# Melding Physics and Biology: Two Novel Concepts

Presented to
The Physics Division Review Committee
(5-6 February 2001)

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## Outline

***Two new directions***

*using magnetic micro/nano particles and SQUID sensors to solve important biological problems.*

- ***'Molecular imaging' and 'Magnetocarcinotherapy' – imaging and therapy with magnetic nanoparticles.***
- ***Massively parallel bioassay with magnetic markers***

***Background & Relevant Technology***
***Basic Concepts***
***Results to date***
***Current Status & Near-Term Plans***

# Our Collaborators

*University of Nebraska, Lincoln*
*University of Nebraska, Omaha Medical Center*
*University of New Mexico*

*B-Division (LANL) – J. Nolan, R. Atcher, et al.*
*C-Division (LANL) – D. Berning*
*SNS-Division (LANL) – W. Reass, et al.*

## Funding

*LANL LDRD; P-Division*



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# Background & Introduction

**Molecular targeting of magnetic nanoparticles for imaging & therapy**

- ***Uses the targeting technologies developed in BNCT, Scintigraphy, etc.***
- ***Combine magnetic nanoparticles with appropriate targeting molecule (antibody, protein, DNA sequence, etc.)***
- ***'Image' localized concentrations of magnetically labeled cells** in vivo **using MEG (SQUID array) technology.***
- ***Energy transfer mechanism to magnetic domains results in therapeutic effect with minimal collateral damage.***

# Detection Concept

## Targeting

Selectively bind *magnetic nanoparticles* to tumor cells

Generally, bind *magnetic nanoparticles* to cell receptors, enabling localization of cell types by the molecular (target-receptor) interactions.

## Detection

SQUID Sensor technology used to detect localized concentrations of magnetic nanoparticles.

## Imaging

Use functional brain imaging methods to 'image' localized concentrations of magnetic nanoparticles. (A method to obtain tomo-

graphic images, as opposed to estimated locations, is being submitted in



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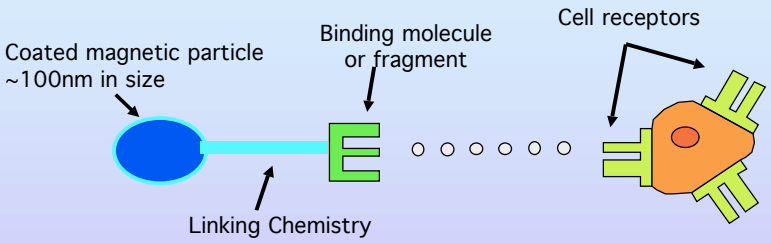
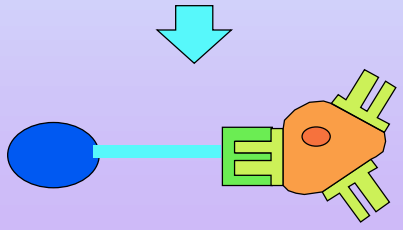



**Targeting Chemistry Concept – Atcher, Berning, et al.**



Magnetic particle bound to cell

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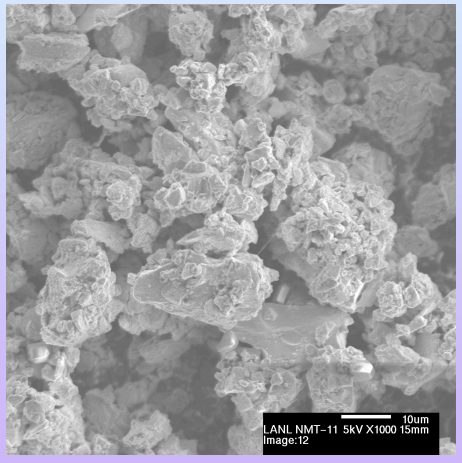
# Magnetic nanoparticle technology




Methods to sort by particle size developed.

Process to produce material with uniform size distribution under development (UNL)

Method to encapsulate particles or groups of particles available (LANL, UNMC, industry)

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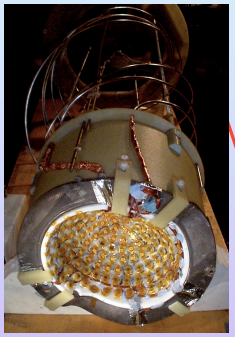
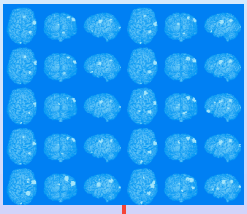
Instrumentation



Modeling & Computation



Visualization


***Localizing*** *concentrations of magnetic particles in vivo uses techniques developed for functional brain mapping*

Concept to obtain true tomographic images currently being reviewed for patent.

