Developing medicines and novel therapeutic agents

Institute for Medicines and Pharmaceutical Sciences

iMed.UL

# Nanomedicine:

## current view, present and future main regulatory challenges

**EMEA, AdHoc Informal Group, April 29th (2009)**


## Rogério Gaspar

rgaspar@ff.ul.pt / http://www.imed.ul.pt

**Nanomedicine & Drug Delivery Systems Group [iMed.UL (Research Institute for Medicines and Pharmaceutical Sciences)]**

http://www.imed.ul.pt/Research/Nanomedicine%20and%20Drug%20Delivery%20Systems.htm

# Current positions

Academic

- Full Professor, Faculty of Pharmacy University of Lisbon (FFUL, Portugal)
- Coordination of Pharmaceutical Technology sector (FFUL)
- Coordinator of Nanomedicine & Drug Delivery Systems research group at the Research Institute for Medicines and Pharmaceutical Sciences (iMed.UL)
- Member of the General Council at the University of Lisbon (Portugal)
- Member of the Medicines Evaluation Committee at INFARMED (Portugal)
- Member of the coordination of $MSc_s$ in
  - Regulatory Affairs,
  - Pharmaceutical Engineering,
  - Advanced Pharmacotechnics
- Doctoral Programme in Bionanotechnology

# Main dates

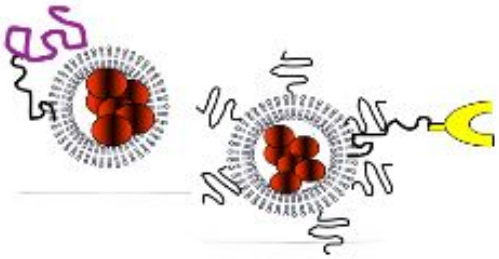
- 1984-2006: University  of Coimbra
- 1995-2002: INFARMED & EMEA (expert, CPMP & QWP member, management board, GMP inspectors group & MRA-Japan); Pharmaceutical Committee and Standing Committee (European Comission); Medicines working group (European Council / EU)
- 2002-2008: Consultant to Pharmaceutical Industry
- 2005-2006: Consultant for training to ASEAN regulatory authorities
- Since 2006: University of Lisbon
- Since 2008: associated to Pharmacies Association (Portugal) as a consultant in issues not related to medicinal products
- Since 2008: back to Medicines Evaluation Committee at INFARMED

# Drug Carriers Unit / Center of Neurosciences and Cell Biology @ University of Coimbra (1993-2000)

- **A few examples of previous research**
  - **Leishmania therapy with polymeric nanoparticles**
    - Gaspar et al, Pharmaceutical Research 9 (6): 782-787 (1992)
  - **Polymeric nanoparticles steric stabilisation: physico-chemical mechanisms**
    - Lourenço et al, International Journal of Pharmaceutics 138: 1-12 (1996)
  - **Nanoparticles for protein delivery**
    - Martins et al, International Journal of Pharmaceutics 142: 75-84 (1996)
  - **Macrophage interactions with polymeric nanoparticles (ROI and NO production)**
    - Cruz et al, Pharmaceutical Research 14 (1): 73-79 (1997)
  - **Nanocapsules and nanoparticles in mechanisms in ocular delivery**
    - Alfar et al, ", II Spanish-Portuguese Congress on Controlled Release, SPLC-CRS, 2-5th February 1997
  - **Polymeric nanoparticles with new contrast agents for MRI**
    - Gameiro , MSc thesis 2004
  - **Lipoplexes and pH sensitive liposomes for gene and antisense oligonucleotide delivery**
    - Simões et al, Gene Therapy , 6, 1798-1807 (1999)
  - **Lentiviral vectors for Huntington's disease**
    - Gene Therapy NFP37 Annual Meeting, Friburg, Switzerland, 6-7 October 2000
  - **Cancer therapy using paclitaxel biodegradable nanoparticles**
    - Fonseca et al, Journal of Controlled Release 83, 273-286 (2002)
  - **Cancer therapy using sterically stabilised targeted liposomes**
    - Moreira et al, Pharmaceutical Research 19, 265-269 (2002)

# Nanopharmaceuticals: overall view of particulate carriers

**Liposomes for targeted drug delivery**



## Clinical Applications

- Cancer
- Intracellular pathogens
- Diseases of the eye
- Imaging agents
- Theranostics

