Kavli Institute of Theoretical Physics: Physical Sciences and Cancer Centers

July 9, 2012

Judith Gasson, Ph.D.
Professor and Director, UCLA's Jonsson Comprehensive Cancer Center
President, Jonsson Cancer Center Foundation
Co-Director, Broad Stem Cell Research Center

UCLA Jonsson Comprehensive Cancer Center

Overview of JCCC Activities and Scientific Program Area

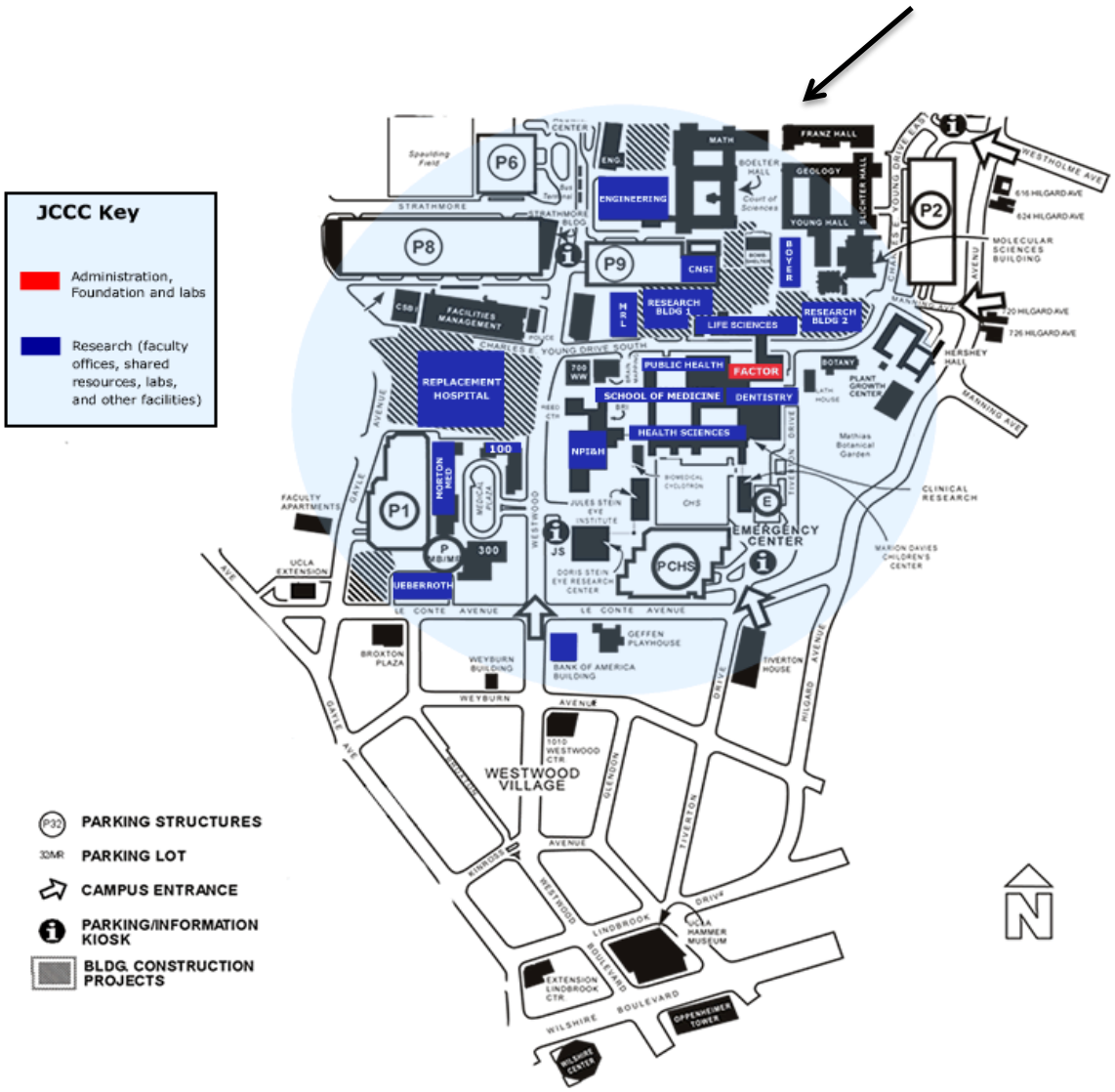
- Very broad overview of our activities
- Highlight successful partnerships
  - Nano-Therapeutics and Nano-Diagnostics
  - Translational Therapeutics
- Physical Sciences and the Provocative Questions
- Cancer Stem Cells and/or Clonal Evolution

Vision for JCCC

To be an international leader conducting transdisciplinary cancer research that advances the most effective approaches to prevention, detection and treatment while delivering the highest quality patient-centered, integrated care.

The Jonsson Comprehensive Cancer Center at UCLA

With 240 investigators located within and throughout the UCLA campus, the JCCC optimizes its powerful potential for partnerships and multi-disciplinary research collaboration.



Funding Base (direct plus indirect) :

total funding: $220,000,000

NCI funding: $40,000,000

Research Initiatives at UCLA's Jonsson Comprehensive Cancer Center

- **Re-Organized into 9 Full Scientific Program Area**
  - *Cancer and Stem Cell Biology*
  - *Cancer Molecular Imaging*
  - *Gene Regulation*
  - *Genito-Urinary Oncology*
  - *Healthy and At-Risk Populations*
  - *Patients and Survivors*
  - *Signal Transduction and Therapeutics*
  - *Tumor Immunology*
  - *Cancer Nanotechnology*

UCLA's Jonsson Comprehensive Cancer Center

Nano-technology partnerships with Engineering, Chemistry and Cal Tech

- California Nano-Systems Institute (CNSI) UCLA-UCSB, public/private funding

- Cal Tech/ UCLA Pharmacology/ JCCC/ ISB Consortium (Heath, Phelps, Hood) NCI-CCNE Center of Nanotechnology Excellence

Cancer Nanotechnology

Program Area Themes

1. **Nanoparticle engineering and delivery**
   - To provide cancer therapeutics and diagnostics (theranostics)

2. **Nanoscale imaging and mechanics**
   - For interrogating population heterogeneity and single cell structure/function

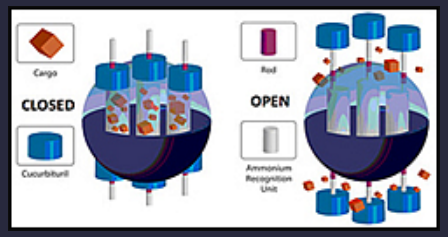
3. **New-age devices**
   - Microfluidic platforms for small sample handling and analysis
   - DNA encoded antibody libraries (DEAL) for analysis of proteins & genes
   - Photothermal Nanoblade for large cargo delivery into cells

4. **Systems biology**
   - Global phosphoproteomics
   - Feedback systems control

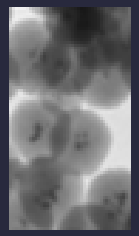
Nanoparticle Engineering & Delivery

Targeted, Controlled Nanoparticle Delivery

A key strength is the range of expertise for engineering nanoparticles for therapy and diagnostics

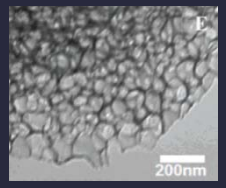


Mechanized NPs

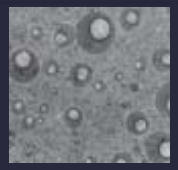


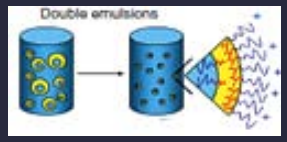
Magnetic NPs

Vaults



Hydrogels





Nanoemulsions

Nanomachine Center for Targeted Delivery and On-Demand Release

Andre Nel
Nanotoxicology

Fuyu Tamanoi
Cancer therapy

Jeff Zink
Nanostructured functional nanoparticles

Fraser Stoddart
Bistable molecular motors

Engineered Vault Group

Leonard Rome

Kathy Kelly

Hal Monbouquette

Nanoemulsion and Protein Nanospheres

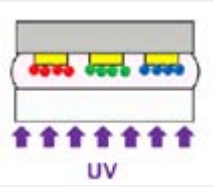
Tim Deming

Tom Mason

Polymerized Liposomal Nanoparticles

Christopher Denny

Protein arrays
Heather Maynard



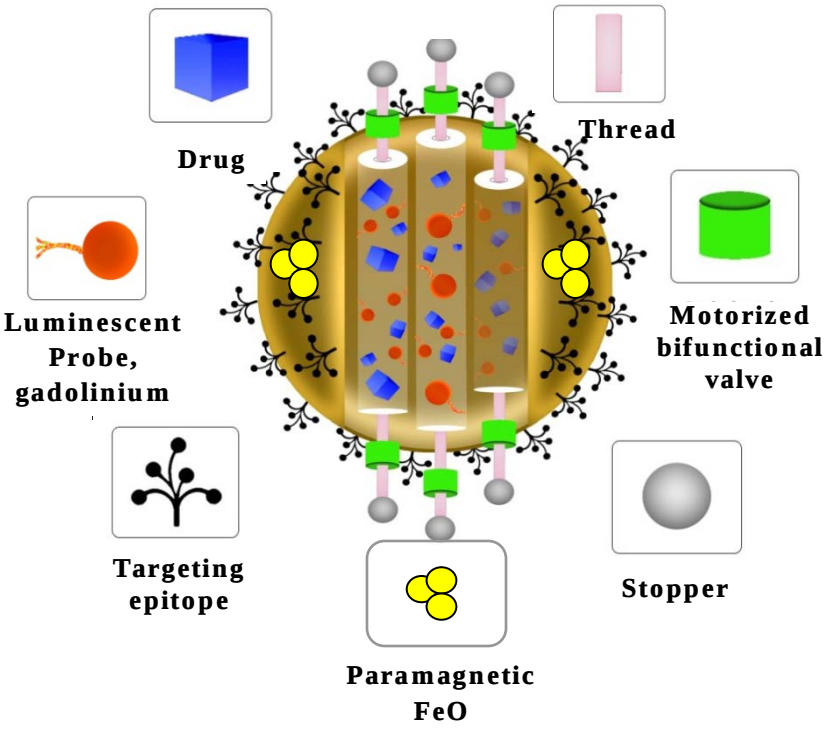
Nanoparticle arrays
Yong Chen

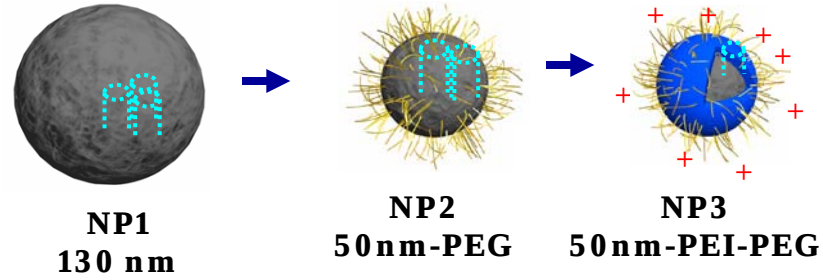
Engineered adenoviruses
Lily Wu

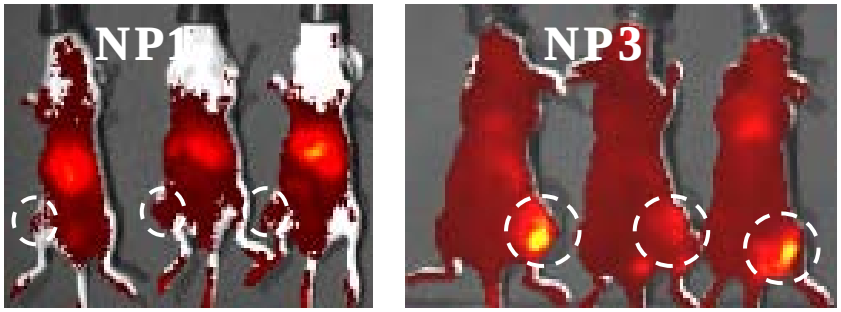
Protein Delivery Systems
Tatiana Segura
Yunfeng Lu, Yi Tang