R.H. Kraus, Jr., Ph.D. Biophysics Group, Los Alamos National Laboratory email: rkraus@lanl.gov

# Particle/Field Requirements to 'Image'

| Nanoparticles (10nm radius) | N particles | Field @ 5cm | particles/ cell* | grams |
|---|---|---|---|---|
| L + n($Fe_2O_3$) | ~3. x $10^6$ | 1pT | ~1 | 2. x$10^{-11}$ |
| L + n($SmCo_5$) | <$10^6$ | 1pT | ~1 | ~3 x$10^{-11}$ |
| | | | | |
| nanoparticles (100nm radius) | N particles | Field @ 5cm | | grams |
| L + n($Fe_2O_3$) | 2.4x$10^3$ | 1pT | ~$10^{-3}$ | 7.8x$10^{-11}$ |
| L + n($SmCo_5$) | ~10 | 1pT | ~$10^{-5}$ | 3.3x$10^{-13}$ |

* Assumes $1mm^3$ tumor

L = Targeting agent (e.g. monoclonal antibody as per:
del Gratta, et al., Phys. Med. Bio. v40, p671-681 (1995))
Remnant magnetization: ($Fe_2O_3$) <10G (7-9 typical)
($SmCo_5$)>10,000G (11,000-12,000 typical)

**Magnetoencephalography practical detection limit ~10fT**



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# Mechanisms of Thermal Deposition
## (Basic concepts)

**Target:** >25°C rapid temperature increase in <<1 min.

Cell necrosis instantaneous at 25°C above body norm.
Onset of cell necrosis 6-10°C above body norm – collateral damage.
Minimize collateral damage due to thermal diffusion.

$$\dot{Q}_{visc} \sim 8\pi a^3 \omega B_o M \qquad \dot{Q}_{hyst} \sim a^3 \omega B_o^2; \quad \dot{Q}_{ohmic} \sim R(\omega B_o)^2$$

$B_o$ = external applied field ~ 1kG
M = particle magnetization > 10kG
R = tissue resistivity; a = particle radius; $\eta$ = viscosity.

Balance heating in tumor against global tissue heating and thermal diffusion.

# Treatment Approach

## Thermal Energy Deposition – Rapid & Significant

Use 'shaped' RF magnetic field coupled to "supermagnets" to induce thermal energy deposition (*distinct* from traditional hyperthermia using magnetic materials)

## Tumor necrosis, Collateral Damage

- >25°C (45°F) temperature rise is ***immediately*** necrotic to cells
- Rapid thermal deposition minimizes thermal diffusion & associated collateral damage
- phagocytosis removes necrotic tissue over time obviating surgery



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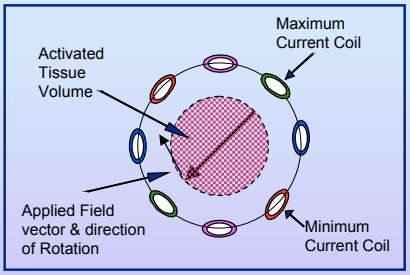
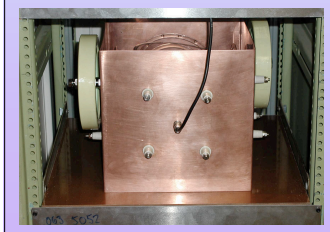
# Therapy array concept & 1st generation hardware



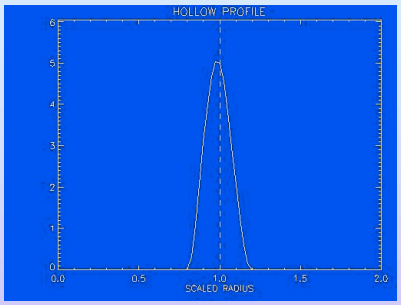



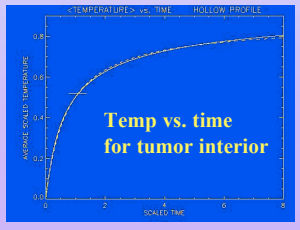
**Phase-coupled power supply and test magnet**