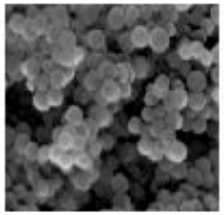
## Lab to Clinic

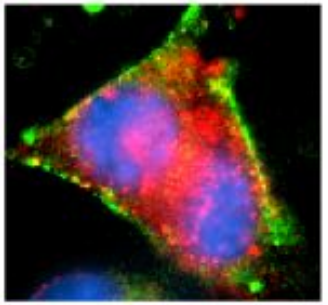
Industrial development
Regulation
Nanosafety

NanoRDR

Lipoplexes for cytosolic delivery

Polymeric nanoparticles For targeted drug and cytosolic delivery e.g. siRNA





## Nanomedicines

- formulation
  - -characterisation
  - -optimisation

## Cellular Mechanisms

- Trafficking
- Cell and membrane interactions (permeabilisation)

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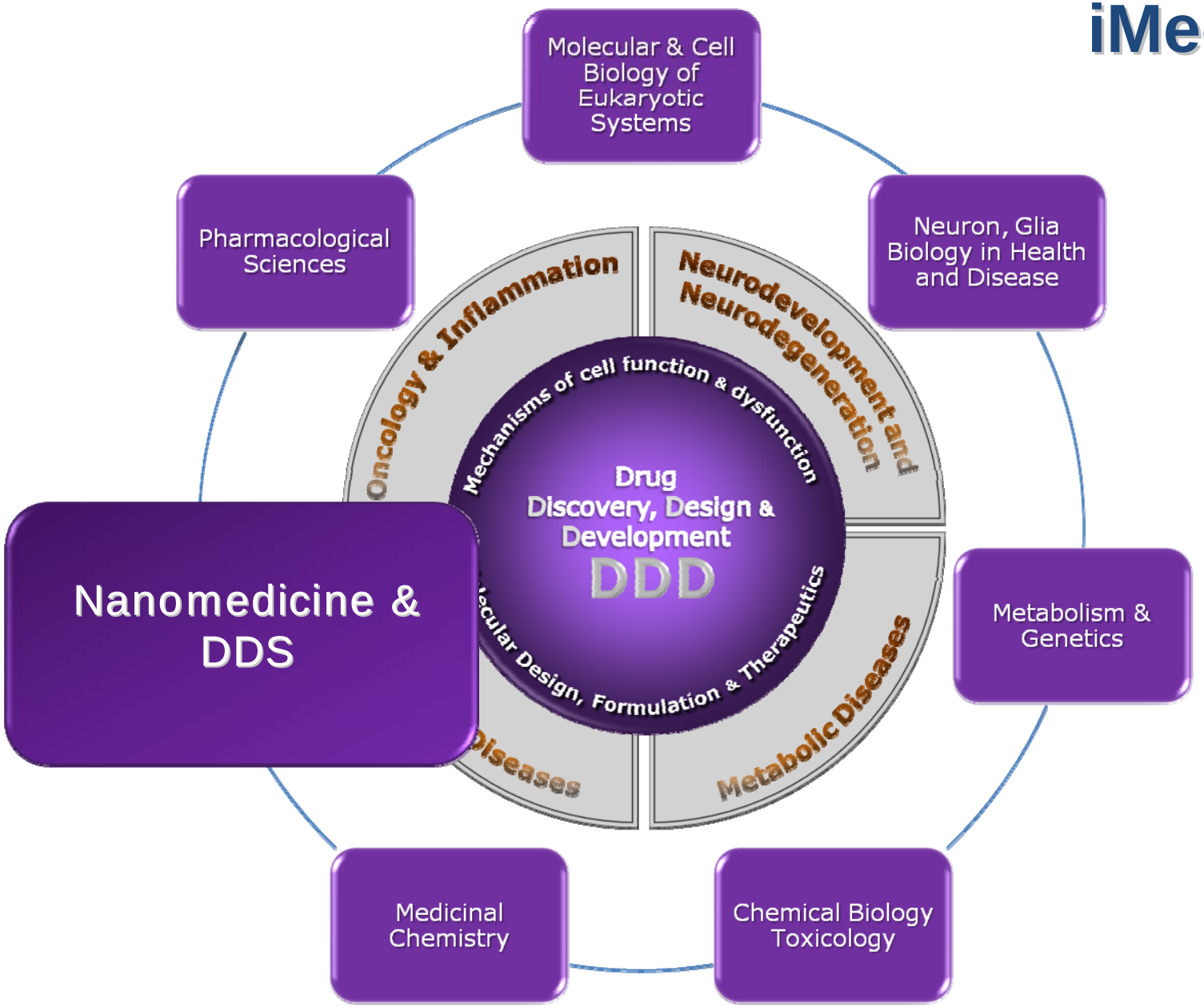
Discovery research | Preclinical develop. | Translational medicine | Clinical develop. | Pharmaco-vigilance

