Nanomedicine:

Background Of a Small Field- CNDs and HPGs

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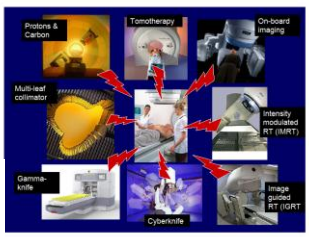
University of British Columbia (UBC)

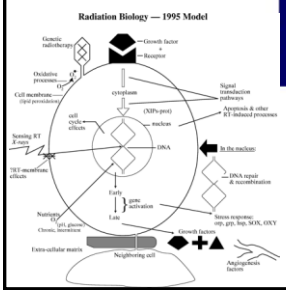
BC Cancer Agency
CARE + RESEARCH

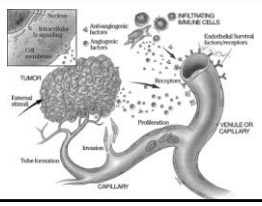
Radiation Oncology in BC

Radiation Oncology

Physical Sciences
Biological Sciences
Medicine



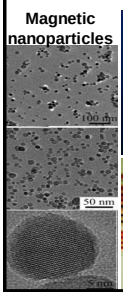


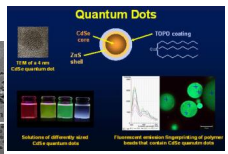


Buckyballs and Carbon Nanotubes

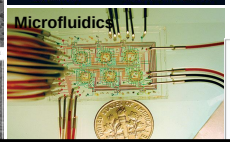
Nanoshells

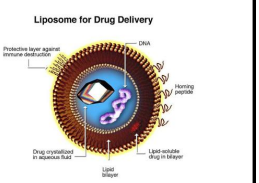
Magnetic nanoparticles





Microfluidics

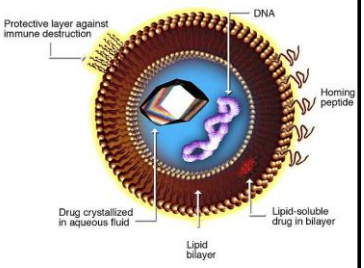




Liposome for Drug Delivery

Liposomes are lipid-based nanoparticles used extensively in the pharmaceutical and cosmetic industries because of their capacity for breaking down inside cells, once their delivery function has been met.

Liposomes were the first engineered nanoparticles used for drug delivery but problems such as their propensity to fuse together in aqueous environments and release their payload, have lead to replacement, or stabilization using newer alternative nanoparticles.



http://en.wikipedia.org/wiki/File:Liposome.jpg
http://biotech.about.com/od/nanotechnology/a/typesnanopart.htm

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Hyperthermia Enables Tumor-specific Nanoparticle Delivery: Effect of Particle Size

1Garheng Kong, Rod D. Braun, and Mark W. Dewhirst2

Department of Biomedical Engineering [G. K.] and Department of Radiation Oncology [R. D. B., M. W. D.], Duke University Medical Center, Durham, North Carolina 27710

ABSTRACT

The efficacy of novel cancer therapeutics has been hampered by the ability to deliver these agents to the tumor at effective concentrations. Liposomes have been used as a method to overcome some delivery issues and, in combination with hyperthermia, have been shown to increase drug delivery to tumors. Particle size has been shown to affect the delivery of liposomes, but it is not known how hyperthermia affects size dependence. This study investigates the effect of hyperthermia (42°C) on the extravasationof different sized nanoparticles (albumin; 100-, 200-, and 400-nm liposomes) from tumor microvasculature in a human tumor (SKOV-3 ovarian carcinoma) xenograft grown in mouse window chambers. In this model (at 34°C), no liposomes were able to extravasate into the tumor interstitium. Hyperthermia enabled liposome extravasation of all sizes. The magnitude of hyperthermia-induced extravasation was inversely proportional to particle size. Thus, at normothermia (34°C), the pore cutoff size for this model was between 7 and 100 nm (e.g., liposomes did not extravasate). At 42°C, the pore cutoff size was increased to >400 nm, allowing all nanoparticles tested to be delivered to the tumor interstitium to some degree. With hyperthermia, the 100-nm liposome experienced the largest relative increase in extravasation from tumor vasculature. Hyperthermia did not enable extravasation of 100-nm liposomes from normal vasculature, potentially allowing for tumor-specific delivery. These experiments indicate that hyperthermia can enable and augment liposomal drug delivery to tumors and potentially help target liposomes specifically to tumors.

[CANCER RESEARCH 60, 4440–4445, August 15, 2000]

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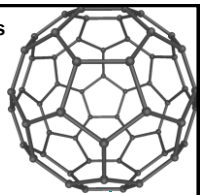
Buckyballs and Carbon Nanotubes

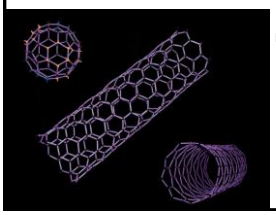
Both members of the fullerene structural class, carbon based, lattice-like, potentially porous molecules.

Buckyballs are spherical in shape

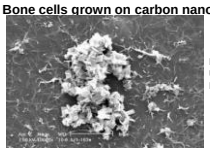
Carbon tubes are cylindrical. The diameter of a carbon tube can be several nm but the length can be much greater, up to several mm, depending on its intended use.



Buckminsterfullerene C60, also known as the buckyball, is the smallest member of the fullerene family.



Bone cells grown on carbon nanotubes



Laura Zanello, University of California, Riverside

http://en.wikipedia.org/wiki/Nanomaterials
http://biotech.about.com/od/nanotechnology/a/typesnanopart.htm

Nanoshells

Also referred to as core-shells, nanoshells are spherical cores of a particular compound surrounded by a shell or outer coating of another, which is a few nanometers thick.