Multifunctional Nanoparticle Cancer Drug Carriers

UCLA NanoMachine Center







Molecular and on-demand delivery of cancer therapeutics by multi-functional mesoporous silica nanoparticles

Exploration of the nano/bio interface with high content screening and iterative design have led to more efficient therapeutic nanomachines

ACS Nano 2008; ACS Nano 2010; JACS 2010
ACS Nano 2011

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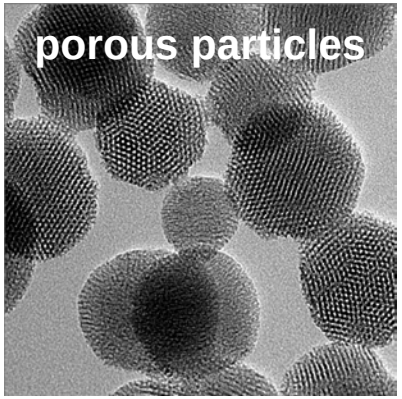
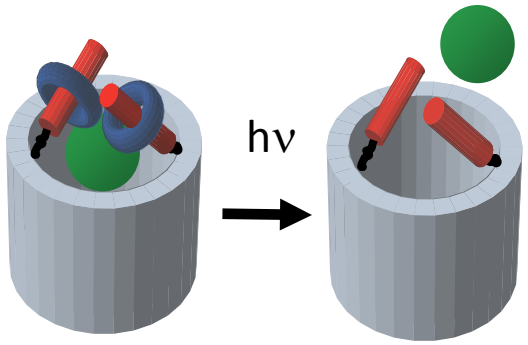
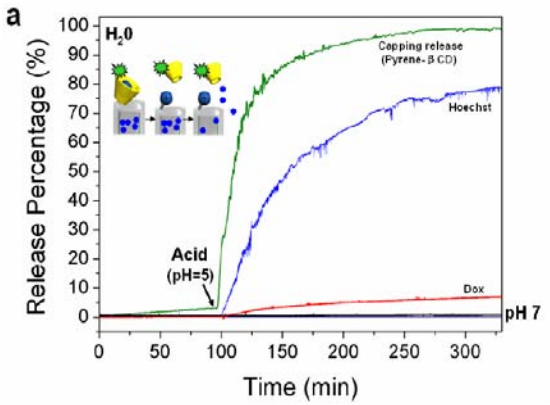
Mesoporous Silica Nanoparticles: Controlled Drug Release and Overcoming Drug Resistance

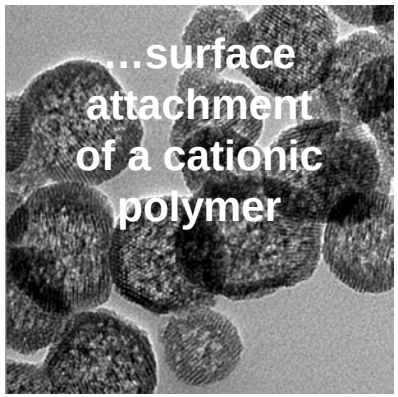


…fitted with a pH-responsive valve controlling pore opening

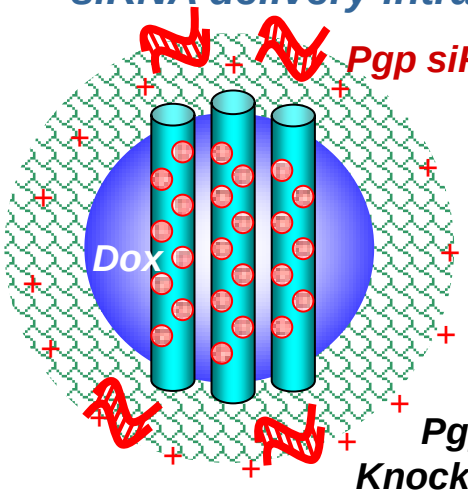


…releases doxirubicin in acidic intracellular compartment

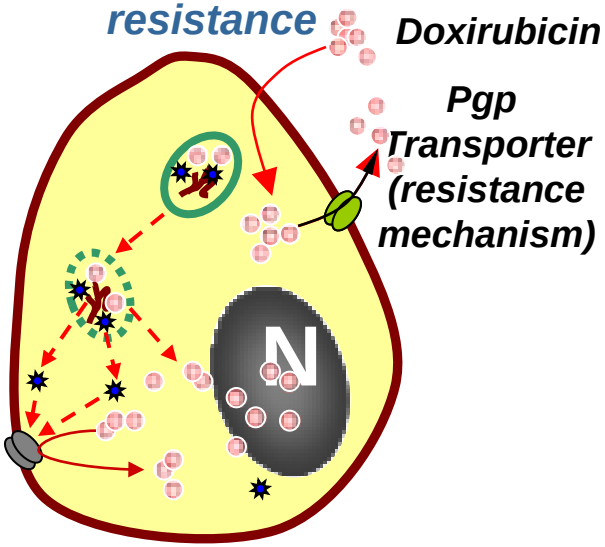




…for protected dual drug and siRNA delivery intracellular



…to overcome drug export resistance



JACS 2010;
ACS Nano 2010

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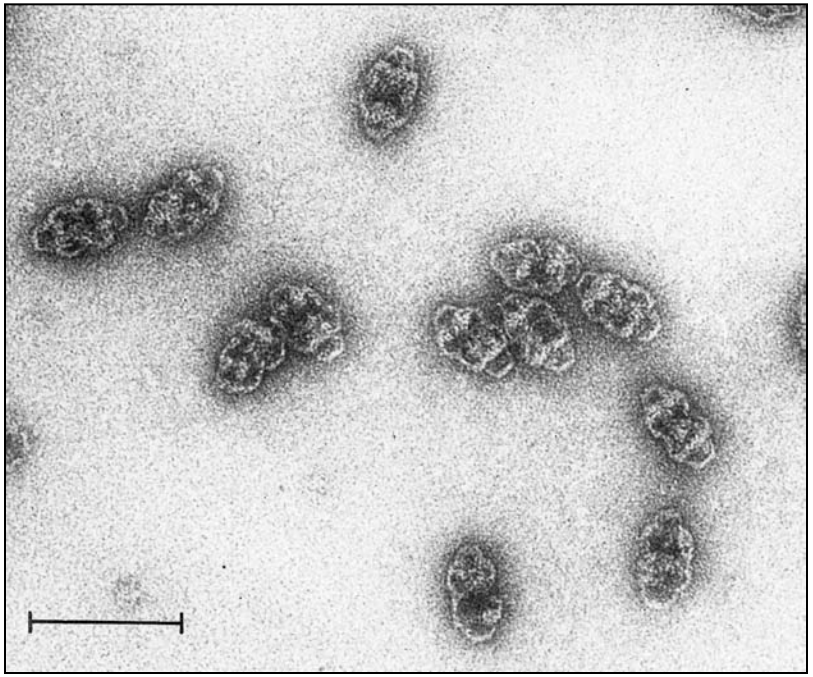
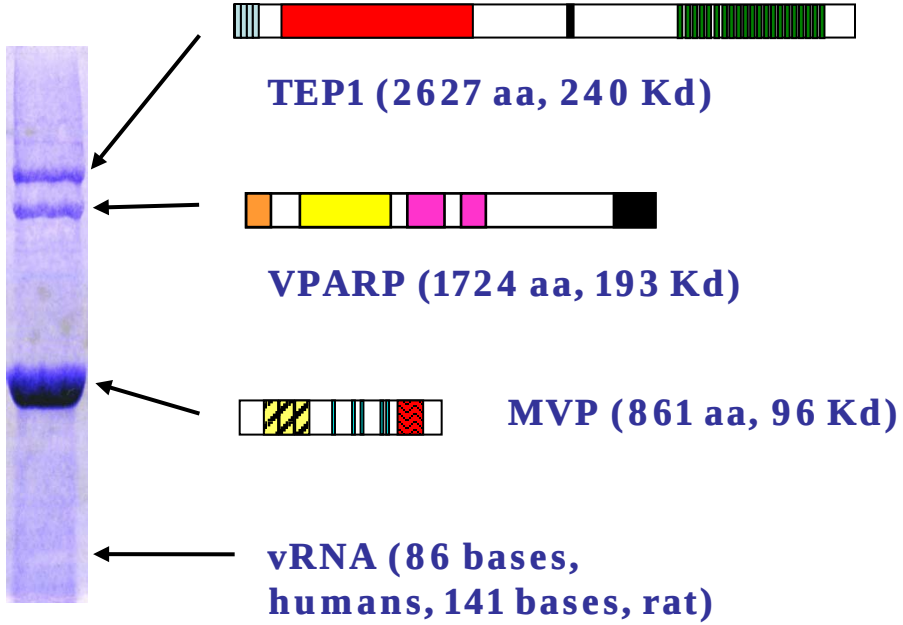
Vault Nanoparticles for Therapeutic Delivery

The Vault Particle



With a mass of 13 MD, vaults are the largest cell particle

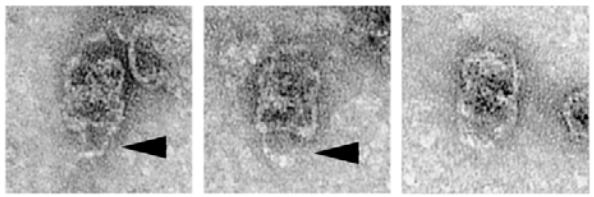


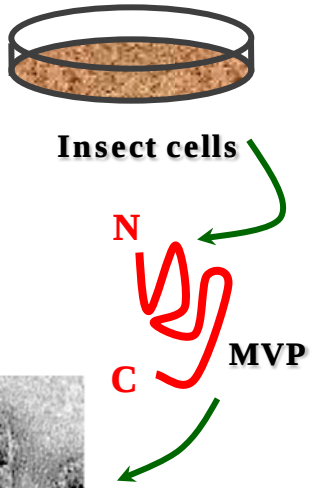
Composed of just three proteins and a small untranslated RNA

J. Cell Biol. 103:699-709, 1986; J. Cell Biol. 110:895-901, 1990; J. Cell Biol. 112:225-235, 1991; Gene 151:257-260, 1994; J. Cell Biol. 146:917-928, 1999; J. Biol. Chem. 274: 32712-32718, 1999