# _isbon approach to 3Ds: iMed.UL



# NANOMEDICINE & Drug Delivery Systems

iMed.UL

Institute for Medicines and Pharmaceutical Sciences

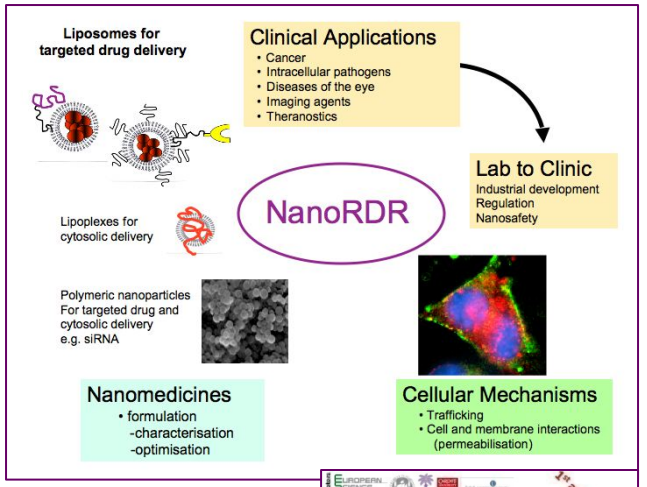

Coordination
**Rogério Gaspar**

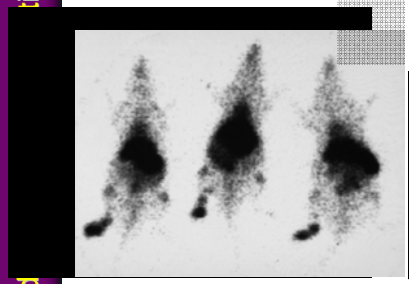
**National & International Colaborations**

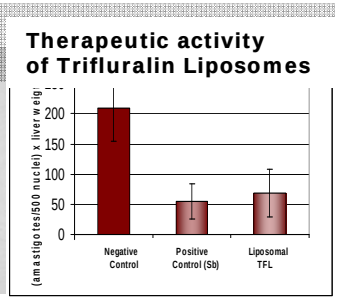
**Projects**

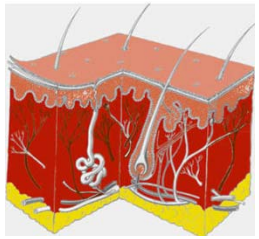
**Basic/Applied Research**

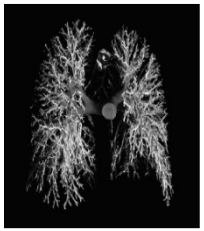
| 1 | 2 | 3 | 4 |
|---|---|---|---|
| **Oncology & Inflamation** | **Infectious Diseases** | **Dermal Research** | **Pulmonary Delivery and macromolecular complexation** |
| **Liposomes** | **Liposomes** | | |
| **Nanoparticles** | **Nanoparticles** | | |
| **Polymeric Ther.** | **Vaccines** | | |