Once the nanoshells enter tumor cells and radiation treatment is applied, they absorb the energy and heat up enough to kill the cancer cells.

Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance

L. R. Hirsch*, R. J. Stafford†, J. A. Bankson†, S. R. Sershen*, B. Rivera‡, R. E. Price‡, J. D. Hazle†, N. J. Halas§, and J. L. West*¶

PNAS November 11, 2003 vol. 100 no. 23 13549–13554

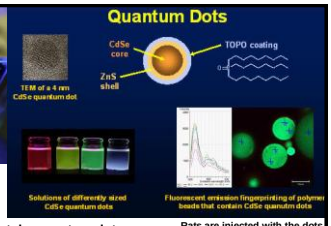
Table 1. Average tumor heating in nanoshell-treated and nanoshell-free controls

	ΔT ± SD	
Mouse	Control	Nanoshell
1	4.7 ± 0.7	39.7 ± 4.7
2	8.4 ± 1.6	60.4 ± 3.4
3	9.1 ± 2.5	44.6 ± 6.0
4	5.9 ± 1.2	32.8 ± 1.2
5	8.7 ± 0.9	28.1 ± 1.0
6	7.6 ± 1.6	32.5 ± 0.7

(AP) Tiny gold nanoshells that contain a bit of mica In their center. A group of Texas researchers injected the nanoshells - so small it would take 5,000 of them to reach the size of a poppy seed - into tumors in mice. They then exposed the tumors to near infrared radiation, heating them enough to kill the cancer but without injuring nearby normal tissue.

http://biotech.about.com

The photoluminescence from different sized quantum dots



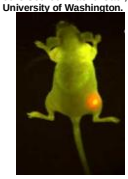
Quantum Dots: Also known as nanocrystals, quantum dots are nanosized semiconductors that, depending on their size, can emit light in all colours of the rainbow.

These nanostructures confine conduction band electrons, valence band holes, or excitons in all three spacial directions.

Examples of quantum dots are semiconductor nanocrystals and core-shell nanocrystals, where there is an interface between different semiconductor materials.

They have been applied in biotechnology for cell labelling and imaging, particularly in cancer imaging studies.

Rats are injected with the dots which find their way to cancer cells.Source: Xiaohu Gao , University of Washington.



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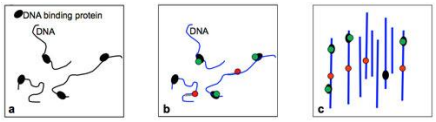
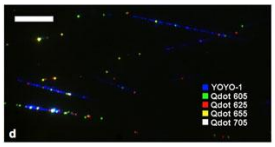
http://biotech.about.com/od/nanotechnology/a/typesnanopart.htm

Quantum dots light up individual DNA binding proteins



DNA-binding proteins

Transcription factors
Various polymerases
Nucleases
Histones



Experimental steps for mapping DNA binding proteins.
a) Crosslinking DNA-binding proteins (black) to DNA
b) Staining DNA (blue), quantum dot labeling of bound proteins (green), and labeling of specific reference sequences on DNA with quantum dots (red).
c) Complexes are aligned on a glass coverslip and imaged by a fluorescence microscope. Image analysis provides information on protein location.
d) Pseudo color image of RNAP-biotin crosslinked to aligned DNA and bound to streptavidin quantum dots of 4 different colors (Scale-bar 10 μm). (Image: Dr. Ebenstein, UCLA)

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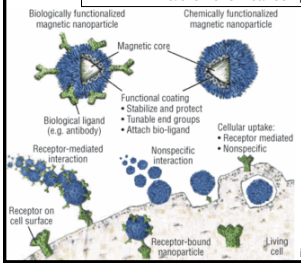
http://www.kusoz.com/blog/
Nano Letters ("Lighting Up Individual DNA Binding Proteins with Quantum Dots"

Magnetic nanoparticles

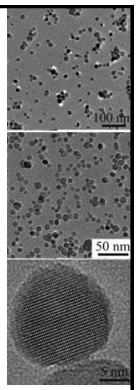
Class of nanoparticle which can be manipulated using magnetic fields

Commonly consist of magnetic elements such as
iron
nickel
cobalt
& their chemical compounds



images.pennnet.com

Hyperthermia
Another interesting therapy is based on the ability of MNPs to be heated when a time-varying magnetic field is applied.



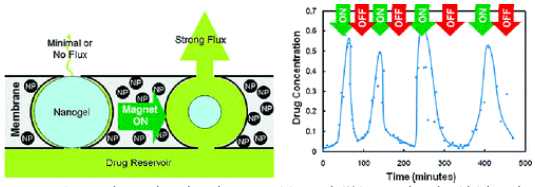
TEM of 15nm Fe3O4 magnetic nano particles

A Magnetically Triggered Composite Membrane for On-Demand Drug Delivery

Todd Hoare†, Jesus Santamaria‡§, Gerardo F. Goya§, Silvia Irusta‡§, Debora Lin., Samantha Lau., Robert Padera., Robert Langer, and Daniel S. Kohane†*

McMaster University, Hamilton, Ontario; University of Zaragoza, Zaragoza, Spain, Harvard Medical School, MA

Nano Lett., 2009, 9 (10), pp 3651–3657



Nanocomposite membranes based on thermosensitive, poly(*N*-isopropylacrylamide)-based nanogels and magnetite nanoparticles have been designed to achieve "on-demand" drug delivery upon the application of an oscillating magnetic field. On−off release of sodium fluorescein over multiple magnetic cycles has been successfully demonstrated using prototype membrane-based devices. The total drug dose delivered was directly proportional to the duration of the "on" pulse. The membranes were noncytotoxic, were biocompatible, and retained their switchable flux properties after 45 days of subcutaneous implantation.