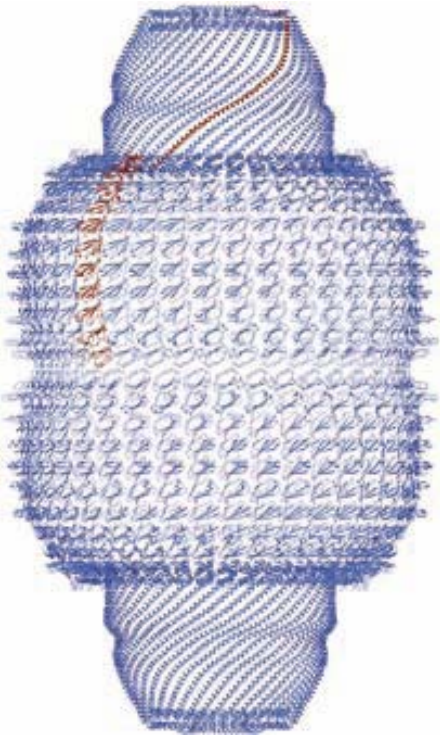
Vault Engineering

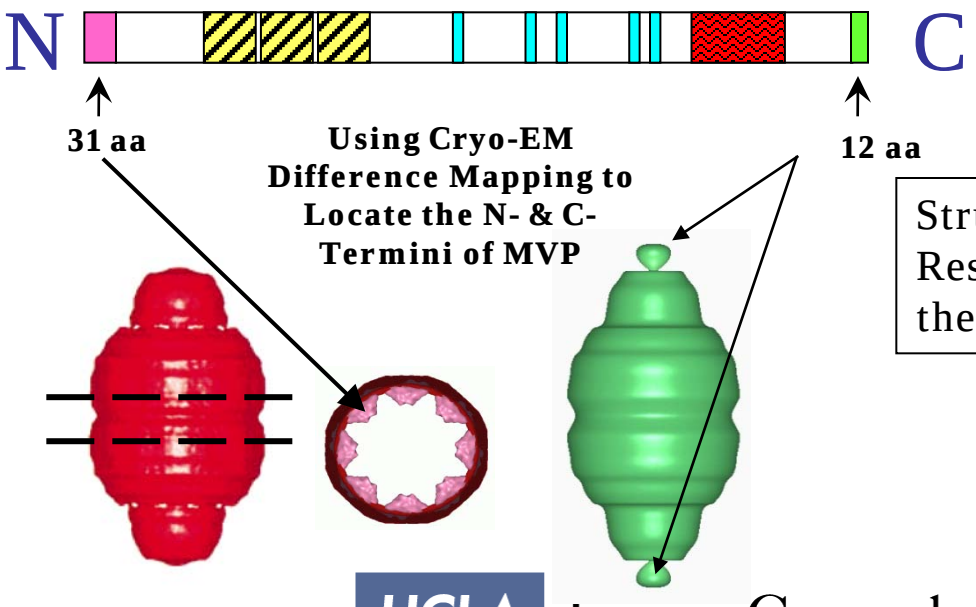
1. Insert MVP gene in an infectious piece of DNA (Bacmid)
2. Insert the gene into SF9 insect cells
3. MVPs (96 copies) self-assemble into a vault





Recombinant vaults can be assembled from a single protein (MVP)

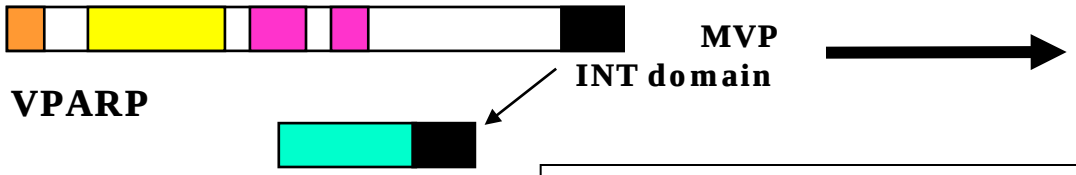




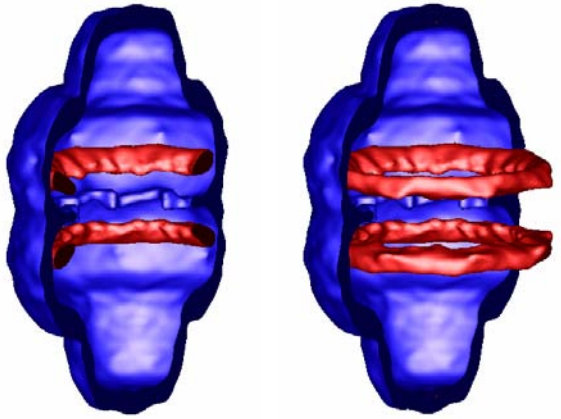
Structure of Rat Liver Vault at 3.5 Angstrom Resolution. Note: Recombinant vaults have the same structure

J. Biol. Chem. 276:23217-20, 2001;
J. Mol. Biol. 344:91-105, 2004;
PLoS Biology, 11:2661-2670, 2007;
Science 323, 384, 2009

Targeting Proteins into Vaults

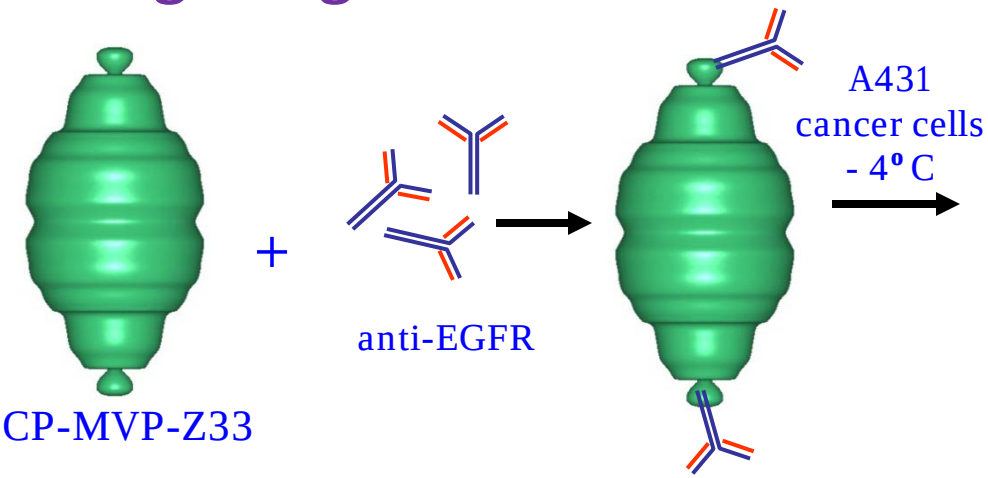


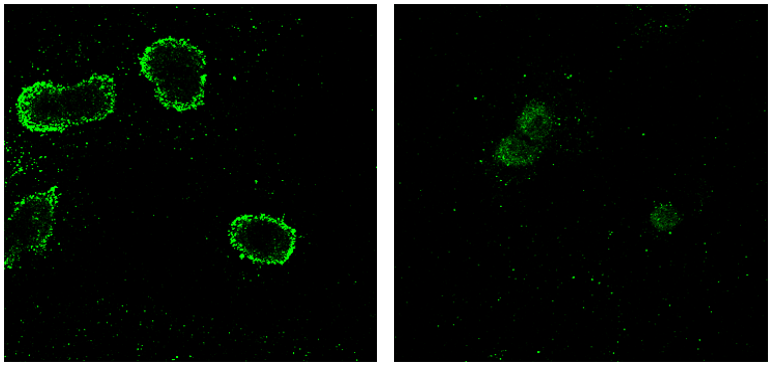
The INT domain serves as a ZIP Code to target any protein into the inside lumen of the vault



Targeting Vaults to Cells

Nano Light Bulbs!





+ anti-EGFR

- anti-EGFR

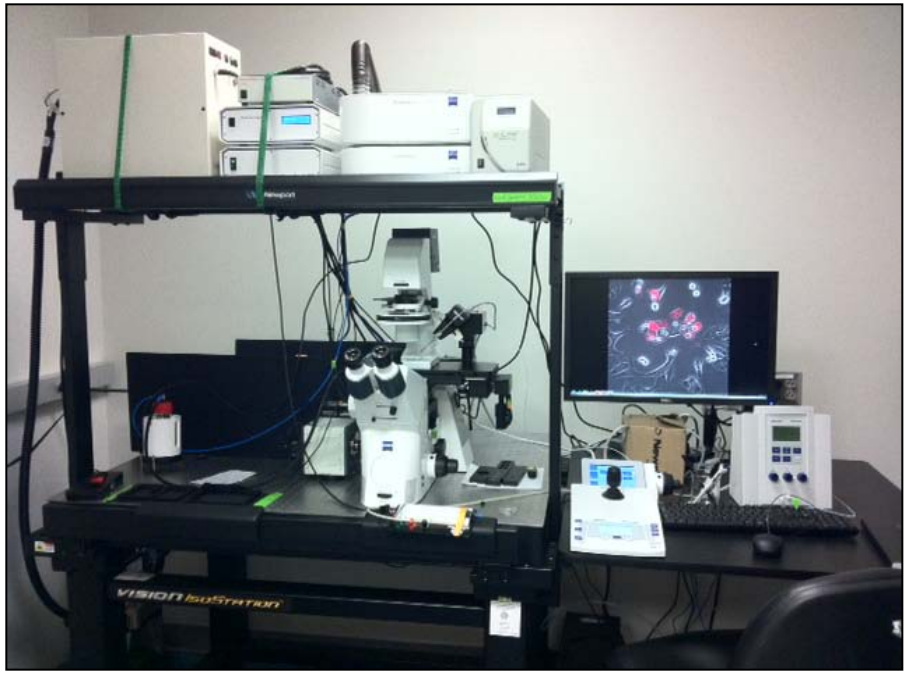
The 33 AA "Z" domain binds to the Fc portion of antibodies with high affinity. When anti-EGF receptor antibodies are bound to fluorescent vaults, these antibodies direct binding of the vaults to cells which express high levels of EGF receptors.

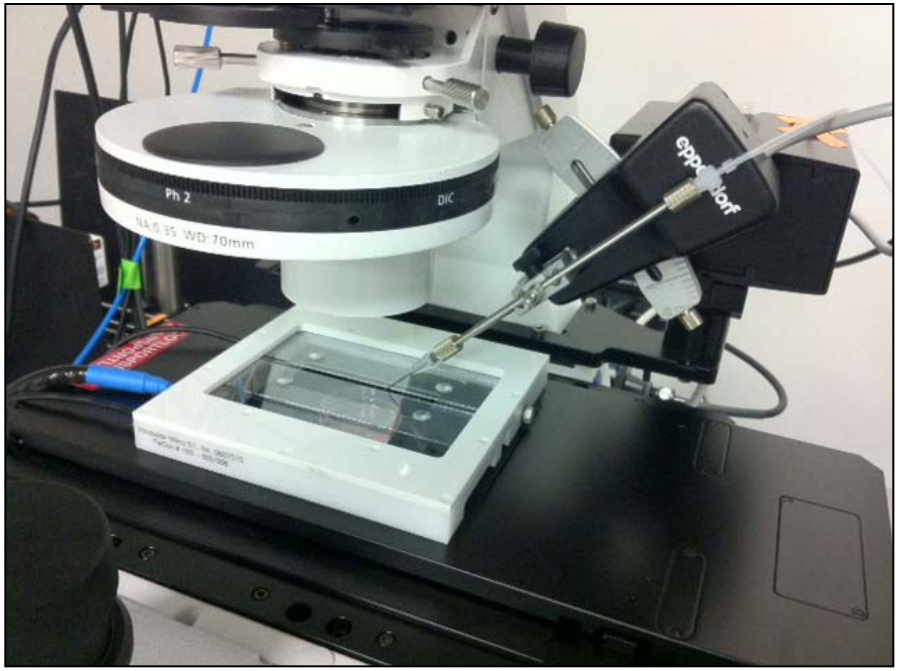
PNAS, 102:4348-4352, 2005;
ACS Nano 3:27–36, 2009;
PLoS ONE 4:e5409, 2009