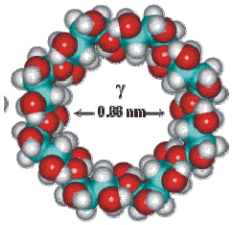


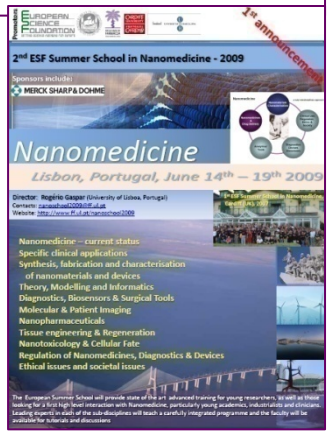









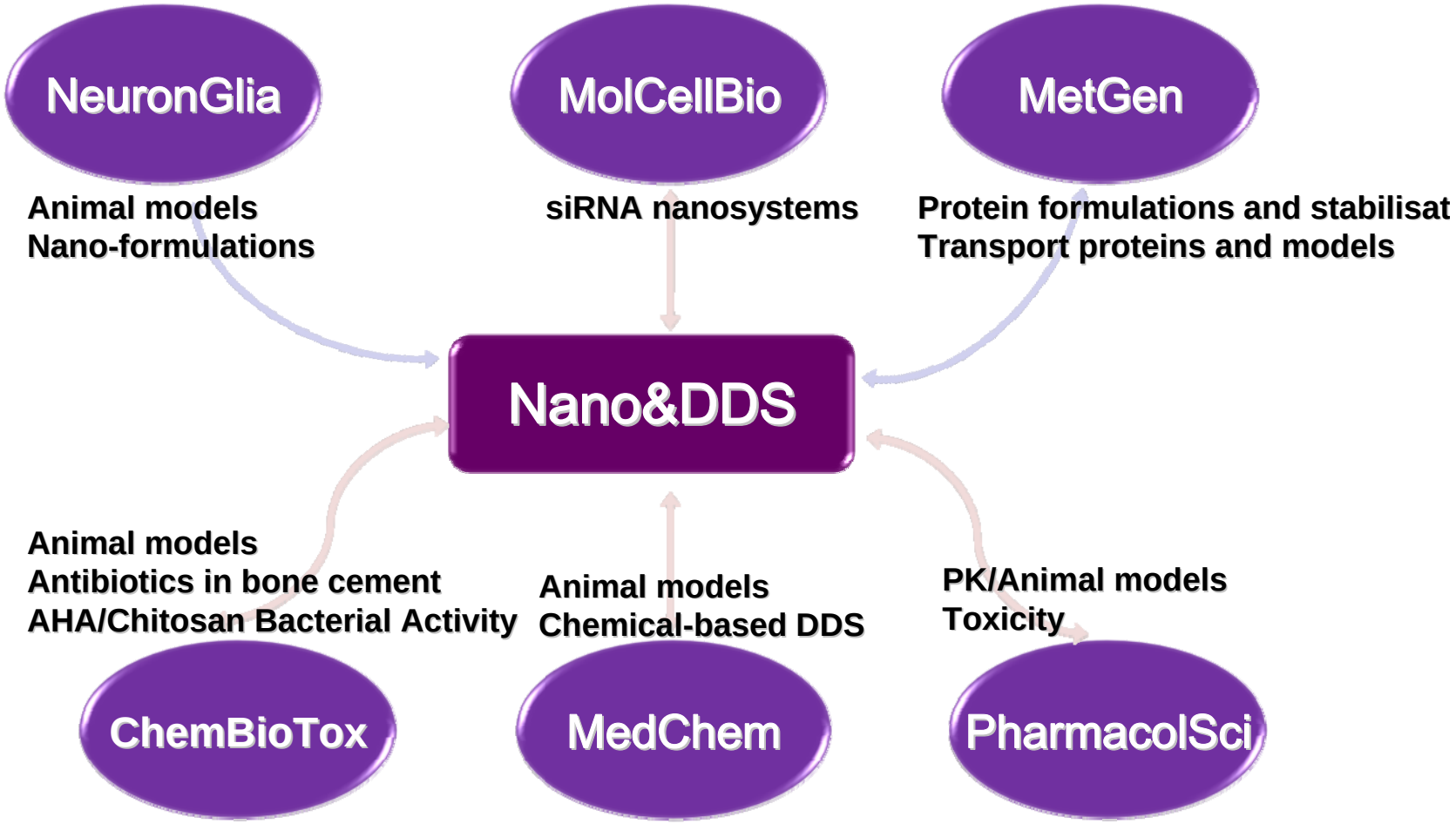




**Team**

| 4 technicians | 7 PhD students | 14 PhD | 2 Research fellows | 2 MSc students |
|---|---|---|---|---|

# Nanomedicine & Drug Delivery Systems

## Internal Network



# Nanomedicine & Drug Delivery Systems

## Main Objectives

**The main overall research objectives currently defined for the area of "Nanomedicine and Drug Delivery Systems":**

**(i)achieving intracellular delivery of nucleic acids and/or combination chemotherapy by the use of nano-systems for cell (cytosolic) specific delivery in oncology and inflammation**

**(ii) attaining effective mucosal vaccination through micro and nano-systems, as well as design of well suited therapeutic systems for intracellular pathogens**