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Microfluidics

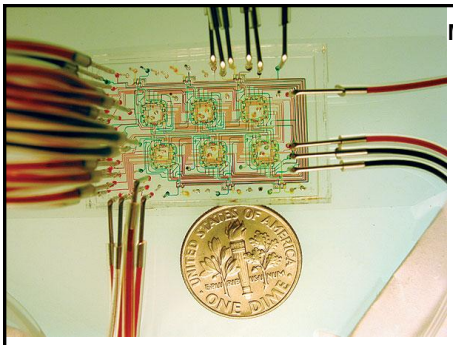

FIGURE 1. A microfluidic chemostat.
From the following article:
The origins and the future of microfluidics
George M. Whitesides
***Nature* 442, 368-373(27 July 2006)**
doi:10.1038/nature05058

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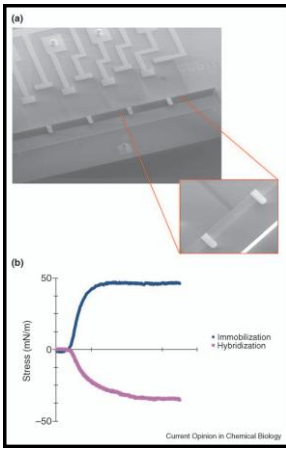
Microfluidic devices — here, a microfluidic chemostat used to study the growth of microbial populations — now routinely incorporate intricate plumbing. This device includes a high density of pneumatic valves. The colours are dyes introduced to trace the channels. (Image reproduced, with permission, from ref. 65.)

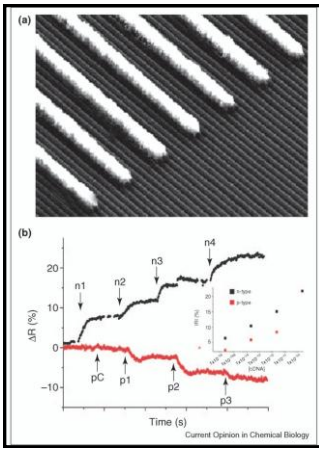
Cantilevers



Nanomechanical detection of biological molecules

Nanocantilevers for ssDNA detection. (a) An array of piezoresistive cantilevers in a fluidic well (Cantion Inc.). The cantilevers are 120 microns long and are separated by 470 microns. (b) Cantilever surface stress variation as a function of ssDNA probe (20-mers) immobilization and hybridization of fully complementary 20-mers using a piezoresistive cantilever array (taken with a reference cantilever). Thiol-modified ssDNA probes (20-mers) were immobilized on one side of a cantilever with a vacuum-deposited gold layer of 40 nm thickness

Mark Ming-Cheng Cheng, et al., Current Opinion in Chemical Biology 2006, 10:11–19



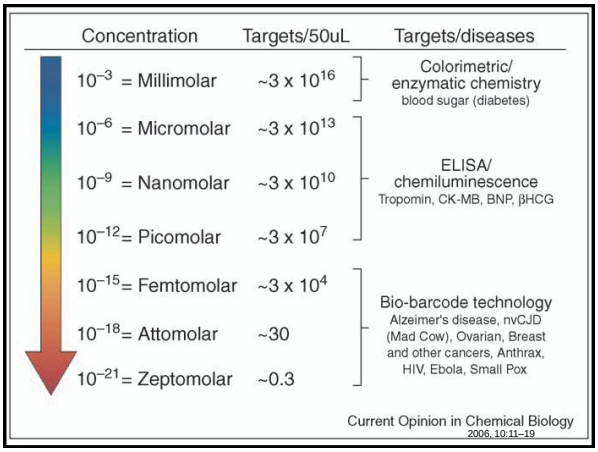
Nanowires

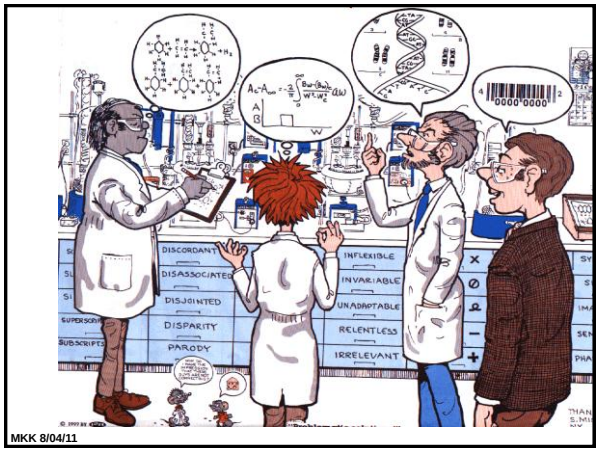
Label-free electronic sensors of genes and proteins

A change in chemical potential accompanying a target/analyte binding event, such as DNA hybridization, can act as a field effect gate upon the nanowire, thereby changing its conductance.

One compelling advantage of nanowire sensors is that the number and density of the sensor elements is limited only by the ability to electronically address individual nanowires. Very dense nanowire sensor circuits may be addressed. Thus, ***large-scale circuits can, in principle, be constructed within very small (microfluidics) environments, thereby enabling measurements of large numbers of different genes and proteins from very small tissue samples, or even single cells.***

Mark Ming-Cheng Cheng, et al., Current Opinion in Chemical Biology 2006, 10:11–19





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An Ideal Smart Therapeutic Nanodevice

- Targets to Tumor or Stromal Elements (Angiogenic Endothelial Cells) Specifically or Non-specifically
- Has Imaging Capability to Document Presence in Tumor
- Delivers Therapeutic Agents Based on Tumor Characteristics
- Might Use Non-invasive External Trigger to Release Therapeutics
- Documents Response to Therapy
- Identifies Residual Tumor cells

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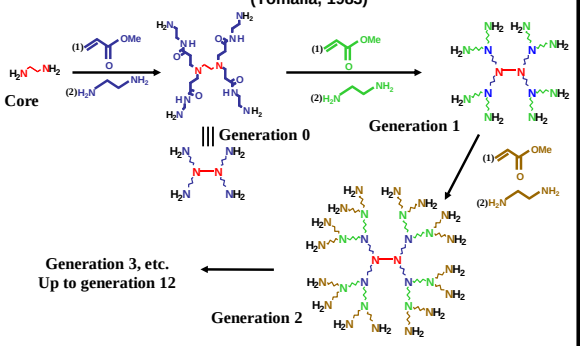
M. Khan,

Poly(amidoamine) PAMAM synthesis

(Tomalia, 1983)



Dendrimers differ from classical polymers by their extraordinary symmetry, high branching, and maximized terminal functionality.