Nanoscale Imaging & Mechanics

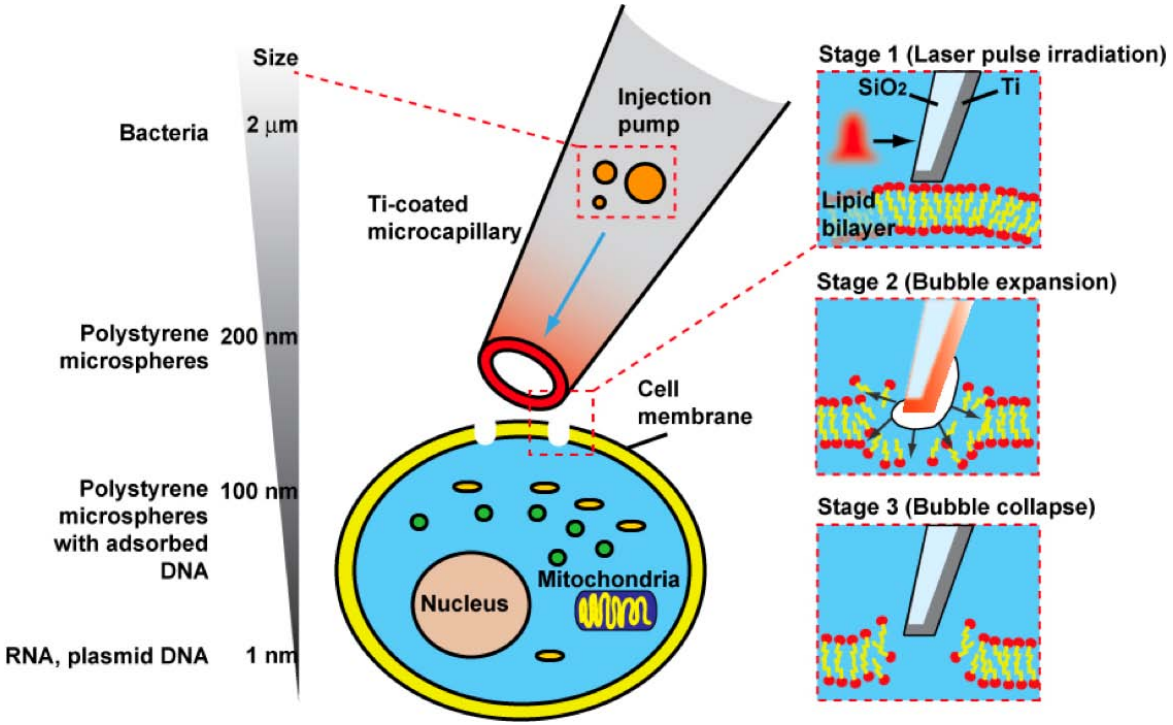
Cell Engineering: Photothermal Nanoblade

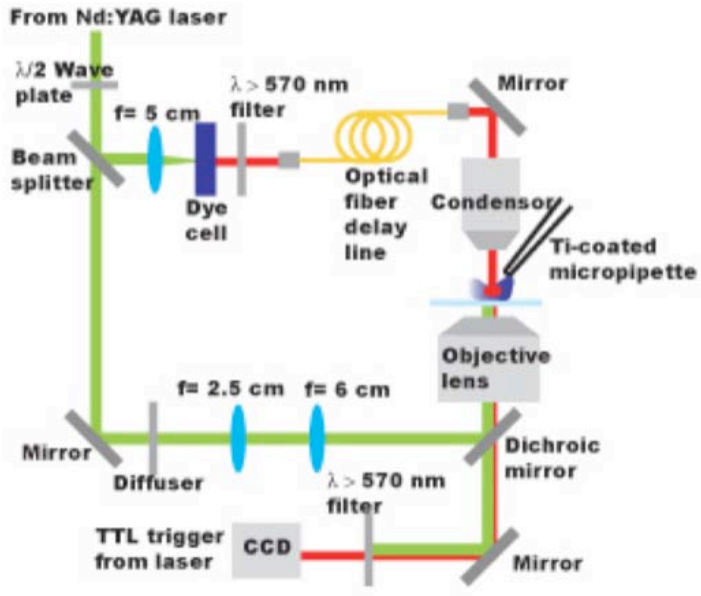
Nicole Rusk, senior editor Nature Methods: “Surprisingly, no methods for efficiently bringing impermeant large molecules into living cells exist” (Nat Methods 8:44, 2011)





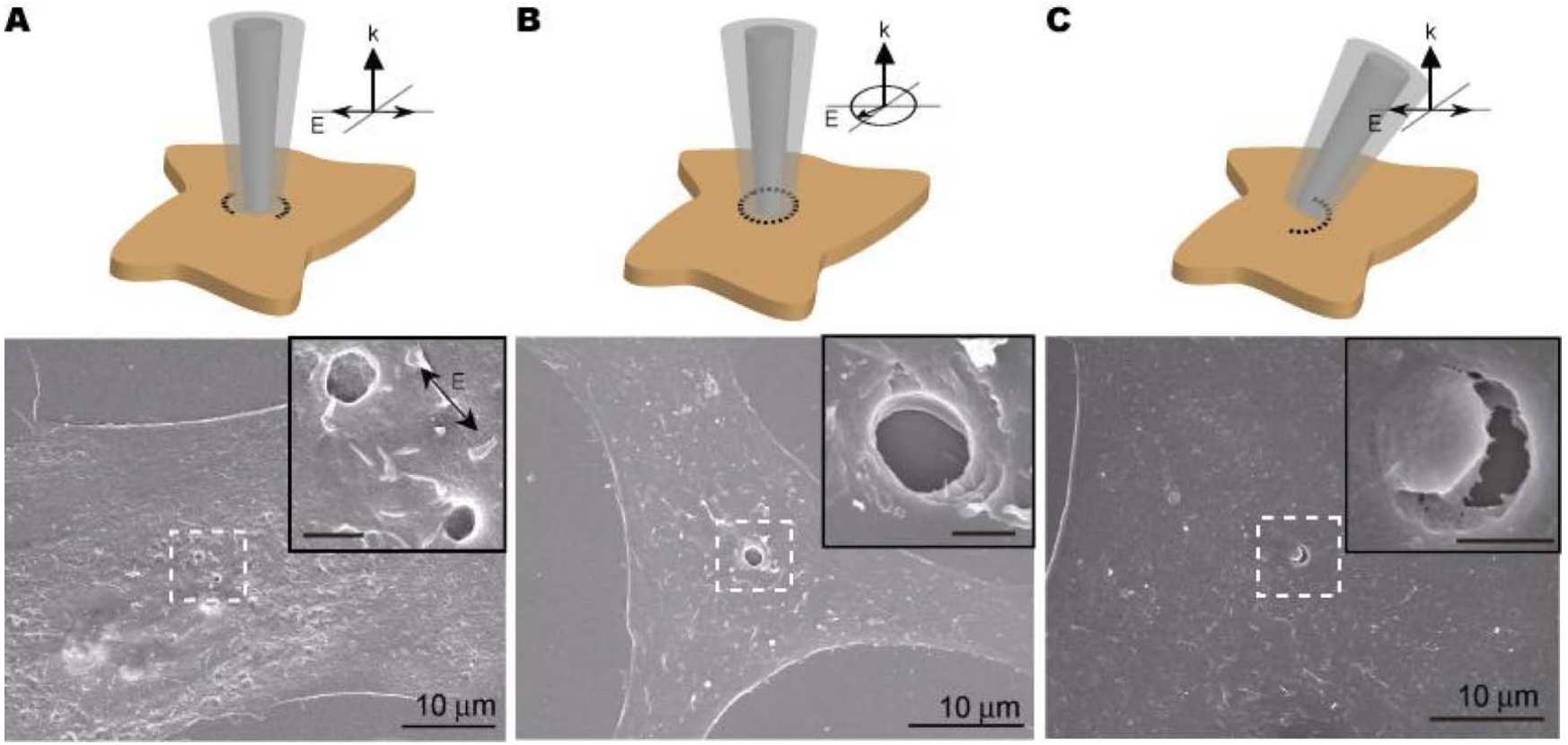
Cell Engineering: Photothermal Nanoblade





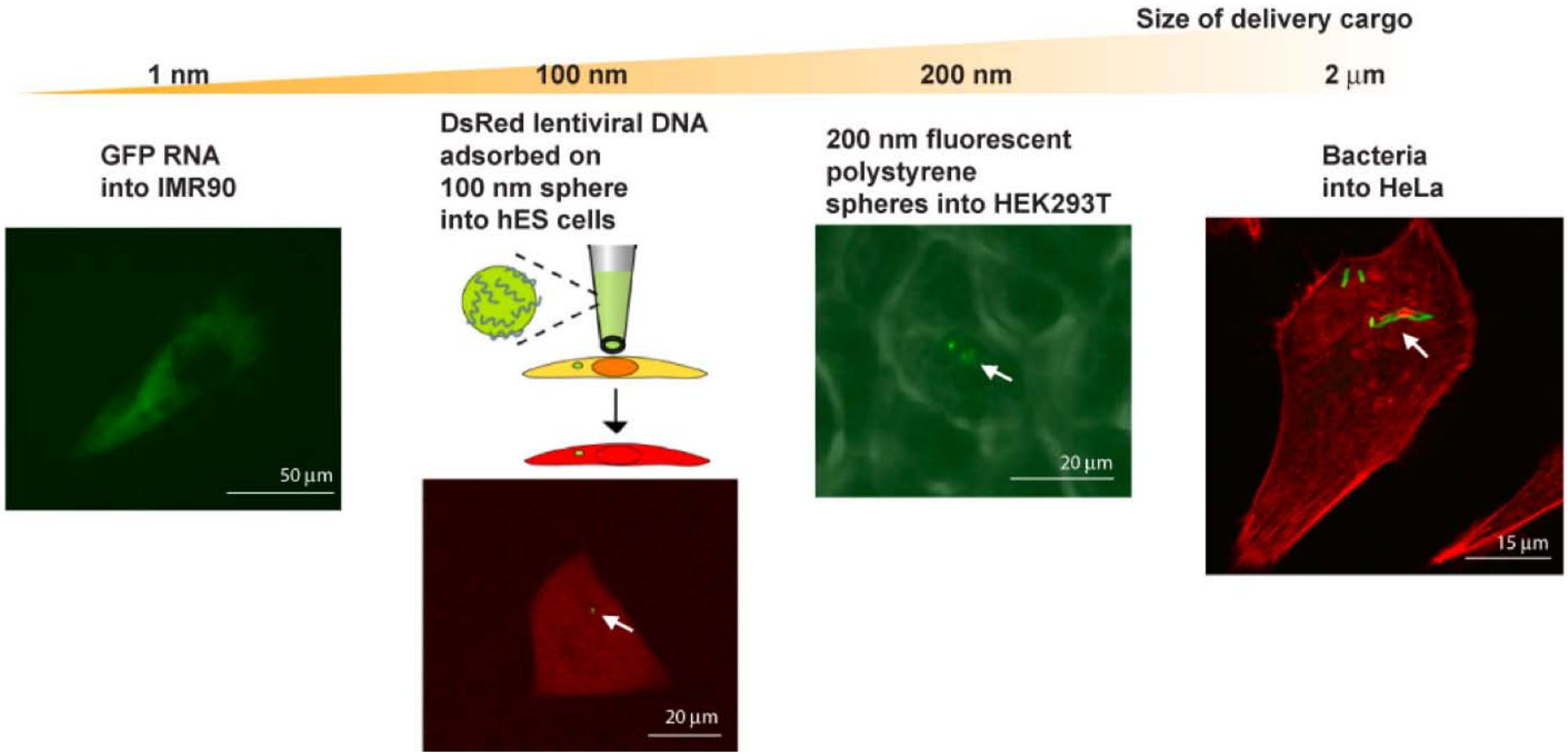
Anal Chem 83: 1321-1327, 2011

Cell Engineering: Photothermal Nanoblade



Anal Chem 83: 1321-1327, 2011

Cargo Delivery Gets “Supersized”