**(iii) developing mechanistic and technological innovative approaches for dermal delivery in different conditions such as cancer and/or autoimmune diseases**

**(iv) using innovative approaches using macromolecular complexation and particle engineering for pulmonary delivery, as well as for other non-parenteral routes.**

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RESEARCH CONFERENCES

ESF-UB Conference in Biomedicine

## Nanomedicine 2008

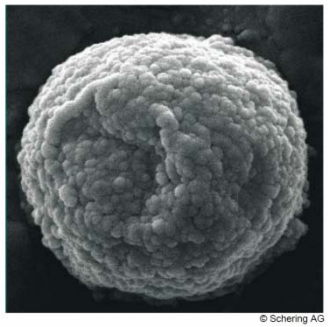
Hotel Eden Roc, Sant Feliu de Guixols • Spain
19-24 September 2008

Chair: **Rogério Gaspar**, University of Lisbon, PT

Co-Chairs:
- **Hans Oberleithner**, Muenster University, DE
- **Mauro Giacca**, ICGEB, Trieste, IT
- **Thomas Kissel**, Marburg University, DE
- **Vicki Stone**, Napier University, UK

www.esf.org/conferences/08218

With support from



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Promotors

## 2nd ESF Summer School in Nanomedicine - 2009

Sponsors include:

# Nanomedicine

Quinta da Marinha, June 12th – 16th 2009

Director: **Rogério Gaspar** (iMed.UL, University of Lisbon, Portugal)
Contacts: nanoschool2009@ff.ul.pt
Website: http://www.ff.ul.pt/nanoschool2009

### Key-note speakers

**Piotr Grodzinski (National Cancer Institute, USA)**
*The N.C.I. Alliance for Nanotechnology in Cancer*

**Kazuonori Kataoka (Univ. Tokyo, Japan)**
*Importance of nanotechnology in healthcare in the 21st century - the Japanese perspective*

**Viola Vogel (ETH/Zurich,Switzerland)**
*Beyond nanoparticles, the next waves of innovation in nanomedicine: A European Perspective*

**Lectures also include the participation of:**
Mauro Ferrari (USA), Alexander Kabanov (USA), Gert Storm (NL), Thomas Kissel (D), Molly Stevens (UK), P. Griffiths (UK),Y. Dufrene (B) Karsten Maeder (D), Mary Baker (UK), Gabriel Lopez-Berenstein (USA) Dusica Maysinger (CN), Wei Yi Ong (SG), N Gadegaard (UK), François Berger (F), Jerome Bibette (F), and others

The European Summer School will provide state of the art advanced training for young researchers, as well as those looking for a first high level interaction with Nanomedicine, particularly young academics, industrialists and clinicians. Leading experts in each of the sub-disciplines will teach a carefully integrated programme and the faculty will be available for tutorials and discussions

### Organising Committee:
Rogério Gaspar (Course Director 2009)
Ruth Duncan (Course Director 2007)
Mauro Giacca (Course Director 2011)

### International Advisory Board:
MJ Alonso (Univ Santiago Compostela)
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R Satchi-Fainaro (Tel Aviv Univ)
M Stevens (Imperial College)
G Storm (Univ Utrecht)
D Thomas (Cardiff Univ)
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MJ Vicent (CIPF, Valencia)
V Vogel (ETH Zurich)
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S Simões (CNC/FFUniv Coimbra)