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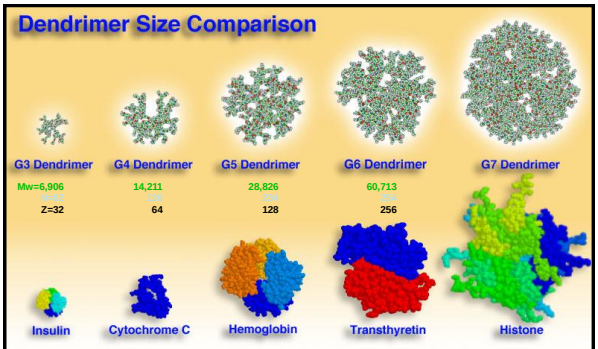
Dendrimer Size Comparison



Synthetic, non-immunogenic, protein-like hybrid particles with tunable properties and in sizes similar to fundamental proteins

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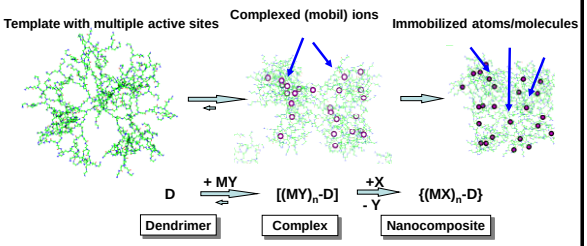
D. Tomalia

Synthesis of Dendrimer Nanocomposites



Dendrimers provide uniform polymeric template molecules in variable sizes and with tunable compatibility. The resulting "soft" composite nanoparticles combine the properties of the encapsulated inorganic matter and the biofriendly macromolecule

Balogh, Swanson, Spindler, Tomalia, *Proc. ACS PMSE*, **1997**, *77*, 118
Balogh and Tomalia: "Nanocomposites of Dendritic Polymers" **US 6,664,315 B2**, (2003), **US 6,475,994** (2002), Balogh,, et al., "Dendrimer-based Nanoscopic Sponges and Metal Composites" **US 5,938,934** (1999).

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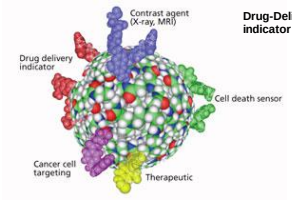
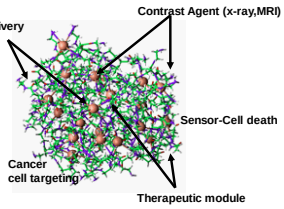
Possible Multifunctional Architectures Based on Dendrimers

Dendrimer



Functional termini are covalently attached to the dendrimer - a tough synthetic task

Composite Nanodevice



The composite nanodevice carries the therapeutic and/or other functions in its interior - a simple approach

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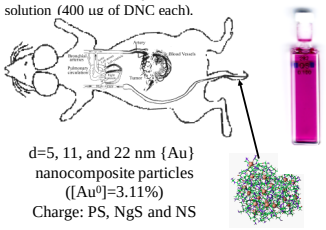
Biodistribution Studies

First task is to know the biodistribution of the host as f(size,charge)

B16F10 melanoma cells (or MatLyLu) were grown on the dorsal surface of a mouse C57Bl6/J (or athymic nude) mice. The mouse was then injected via tail vein with the nanocomposite solution (400 ug of DNC each).



d=5, 11, and 22 nm {Au} nanocomposite particles
([Au^0]=3.11%)
Charge: PS, NgS and NS

http://www.braintreesci.com/metabolic.htm

L.Balogh……M K. Khan., Nanomedicine 2007

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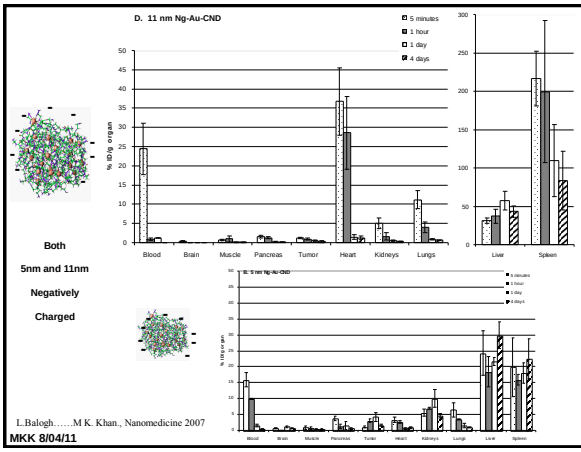

L.Balogh……M K. Khan., Nanomedicine 2007

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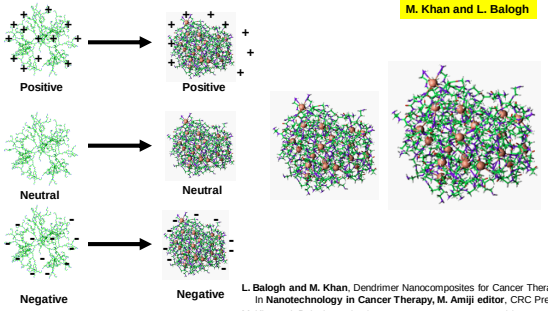
Size, Charge and Other Factors Effect Interaction of Nanoparticles with Complex Biologic Systems