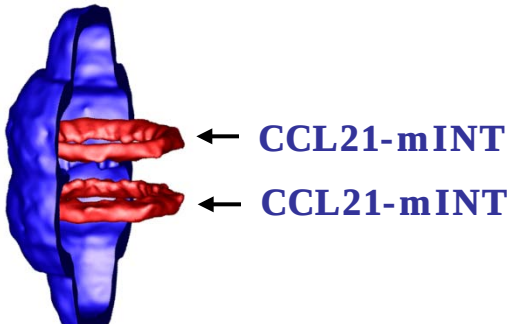
PNAS 108: 12095-12100, 2011

Translational Science

Vault Immunotherapy for Lung Cancer

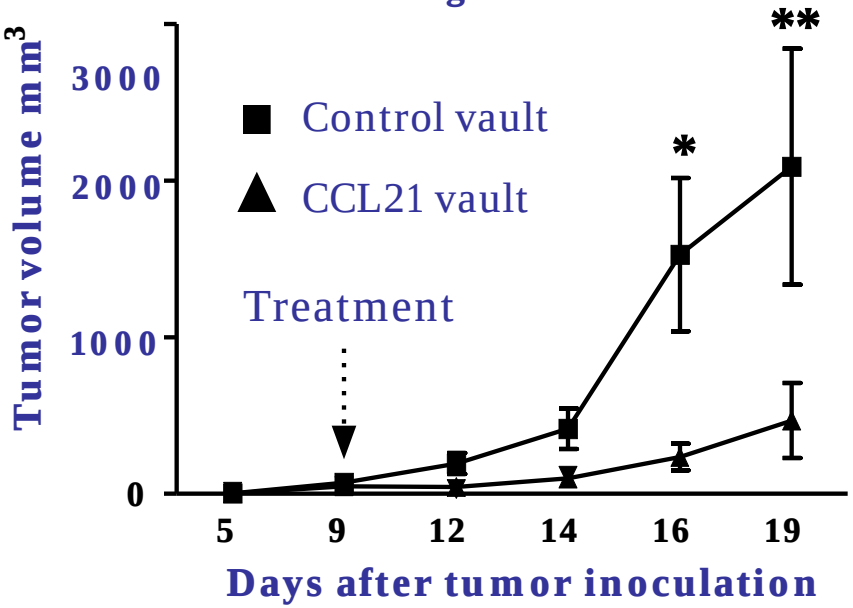
Dubinett, Sharma, & Rome

Engineering of the CCL21-INT Vault.

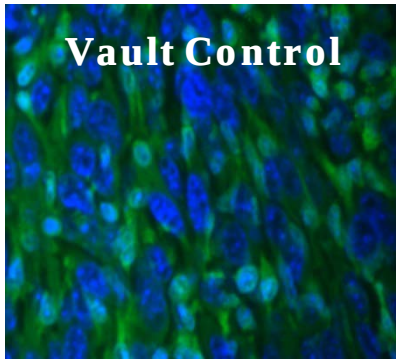


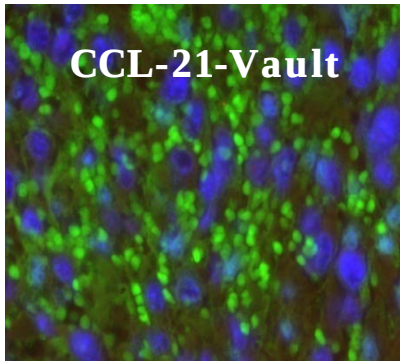
CCL21 chemokine attracts both naïve lymphocytes and antigen stimulated dendritic cells, leading to T cell activation.
CCL21 is in a phase 1 clinical trial for lung cancer.
Our goal is to follow this trial with a CCL21 vault.

Tumor regression with Vault-CCL-21 in the Lewis Lung Cancer Model



Enhanced T lymphocyte Tumor Infiltration Following CCL21-vault Treatment





PLoS One 6(5) e18758, 2011

UCLA Jonsson Comprehensive Cancer Center

We want to measure many proteins (~50) at a low price

We need state of the art sensitivity and accuracy

We get only a pinprick of blood (allows us to sample patients frequently)

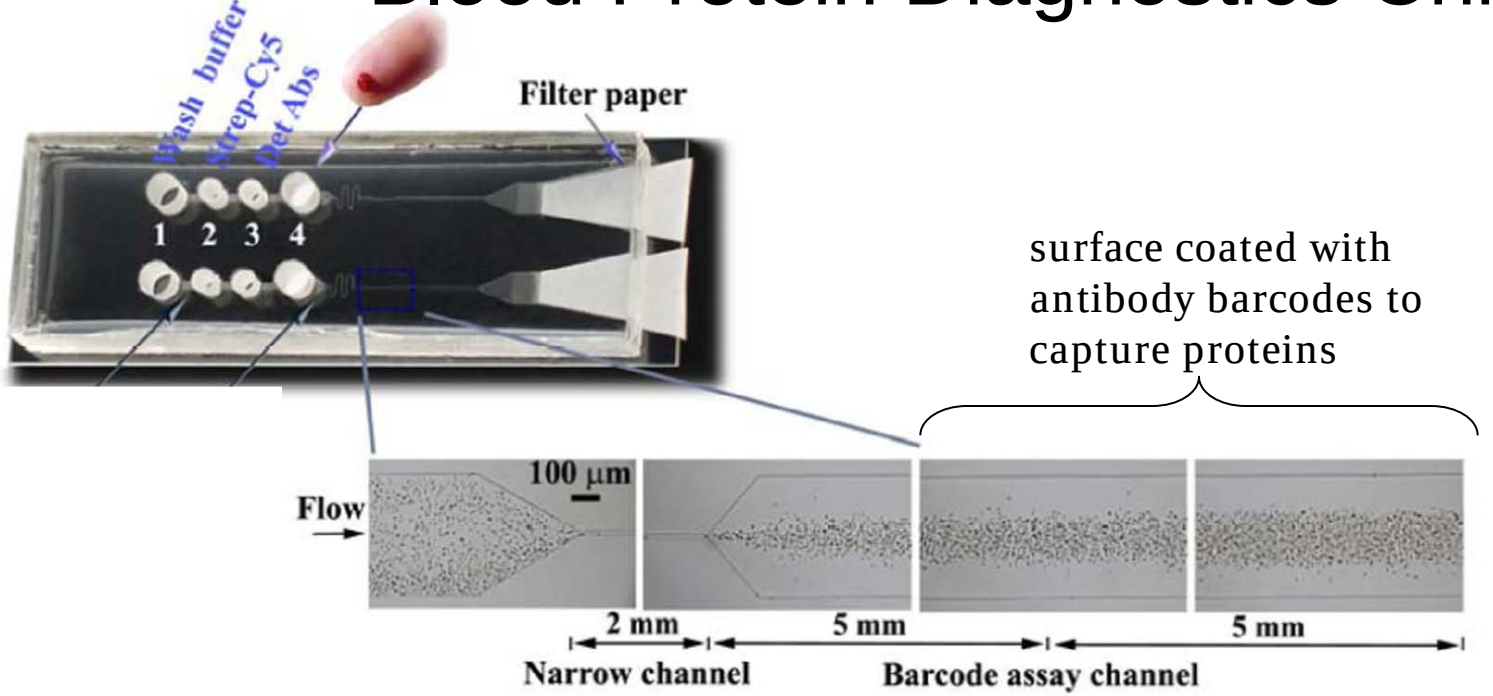
No electricity or plumbing allowed

Measurements completed in ~30-45 minutes

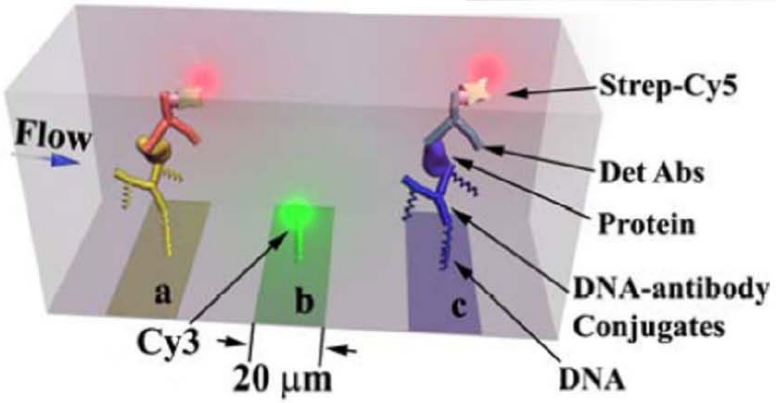
A disgruntled high school student should be able to do the measurement

UCLA Jonsson Comprehensive Cancer Center

Blood Protein Diagnostics Chip



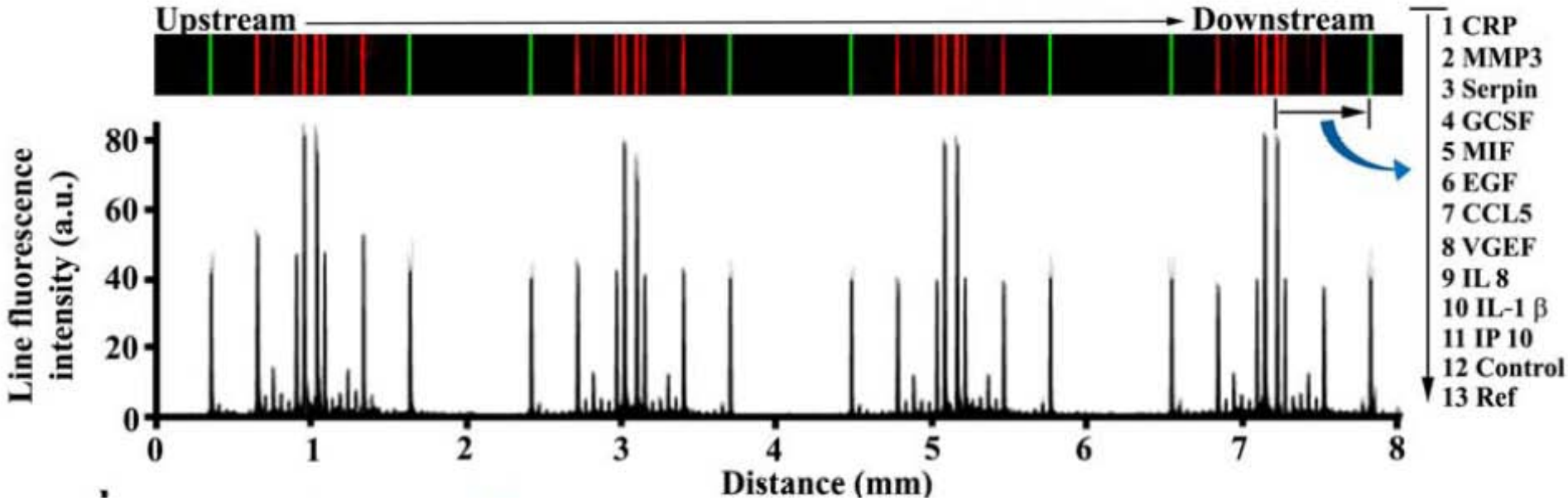
a developed barcode



The antibody barcode (a miniaturized protein chip) is the critical technology piece