**Capable of 1.8-3MHz >10kW power**

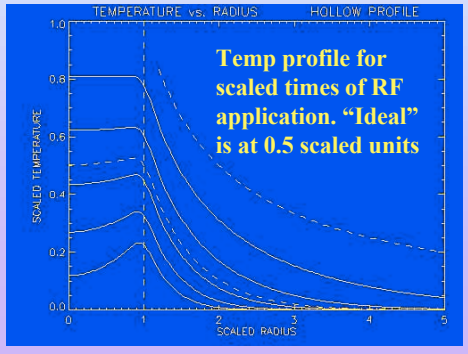
## Modeling the temporal evolution of thermal energy deposition.

Assume: ~1 nanoparticle/cell
Populate only outer layers of tumor




Temp vs. time for tumor interior




Temp profile for scaled times of RF application. "Ideal" is at 0.5 scaled units



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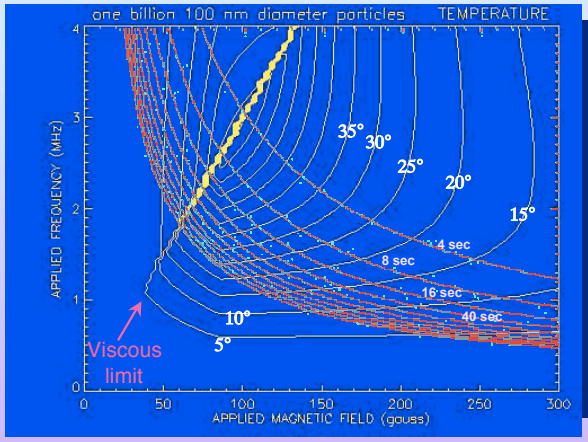


## Modeled thermal energy deposition into tissue using the following assumptions:

- Viscosity = ~water
- Conductivity = 0.5% saline
- Global ΔT = 3 degrees
- Uniform field globally applied
- Spherical nanoparticles
- No "spin-up" needed

* Rotational energy >> covalent bond energy

# MCT Status

- Broad patent allowed
- Magnetic material technology in hand
  - nanoparticle SmCo
- Detection method & 'imaging' methods in hand
  - SQUID array and source localization codes at LANL
  - True tomographic imaging approach conceived recently
- RF PS and magnet in fabrication
  - complete ~March 2002
- Thermal imaging experimental hardware in hand
- Target-binding chemistry options developed
  - Atcher, et al. at LANL



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# MCT Program Development

- Significant interest generated at NIH (NCI, NIBIB)
- Encouraging feedback from DOE/OBER
- Recent interest generated with P&G
- Molecular imaging LDRD/DR and NASA/NCI "Program-Project" grant (Swanson, et al.)
- NIH Grants in preparation – NCI, NIBIB institutes targeted; BRP funding mechanism suggested.

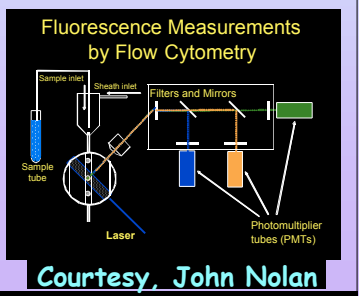
# Bioassay with Magnetic Nanoparticles

## Collaborators

J. Nolen, et al. – LANL NIH Flow Resource
(Builds on existing world-leading expertise in Flow Resource)
D. Leslie-Pelecky, et al. – U. Nebraska, Lincoln

## Funding

LANL LDRD



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# Novel Bioassay Technique - LDRD:

- **Perform bioassay measurements with large number of agents simultaneously (massively parallel).**

- **Magnetic particles are used to "label" different assay agents (magnetic moment).**

- **Assay "bins" are separated …**
  - **By measuring the magnetic moment directly**
  - **Use a spectrometer-like apparatus**

- **~$10^3$ and $10^4$ separable bins are envisioned for range of 100nm to 5□m magnetic particles. First generation system will target ~$10^2$**