DOD- DAMD17-03-1-0018
M. Khan and L. Balogh



L. Balogh and M. Khan, Dendrimer Nanocomposites for Cancer Therapy, In **Nanotechnology in Cancer Therapy, M. Amiji editor**, CRC Press

M. Khan….L Balogh, *Technol Cancer Res Treat.* 2005 Dec;4(6):603-13

L.Balogh……M K. Khan., Nanomedicine 2007

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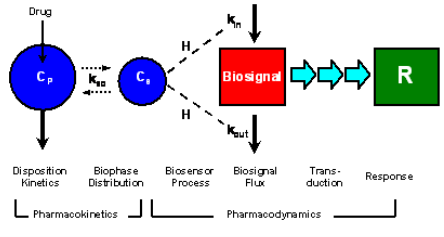

Fig. B3. Basic components of pharmacodynamic models.[35]

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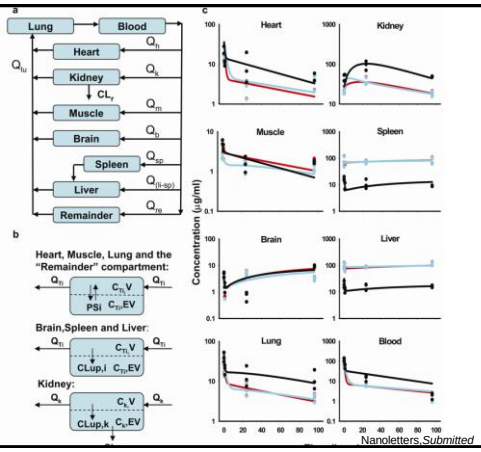

Nanoletters,*Submitted*

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Toxicity Assessment

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In Vitro Toxicity Analysis
- **Tumor Cell and Normal Cells**

In Vivo Toxicity Analysis (Long and Short-term)
- **Clinical toxicity tables**
- **Weight measures**
- **Serum Analysis**
- **Histochemical tissue analysis**
- **Inflammation markers**
- **Immune reactions**

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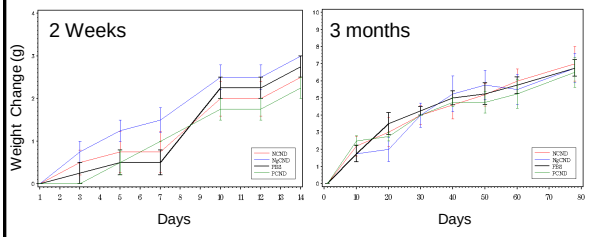
5 nm {Au} Composite Nanodevices Shows No Clinical Toxicity



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Submitted to Nanomedicine

In Vivo – Serum Analysis {Au} Composite Nanodevices

Routine CBC
(Complete Blood Cell Count)

WBC	White Blood Cells
RBC	Red Blood Cells
HGB	Hemoglobin
HCT	Hematocrit
PLT	Platelet Count

Routine Differential

White Blood Cells
Neutrophils
Monocytes
Eosinophils
Basophils

Electrolytes

Na
K
Ca
Phos
Glucose
BUN
Creatinine
Total Protein
Albumin
Cholesterol

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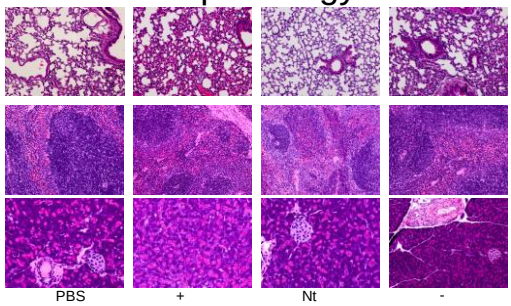
Histopathology



Other Organs:

Esophagus	Thyroid Gland	Brain	Trachea
Stomach	Adrenal gland	Bladder	Thymus
Duodenum	Testicle / Epididymis	Skeletal Muscle	Eye
Small and Large Intestine	Seminal Vesicle	Skin	

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Submitted to Nanomedicine

Inflammation

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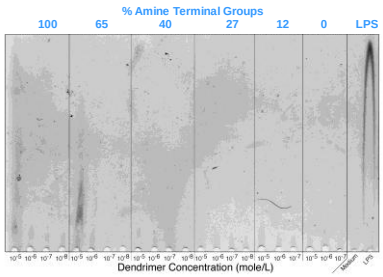
Inflammation: Rocket Immuno-Electrophoresis



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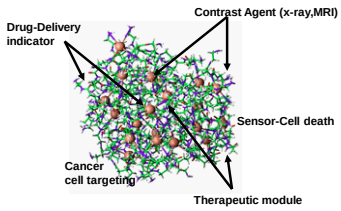
Nanoletters, *Submitted*

Possible Multifunctional Nanodevice Architectures

Nanocomposite



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Can we Modify the Surface of the Nanoparticles to Permit Direct Targeting?