J Am. Chem. Soc. 2007; Nat Biotech 2008; Lab Chip 2009; J Am. Chem. Soc. 2009; ChemPhysChem 2010; Lab Chip 2010

Blood Protein Diagnostics Chip



The molecular patterning approaches we developed for building clinical-quality diagnostic barcodes represented non-trivial chemistry and engineering

Technology now in use in various clinical studies of Glioblastoma Multiforme patients (w/ Tim Cloughesy and Paul Mischel)

UCLA Jonsson Comprehensive Cancer Center

Cancer Nanotechnology

Program Area Opportunities (Non-Exhaustive)

1. **Taking advantage of unique location for major medical school campus**
   - **Physical/Engineering sciences, Life Sciences, Medical/Dental Schools**

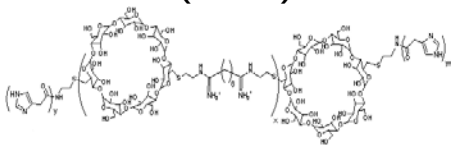
2. **Program area members in campus/national leadership positions**
   - **Senior Associate Dean of Medical School and CNSI Co-Director (Rome)**
   - **NCI Center for Cancer Nanotechnology Excellence (CCNE) Director (Heath)**
   - **NIH Clinical and Translational Science Institute (CTSI) Director (Dubinett)**
   - **UC Center for Environmental Implications of Nanotech (UC CEIN) Director (Nel)**
   - **JCCC Molecular Shared Screening Resource (MSSR) Director (Bradley)**
   - **NIH Roadmap Nanotech Development Center (NDC) Directors (Ho & Teitell)**

3. **Interactions and interprogrammatic projects with Caltech Faculty**

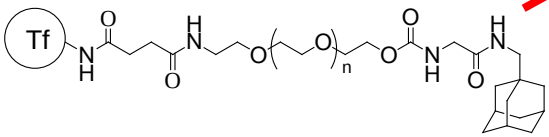
4. **Program area clinicians (Denny, Dubinett, Federman, Nel, Rao, Teitell) moving discoveries into cancer patient therapies**

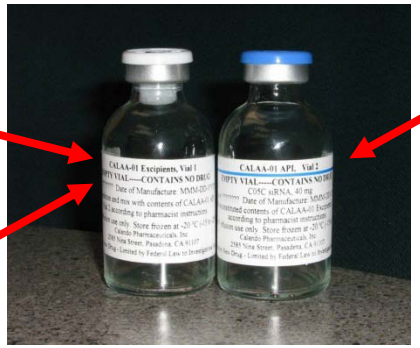
Targeted Nanoparticle Delivery of siRNA in Humans: First-in-class Phase 1 Clinical Trial

Cyclodextrin containing polymer (CDP)



AD-PEG-hTf

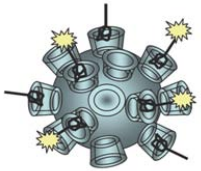




RRM2 siRNA:

5’ gauuuagccaagaaguucaga 3’
3‘ cgcuaaaucgguucuucaagu 5'

Mark E. Davis, Ph.D.
Chemical Engineering
California Institute of Technology



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Translational Therapeutics

- 283 actively accruing therapeutic clinical trials
  - 45% institutional
  - 16.5% new patients accrued to studies

- UCLA Human Gene Medicine Program (Economou, Kohn)
  - 48 trials; 340 patients; 85% cancer patients
  - FDA-compliant GMP suite
  - 5% of all patients entered on gene therapy trials worldwide

UCLA's Jonsson Comprehensive Cancer Center

Translational therapeutics

Translational Research in Oncology (TRIO)

Formed in 2003

Sites: California, Colorado, Florida, Georgia, Indiana, Maryland, Nevada, New Mexico, Texas

TRIO Global:

Partnership among JCCC, TRIO and former CIRG (Cancer International Research Group, based at the University of Alberta) to conduct large global trials.

Phase I: Special Capabilities

Lee Rosen, MD Director

- Signal transduction laboratory
  - By putting compounds through the cell line panels prior to and/or concurrent with the first-in-human phase I trial, we identify target populations for phase I expansion cohorts and future phase II/III trials
- Experienced Staff & Comprehensive Facilities
  - GCRC at Ronald Reagan Hospital
- Special disease site-specific programs
  - Including orphan indications, such as HCC, sarcoma, melanoma, CNS
- Tumor and normal tissue procurement
  - We have performed timed tumor biopsies on phase 1 clinical trials
- Expertise in imaging studies
  - Especially PET – FDG, novel isotopes, and animal studies
- Successful FDA audits

Recent First-In-Human Phase I Clinical Trials

- AUY922 (Hsp90 inhibitor)*
- BEZ235 (PI3K/MTOR inhibitor)*
- PF-04691502 (PI3K/MTOR inhibitor)*
- PF00477736 (CHK1 inhibitor)
- CALAA-01 (siRNA/nanoparticle)
- XL228 (IGF-1R, Aurora, Src inhibitor)
- BIIB022 (IGF-1R mAb)
- PF-299804 (panErbB inhibitor)*

*Preclinical studies were done at UCLA concurrent with or prior to the phase I trial.

TRIO Global

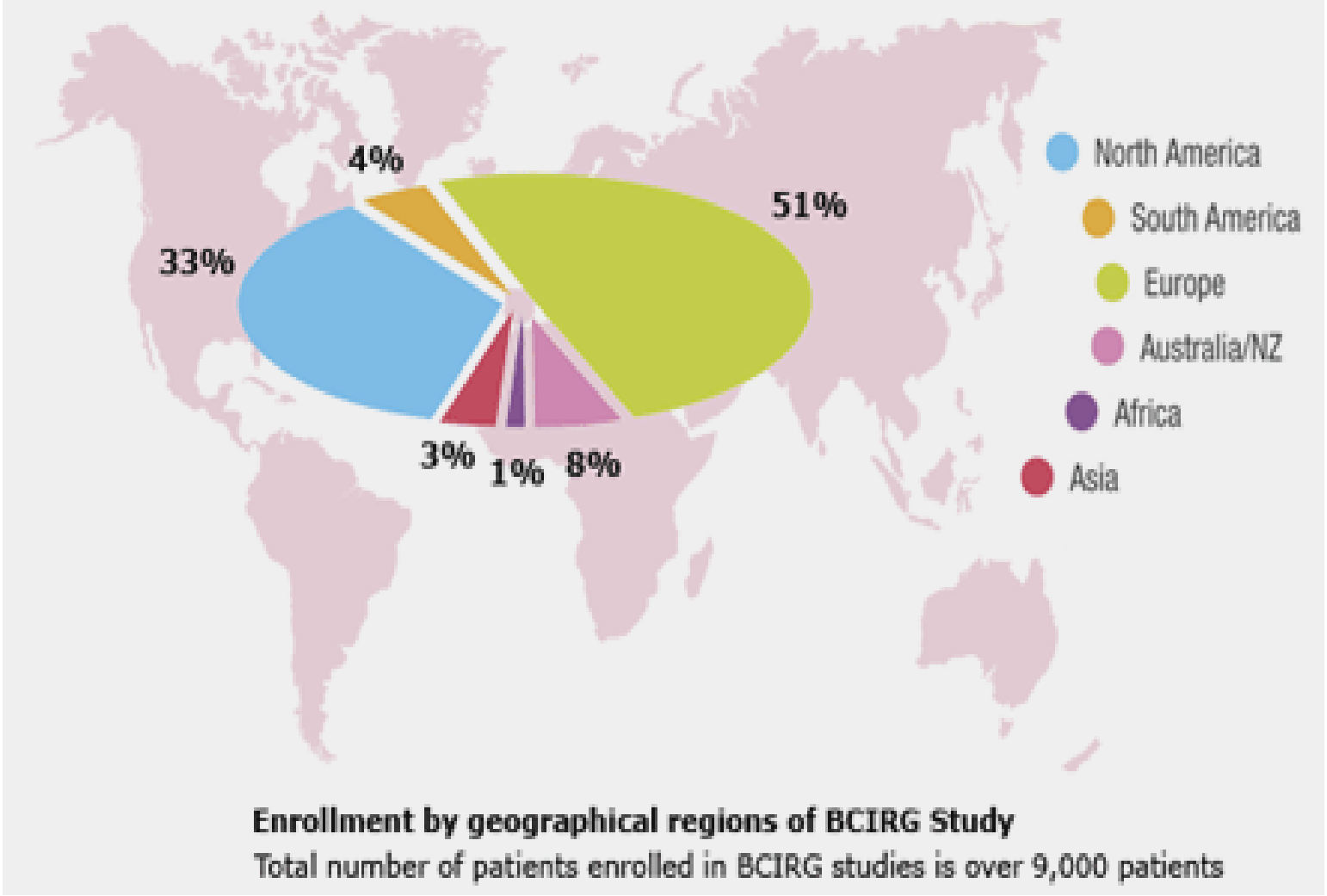
- Worldwide network of 2,000 investigators comprised of 500 centers in 45 countries.
- Independent Investigators
- Research Networks (in USA)
- Cooperative Groups: ANZ-BCTG (Australia/NZ), GEICAM (Spain), ICORG (Ireland), KCSG (South Korea), Austria
- Ability to recruit quickly and generate high quality data

TRIO Accruals

- A total of 5,417 patients enrolled worldwide on new, innovative therapeutic trials since 1996
- 10-20% are from the UCLA campus and the remaining 80-90% of patients are from UCLA/TRIO-US Network sites in the US
- Over 50% of all patients were on breast studies. The remaining studies cover lung, colorectal, prostate, ovary, pancreas and head/neck malignancies as well as lymphomas

TRIO(CIRG) ENROLLING REGIONS

(Historical Studies)



Enrollment by geographical regions of BCIRG Study

Total number of patients enrolled in BCIRG studies is over 9,000 patients

How do we measure success?