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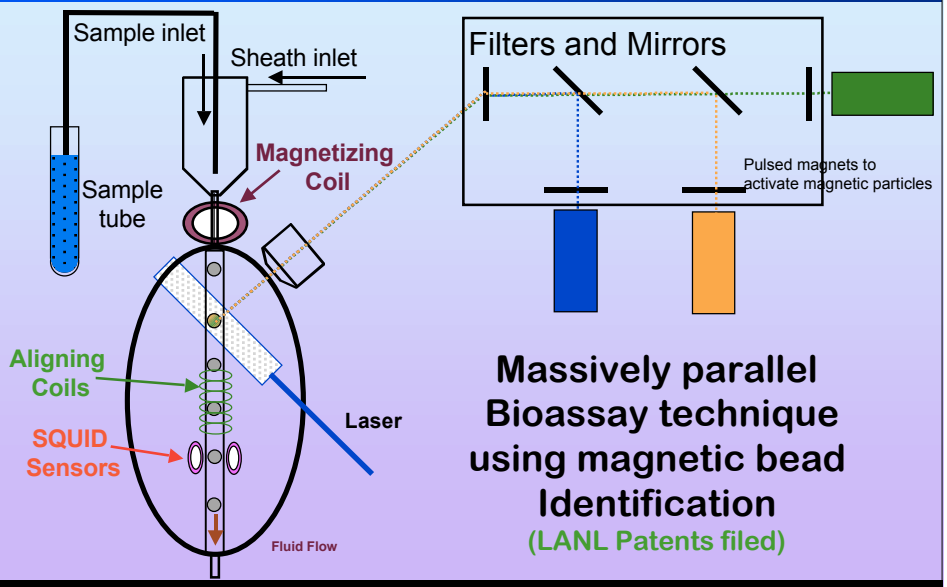


**Massively parallel Bioassay technique using magnetic bead Identification**

(LANL Patents filed)



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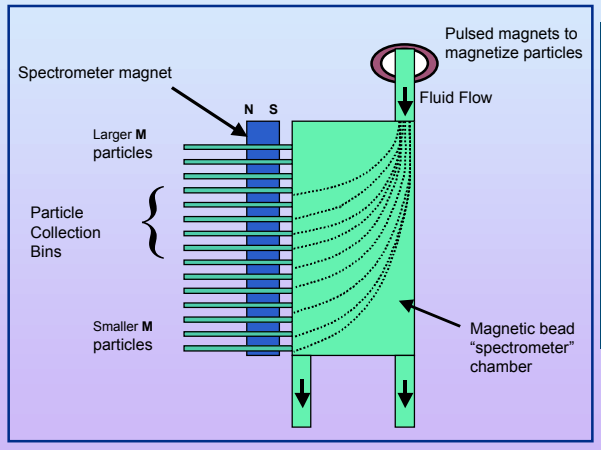
# Magnetic beads enable …

- **Avoiding the need for '*a priori*' stringent QC in bead preparation**
- **Parallel separation and collection of agents**
  - **prepare protein samples for crystallography**
  - **preparation of specifically identified DNA fragments**
  - **collection of antibodies for variety of receptors**
  - **etc.**

**Through application of a 'fluid spectrometer'**

# Bioassay Magnetic bead separation




The magnetic bead spectrometer can readily be coupled to laser fluorescence detection (to monitor chemistry) at flow inlet or any (or all) of the particle collection channels.



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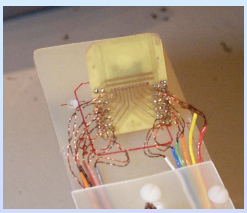
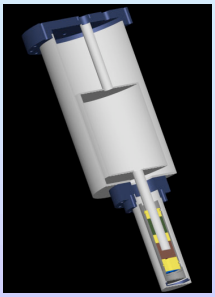
# Bioassay Status:





- Flow system complete.
- Particles encapsulated
  (in variety of polymers).
- Particles detected with SQUID
  (High-$T_c$ Jena array SQUID).
- SQUID dewar in fabrication.
- First generation spectrometer flow chamber fabricated.

**Near term:**
- Magnetic moment S/N and error study
- Coincident chemical (laser fluorescent) interrogation with SQUID

**Future:**
- NIH Grant proposal in conjunction with LANL Flow Resource
- Commercialization (contacts being investigated, CBD ad placed.)