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Folate

Human oral squamous cell carcinoma xenograft in athymic (nu/nu) mice

KB cells are known to overexpress folate binding membrane protein

- Athymic mice were fed folate-free diet for one week before tumor cell inoculation
- Subcutaneous flank inoculations of KB tumor cells
- Growth for Two weeks followed by Dendrimer Injections

Dendrimers tested
- 5 nm Neutral Surface Dendrimer (NSD) = control
- 5 nm Folate conjugated Dendrimer (G5-FA)

KB athymic mouse model

5 mins
2 hour
1 day

4 days
7 days

5 mins
1 day
4 days

Dendrimers tested
- Free Folic Acid (dihydrate) IV injected 5 mins before dendrimer injection
- 5 nm Folate conjugated Dendrimer (G5-FA)

Organs & Tissues harvested, processed and counted

Kukowska-Latallo JF et al, *Cancer Res.* 2005 Jun 15;65(12):5317-24

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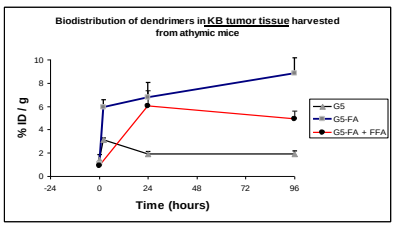
Target matters

Biodistribution of targeted dendrimer nanodevice in KB tumor bearing nu/nu mice

Folate



Cancer Research 2005, 65, 5317-5324

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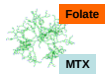
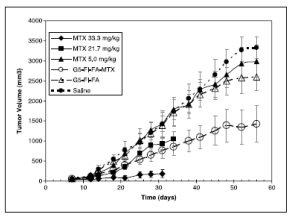
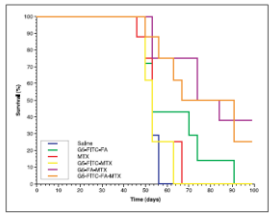
Folate-Targeted Nanoparticle Delivery of Chemotherapy

Decreased Tumor Growth
Increased Survival
Decreased Toxicity







Cancer Res. 2005 Jun 15;65(12):5317-24

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IMAGING

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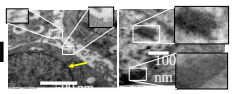
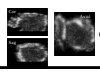
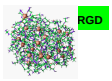
Nanocomposite Molecular Imaging Currently Under Investigation

- •SPECT
- •PET
- •MRI
- •CT
- •TEM
- •X-ray Detector (Intratumoral)







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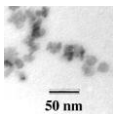
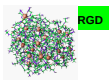
Imaging Nanocomposites Targeting Tumor Microvasculature

RO1 - Mohamed Khan, M.D., Ph.D.
L. Balogh, Ph.D., Co-PI

The objective is to **improve early detection and understanding of cancer** by developing an imaging approach based on radioactive nanocomposite devices (NCDs) allowing **multi-modality imaging**





Target: $\alpha_v\beta_3$ integrin

Methods:
TEM - *Intracellular/Cellular Imaging*
Autoradiography - *Multicellular/Tissue*
SPECT - *Whole Animal Imaging*

^{198}Au and ^{67}Cu containing nanocomposites

Nanocomposites may be directed to the tumor microvasculature by: *differing size and charge*, or
by using *surface moieties that specifically target* the angiogenic tumor microvasculature

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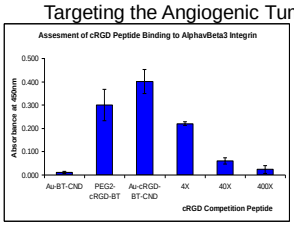
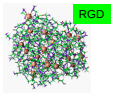
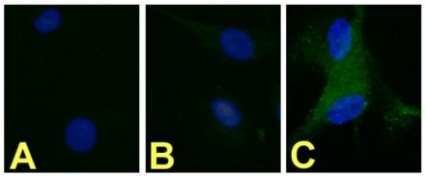
Targeting the Angiogenic Tumor Microvasculature



Binding to $\alpha_v\beta_3$ receptor



Confocal Fluorescence Microscopy of HDMECs Exposed to cRGD-BT-Au-CND



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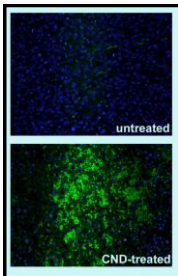
Lesniak et al., Bioconjugate Chemistry (2007) 18 (4): 1148-1154

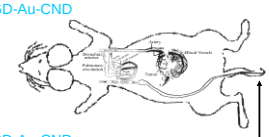
Tumor Microvascular Targeting



PBS Injected

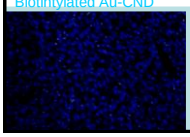
- **Intravascular Injection**
- **MatLyLu Prostate Cancer Mouse Tumor Model System**

Biotintylated 5cRGD-Au-CND

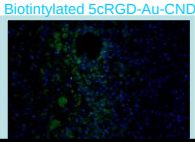


Tail vein injections

Biotintylated Au-CND

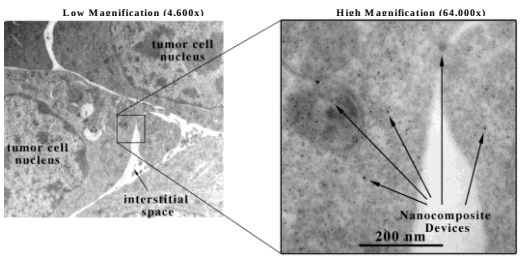


Biotintylated 5cRGD-Au-CND



Kariapper et al., in preparation

Electron Micrograph of *In Vivo* 5 nm Nanocomposite Deposition in Mouse B16 Melanoma Tumor Tissue



Mouse B16 Melanoma: Balogh LP..... Khan M.K., Chimica Oggi (Chemistry today), 2002, 20 (5): 35-40
Human DU145 Prostate CA: Balogh LP.....Khan M.K., PharmaChem, 2003, 2 (4) 94-99

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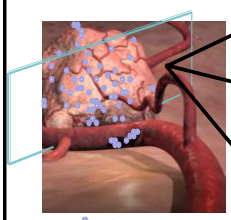
Intratumoral Imaging