Herceptin *FDA-approved in 1998*

Breast cancer (Slamon)

Gleevec *FDA-approved in 2001*

Chronic myeloid leukemia (Witte, Sawyers)

Avastin *FDA-approved 2004*

Colon cancer (Kabbinavar)

Tarceva FDA-approved 2004

lung cancer (Prager)

Sprycel FDA-approved 2006

Chronic Myeloid leukemia (Sawyers, Shah)

Tykerb FDA-approved 2007

for HER-2+ breast cancer (Britten, Hurvitz)

THE UCLA•CALTECH•CHLA•USC•UCONN TRANSLATIONAL PROGRAM IN ENGINEERED TUMOR IMMUNITY

Program Investigators

James Economou, UCLA
Mike Phelps, UCLA
Caius Radu, UCLA
Antoni Ribas, UCLA
Owen Witte, UCLA
Jerry Zack, UCLA

David Baltimore, California Institute of Technology
Lili Yang, California Institute of Technology

Donald Kohn, Children's Hospital of Los Angeles/USC
Pin Wang, USC

Bijay Mukherji, University of Connecticut

UCLA Jonsson Comprehensive Cancer Center

A Clinical Trial Currently Recruiting Melanoma Patients

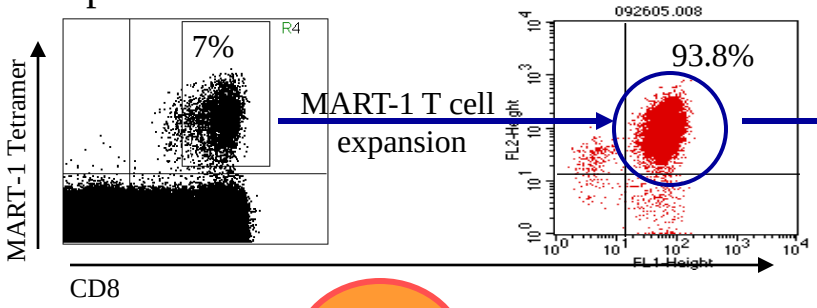
- **Adoptive Transfer of MART-1 F5 TCR Engineered Peripheral Blood Mononuclear Cells (PBMC) after a Nonmyeloablative Conditioning Regimen, with Administration of MART-1 26-35-Pulsed Dendritic Cells and Interleukin-2, in Patients with Advanced Melanoma**

- **This study is currently recruiting participants at UCLA.**

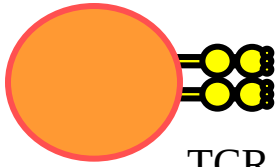
- The purpose of this study is to determine the safety, feasibility, and helpfulness against advanced melanoma of a special treatment that involves chemotherapy and an experimental treatment called gene therapy

MART-1 TCR Cloning

Patient #109 melanoma-specific T cells



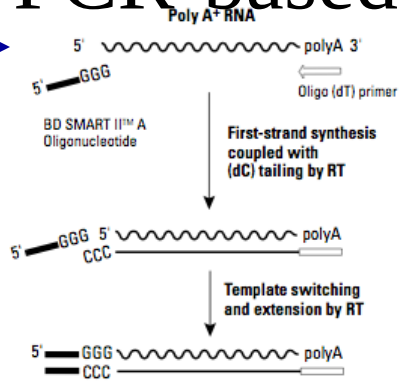
B. Comin-Anduix
J. Economou
A. Ribas



TCR

B. Mukherji

PCR-based cloning

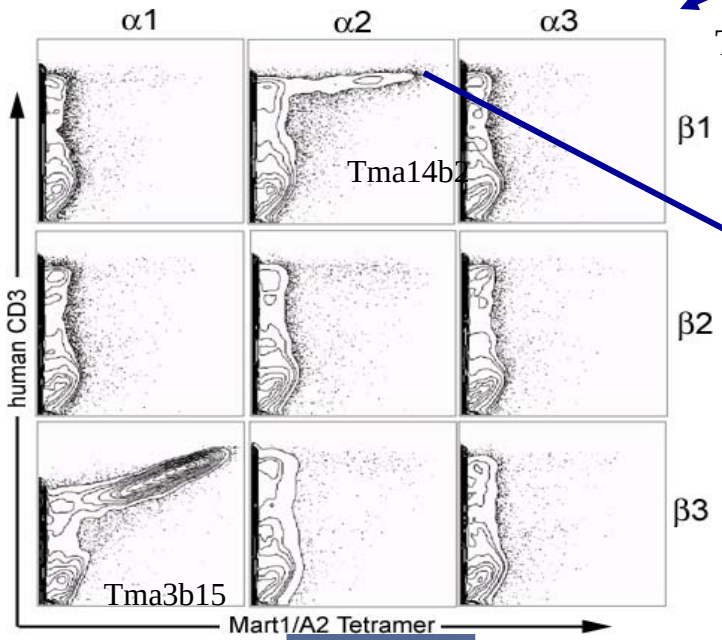


L. Yang
D. Baltimore

TCRα/TCRβ cDNAs

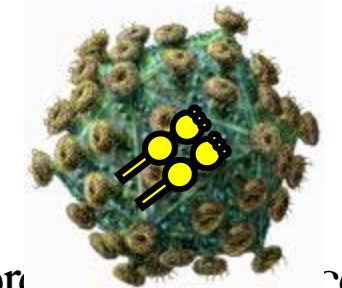
Transfection to 293T + CD3

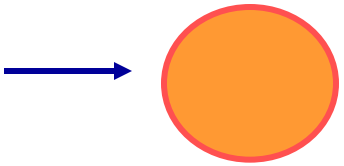
MHC Tetramer



L. Yang
D. Baltimore

FUW-M1-TCR/sr39tk Tri-cistronic Lentiviral Vector

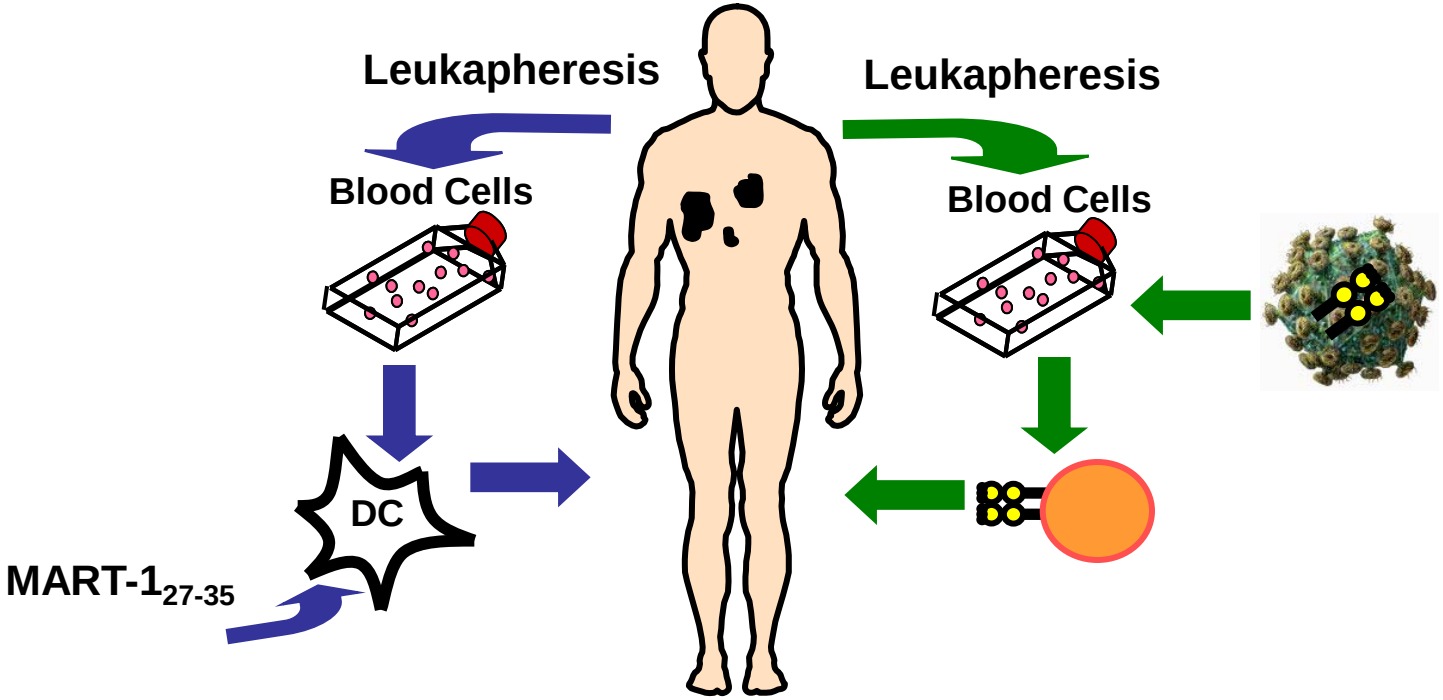




P. Wang
L. Yang
D. Baltimore

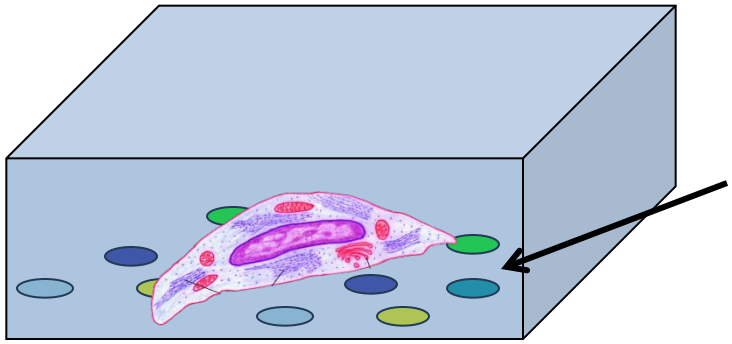
UCLA Jonsson Comprehensive Cancer Center

MART-1 TCR Engineered Immunity Clinical Trial



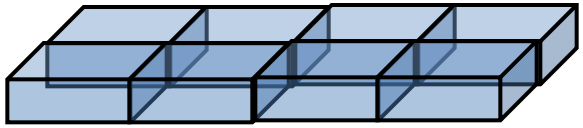
Single Cell Proteomics for In Vivo Diagnosis

Our basic concept: Put cell into tiny (1-2 nanoliter) chamber



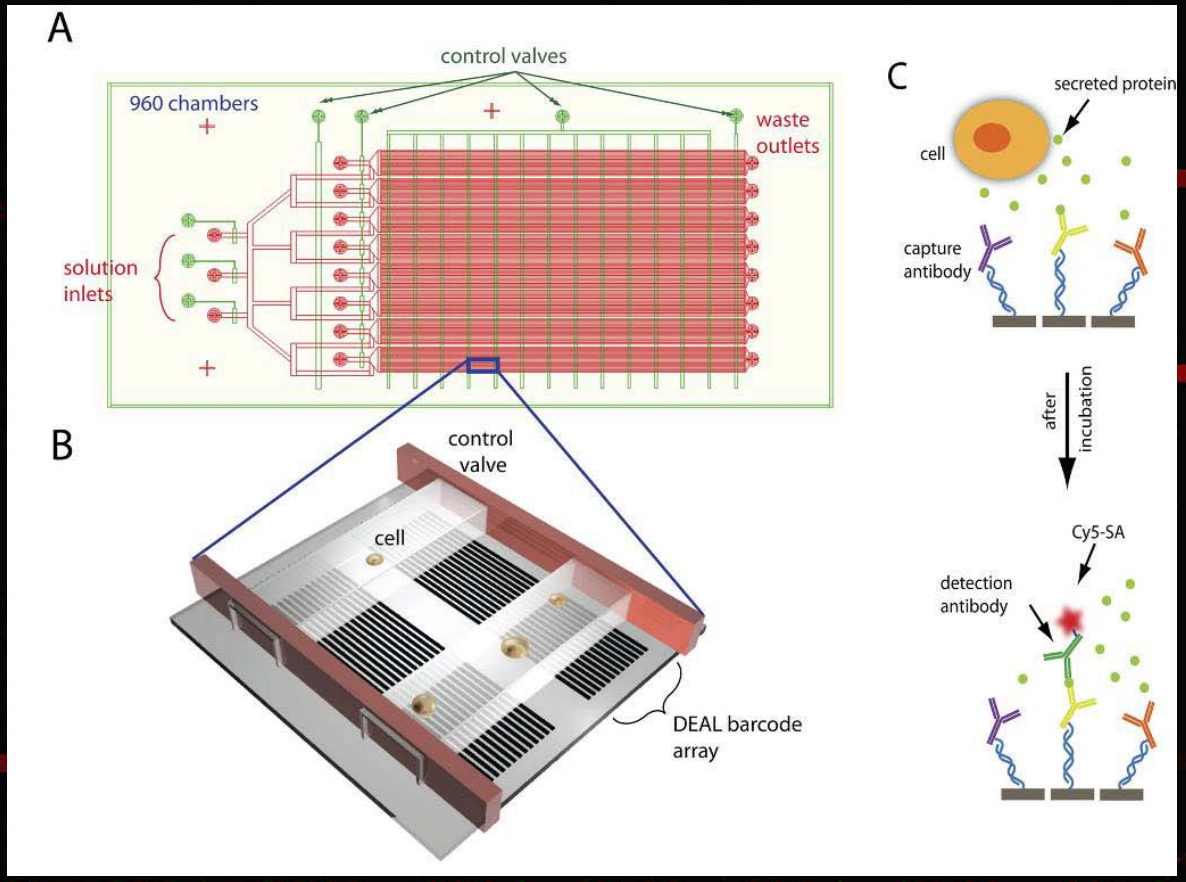
put a miniaturized antibody chip into that same chamber to assay for lots of chambers

repeat over chip surface



etc.

