li et al Biomaterial 32: 6633 (2011)

Summary & Future Plan: From Bench to Bedside

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Future Plan

- Start Phase I trials of two in-house drugs (anti-CD22 MAb and LMN-002).
- Develop Phase 0/I imaging trials of [^{124}I]-labeled nanoparticle drugs, and [^{124}I]-labeled ligands.
- Complete the NSG mouse xenotransplant co-clinical trials.
- Recruitment of a Cancer Pharmacologist into Department of Biochem & Mol Med, and a "drug developer" into Dept Biochem/Chem. Joyce Lee (Pharm D) will join Hem/onc soon. Utilize the GMP facility and hot cell.
- Leverage PK, molecular modelling and AMS expertise from LLNL.

Team Science

Glioblastoma (Vet and Med)

Lam, Liu, Li (nanoRx: murine model, BBB)

Sturges, Dickinson, Zwingenberger, Wisner (nanoRx: canine model)

Sutcliff, Badawi, Lam (Imaging, human)

Gorin (urokinase plasminogen activator inhibitor)

Lara, Lee (Rx: nanoRx clinical trial)

Neuroblastoma

Satake, Diaz and Nitin (targeting siRNA)

Lam, Lara, Lee (Targeting nanoRx)

Lymphoma and Leukemia

Tuscano, Satake, Lam (CD22-MMAE2 conjugates, lymphoma and leukemia)

Lam, Lara, Kent, Lee (nanoDox, nanoBortezomib and nanoCTN06; human and canine)

Kung, Maverakis, Lam, Kent (CTN06, Btk and Itk biology, inhibitor, murine and canine model)

Pan, Lam, Lee (AML stem cell targeting nanoRx)

Bladder Cancer

Pan, Lam, Rodriguez (Targeting nanoRx, mice, dog, human)

Henderson, Pan (AMS, platinum resistance: clinical trial)

deVere White (microRNA)

Kung and Lam (CTN06, Etk and Itk inhibitor, Rx)

Team Science, cont'

Ovarian Cancer

Lam, Lara, Lee, Li, Leiserowitz (nanoRx, iv and ip)

Leiserowitz, Lebrilla, Miyamoto (serum glycan markers)

Lam, Sutcliff, Badawi (Targeting ligands: Imaging, human)

Immunotherapy

Tuscano, Satake, Lam (CD22-MMAE2 conjugates, lymphoma and leukemia)

Murphy, Berti, Coleman (iron particles and nanoimmunomodulation)

Lam, Abeidi, Kent (active recruitment of anti-tumor immune cells with ligands; mice, dog, human)

Other immunoRx projects

NanoTechnology

Cheng and Lam (viral capsid as drug carrier)

Murphy, Berti, Coleman (iron particles and nanoimmunomodulation)

Ferrara (liposome and micelle-based nanoRx and imaging)

Lam, Voss, Faller, Li, Lee (targeted, cross-linked, micelle-based nanotherapeutics)

Lam, Li, Lee (polymer-based targeted nanotherapeutics & microRNA delivery)

Nitin and Satake (gold nanoparticle, siRNA delivery)

Coleman and Hoeprich (nanolipoprotein particles)

Kauzlarich, Lam, Satake (Si-based nanoplatform for Rx and Imaging)

Berti, Lam (SPIO nanoparticle, AMF, breast cancer)