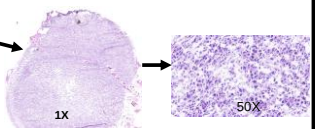


= CND

Radiograph

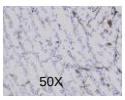
Nanodevice distribution

1X



Haematoxylin & Eosin Staining

Tissue & Cellular Architecture



Immunohistochemistry

Microvasculature

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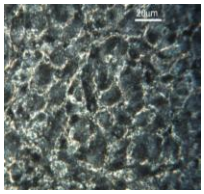
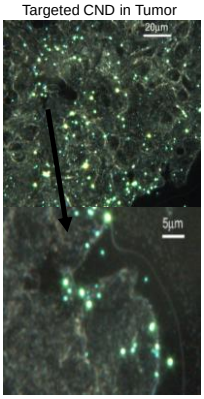
Hyperspectral Imaging of Mouse Prostate Tumor

Untreated Tumor



Targeted CND in Tumor



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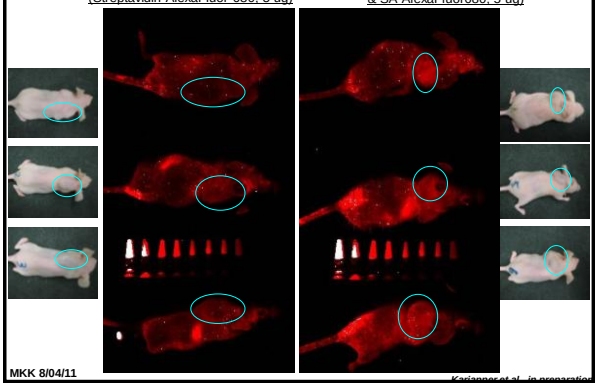
Images post 48-hr-In Vivo, Real-time, Live Mice

Control (Streptavidin-AlexaFluor-680; 5 ug)

LBMK-21 (Au-5cRGD-BT6-CND; 2.5 ug & SA-AlexaFluor680; 5 ug)



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Kadapper et al., in preparation

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Radiation THERAPY and Isotopes

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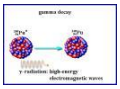
Potential Forms of Radiotherapy:

Gamma rays



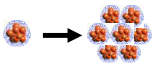
Electrons

Beta particles 

(e-'s generated in nuclear decay)

Protons

Neutrons



Alpha Particles 

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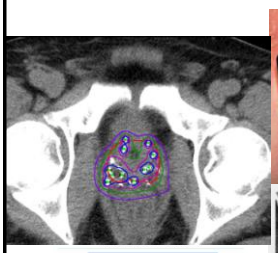
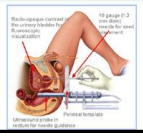
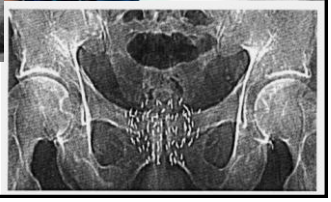
Prostate Brachytherapy







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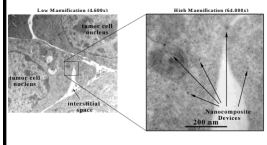
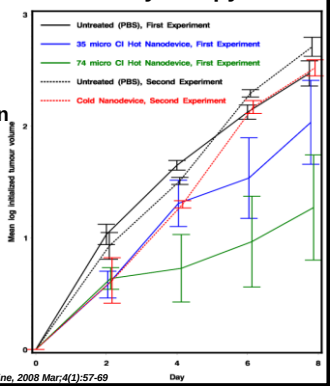
Radioactive Gold Nanodevice Treated Mice - Nanobrachytherapy

50% reduction was achieved in eight days as a result of a single injection

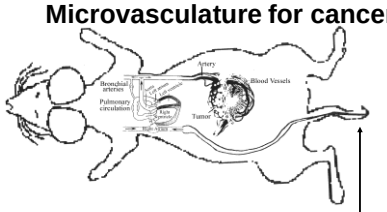
Mice were injected intratumorally (B16 melanoma, C57Bl6/J mice)



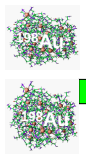


MKK 8/04/11 Khan…..Balogh, *Nanomedicine, 2008 Mar;4(1):57-69*

NanoBrachytherapy and NanoSTART (Systemic Targeted NanoRadiation Therapy): Targeting the Angiogenic Microvasculature for cancer TREATMENT



DOD-
M. Khan and L. Balogh



RGD

Tail vein injections

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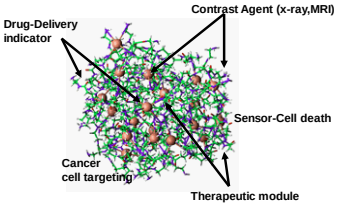
Target = $a_v b_3$ integrin

Possible Multifunctional Nanodevice Architectures

Nanocomposite



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Nanocomposites-Imaging and Therapy

Mohamed Khan, MD, PhD
and
Lajos Balogh, PhD

**Muhammad Taju Kariapper, PhD*
**Venu Kastagopolan, PhD*
Bindu Nair, PhD
**Wojchiech Lesniak, PhD*
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Nuclear Reactor
**Leah Minc, PhD*
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Physics-Imaging/Therapy
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**Andras Sablauer, MD,PhD*
Manju Sharma, PhD
**Dariel Nazereth, PhD*
**Matthew Podgorsak, Ph.D.*

Nuclear Medicine-Imaging
**Michael Haka, MD*

Folate Collaborators
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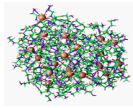
Kimberly Candido, MD
Istvan Majoros, PhD
Balazs Keszler, PhD



Lok Yun Sung
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Christopher Edwards, BA

Toxicity Analysis:
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**K. Toth, MD*

Immunology-Inflammation:
**Heinz Bauman, Ph.D.*

Statistics:
**Alan Hutson, PhD*
Matthew Schipper, PhD

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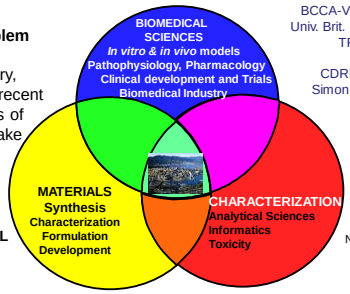
Partnership for Cancer Nanomedicine
Vancouver

- **Medical problem driven;**
- Interdisciplinary,
- Utilizes most recent achievements of science to make



Vancouver Collaborations:
BCCA-VC and BCCRC
Univ. Brit. Columbia (UBC)
TRIUMPH
VGH
CDRD (Industry)
Simon Frasier Univ.