ChemPhysChem 2010 (molecular patterning for these chips)
Biophys J 2011 (macrophage secretome, information theory)
Nature Medicine, 2011 (applied to melanoma immunotherapy patients)

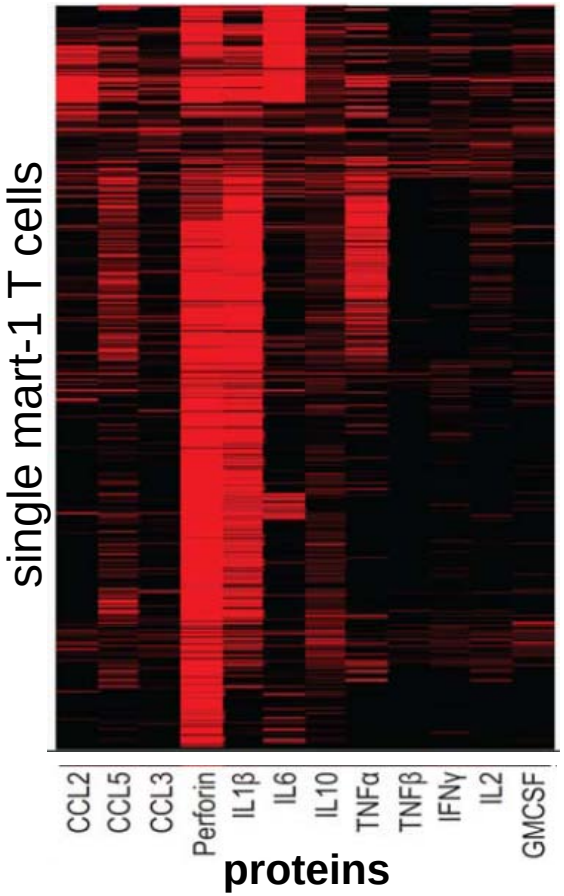


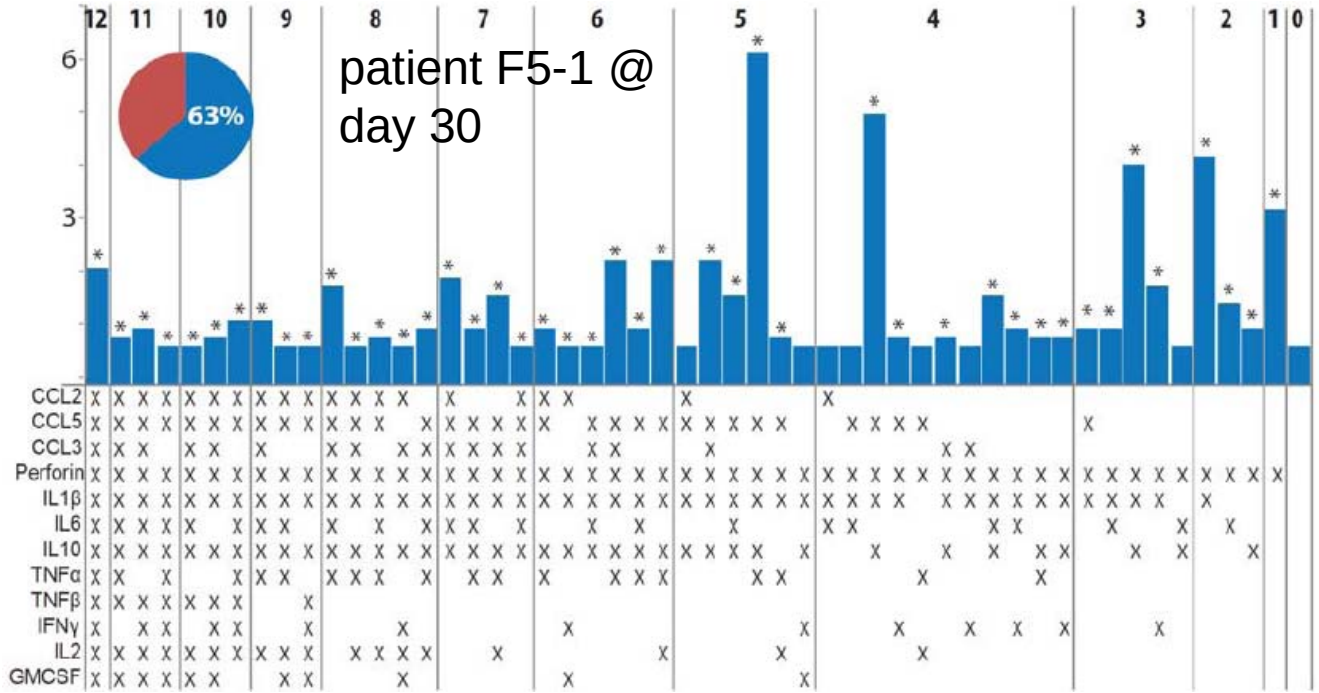
one single experiment
20 functional proteins measured from 1 T-cell

Nat. Med. 2011

a small subset of one data set

Single Cell Proteomics Reveals High Functional Heterogeneity of MART-1 CTLs that are 90% Homogeneous by Phenotyping





sample	# functional subsets in top 60% of population	avg # of functions per cell
Patient CD3+Mart1+	45	5.3
healthy donor #1	17	1.3
healthy donor #81	6	1.3
healthy donor #6	4	.36

Technology in current use in immunotherapy trials on late stage melanoma cancer patients

Nature Med. 2011

Conclusions

- Cancer Centers can play crucial roles in the translation of new therapeutics/diagnostics to patients.
- Cancer Center researchers can help to define fundamental questions of cancer biology that the physical scientists can address.
- The advent of genomic and other “omic” technologies creates challenges/opportunities to address issues related to metastatic lesions as well as “cancer stem cell” and “clonal evolution hypotheses”.

NCI Provocative Questions

PQ - 16

How do we determine the clinical significance of finding cells from a primary tumor at another site?

Feasibility: New experimental methods allow sensitive techniques for detecting and characterizing small numbers of tumor cells at secondary sites, and improved animal models of cancer have created opportunities for expanding our knowledge of disseminated cells and refining our lexicon for classifying them. **For instance, recent advances in DNA sequencing enable the generation of phylogenetic trees of tumor cell populations to determine their clonal relationships and evolutionary distance from each other, and from portions of the primary tumor that are at different stages of progression**. With these new tools, it may now be possible to define the malignant potential of disseminated cells.

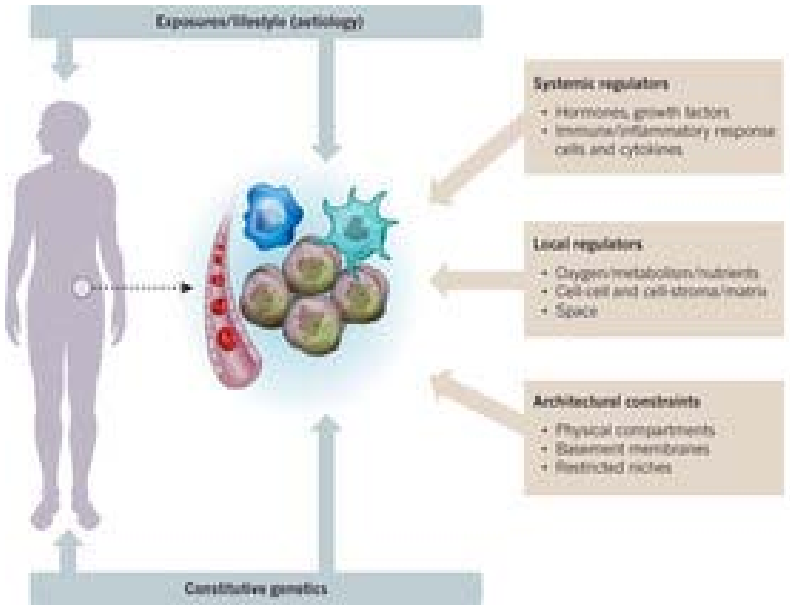
Implications of success: Such analyses could enhance our understanding of the mechanisms that account for either a lack of oncogenicity or malignant behavior of tumor cells at a secondary site, as well as improve our ability to predict the biological behavior of tumor cells found at those sites. This information would give clinicians a clearer picture of when intervention is needed and when such tumor cells can be safely left alone or followed for potential later action.

NCI Provocative Questions

Clonal evolution in cancer

Mel Greaves & Carlo C. Maley

Nature 481,306–313(19 January 2012)



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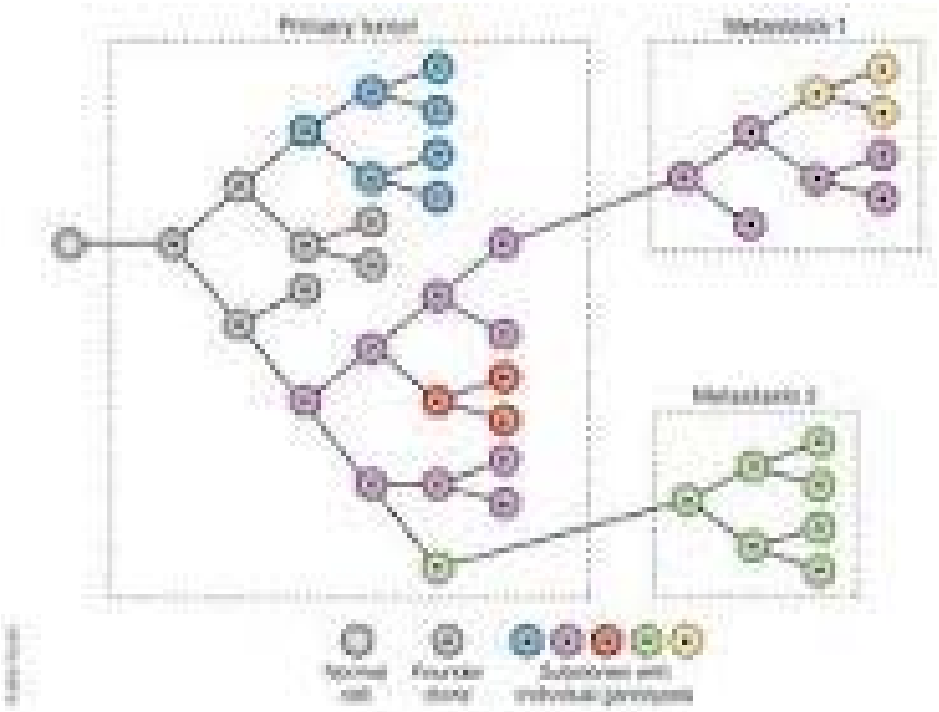

The National Cancer Institute's Office of Cancer Genomics (OCG) aims to advance the understanding of cancer at the molecular level with the ultimate goal of improving clinical outcomes. Through its various innovative and collaborative research programs, OCG fosters cancer genomics research (the systematic analysis of changes in the genomes of tumors) and the rapid translation of the resulting molecular insights into the clinic.