Other Existing Collaborations:
Univ. Buffalo-SUNY
Nuclear Reactor (OSU)
Vet School (Cornell)
Univ. of HI

NANO-DEVICES → **TRANSLATIONAL RESEARCH** → **CLINICAL RESEARCH**

Biophysical Nanotechnology for Cancer Diagnosis, Therapy, and Prevention

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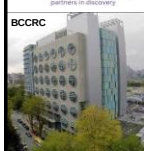
Partnership for Cancer Nanomedicine

BCCA-VC and BCCRC
Univ. Brit. Columbia (UBC)
TRIUMPH
VGH
CDRD (Industry)
Simon Fraser Univ.

Vancouver Centre

BC Cancer Agency
BC CANCER FOUNDATION

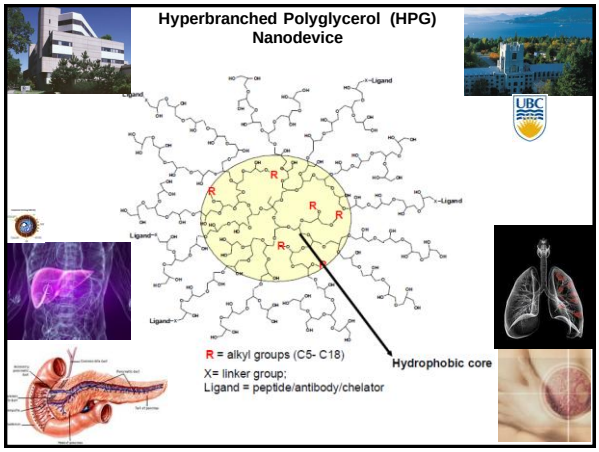
BCCRC

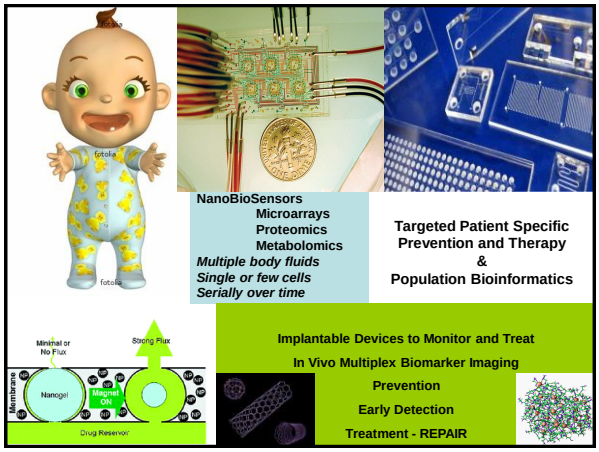


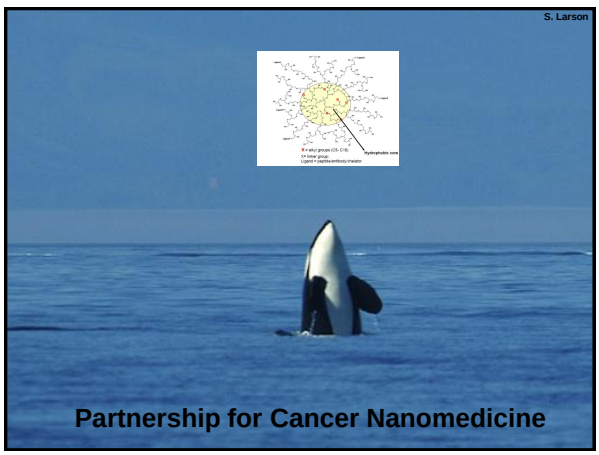
cdrd The Centre for Drug Research and Development

MiNa
Microsystems and Nanotechnology Group

Simon Fraser University


Hyperbranched Polyglycerol (HPG)
Nanodevice
R = alkyl groups (C5- C18)
X= linker group;
Ligand = peptide/antibody/chelator
Hydrophobic core


NanoBioSensors
Microarrays
Proteomics
Metabolomics
Multiple body fluids
Single or few cells
Serially over time
Targeted Patient Specific
Prevention and Therapy
&
Population Bioinformatics
Implantable Devices to Monitor and Treat
In Vivo Multiplex Biomarker Imaging
Prevention
Early Detection
Treatment - REPAIR
Minimal or No Flux
Strong Flux
Nanogel
Magnet ON
Drug Reservoir
Membrane


S. Larson
Partnership for Cancer Nanomedicine

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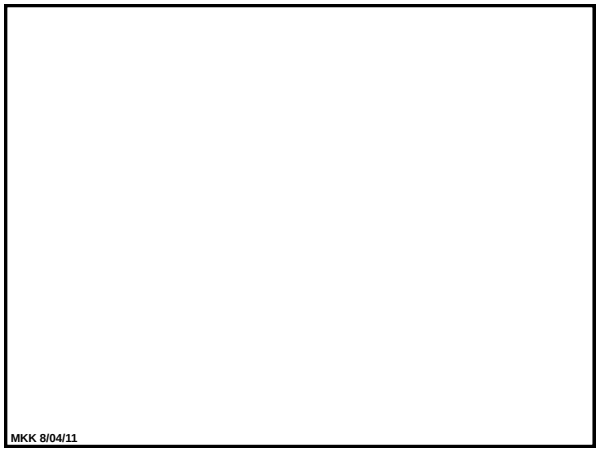
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