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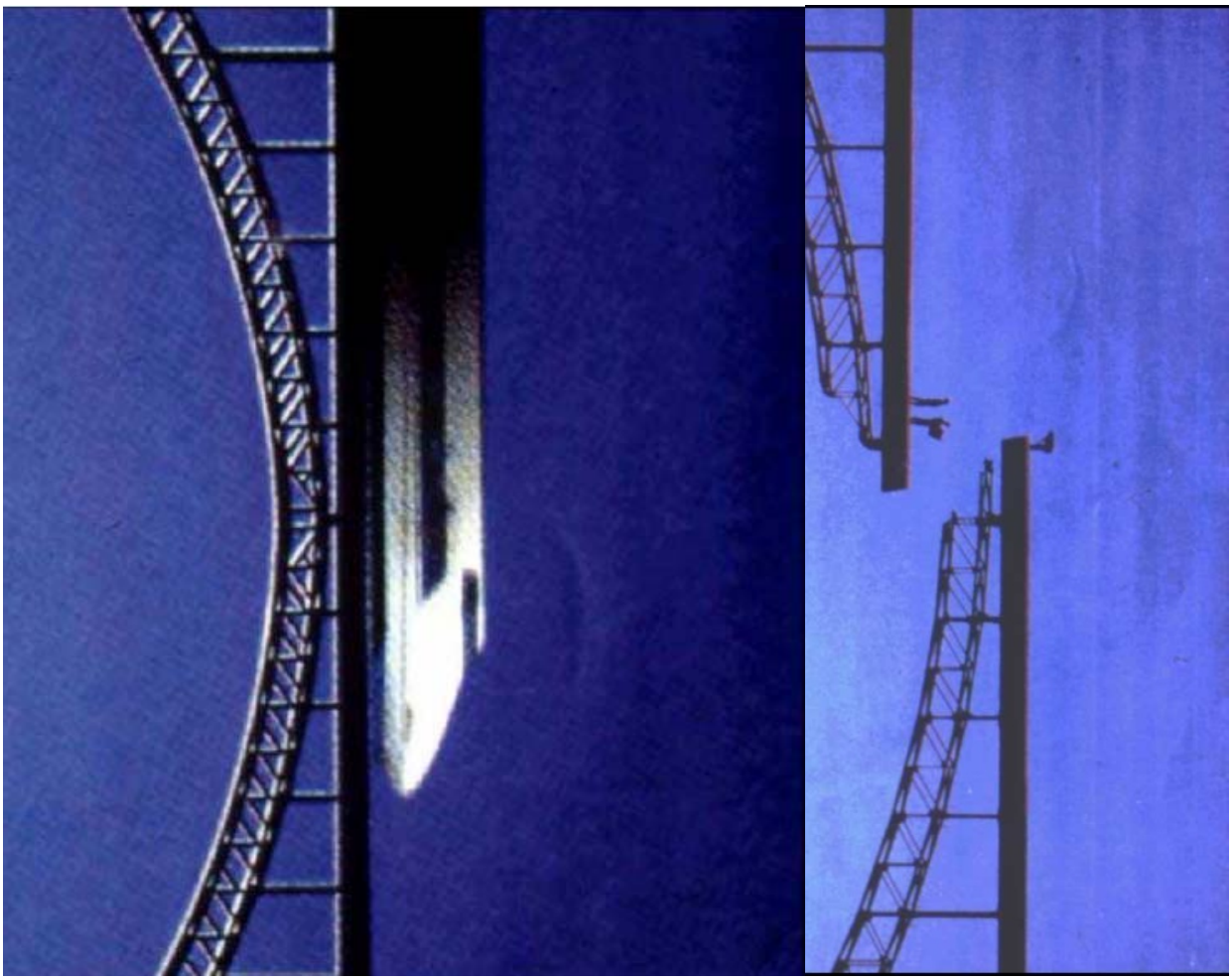
Developing medicines
and novel therapeutic agents



# Current gaps and how to fill them…

**Areas impacted by nanomaterial-containing products**

- Product quality assessment studies
  - **Characterization & Quality control**
  - **Manufacturing**
- Product safety assessment studies
  - **Biodistribution**
    - **Clearance**
    - **Metabolism**
  - **Toxicology**

# Current gaps and how to fill them…

**Characterisation needs**

- Development of appropriate tools and methodologies to
  - **product chemistry and unique characteristics of product (complete formulation)**
  - **quality control measures**
  - **consistent formulations with low batch-to-batch variability**
  - **product quality and performance**

# Current gaps and how to fill them…

**Examples of features to analyse**

- Size
  - **Primary particle size (AFM/PCS/LD)**
  - **Aggregation/agglomeration state**
  - **2D and 3 D distribution (TEM/AFM)**
  - **Particle size distribution**
- Chemical composition
  - **Element identification and distribution**
  - **Crystal form (Diffraction studies)**
  - **Surface composition; surface charge (zeta potential)**
  - **Reactivity**

# Current gaps and how to fill them…

**Current Preclinical Tests for Safety Evaluation of Drugs Include**

- Pharmacology
- Safety pharmacology
- Toxicology (including clinical pathology and histopathologic analysis)
- (A)DME
- Genotoxicity
- Developmental toxicity
- Immunotoxicity
- Carcinogenicity
- Other

# Current gaps and how to fill them…

## Safety considerations

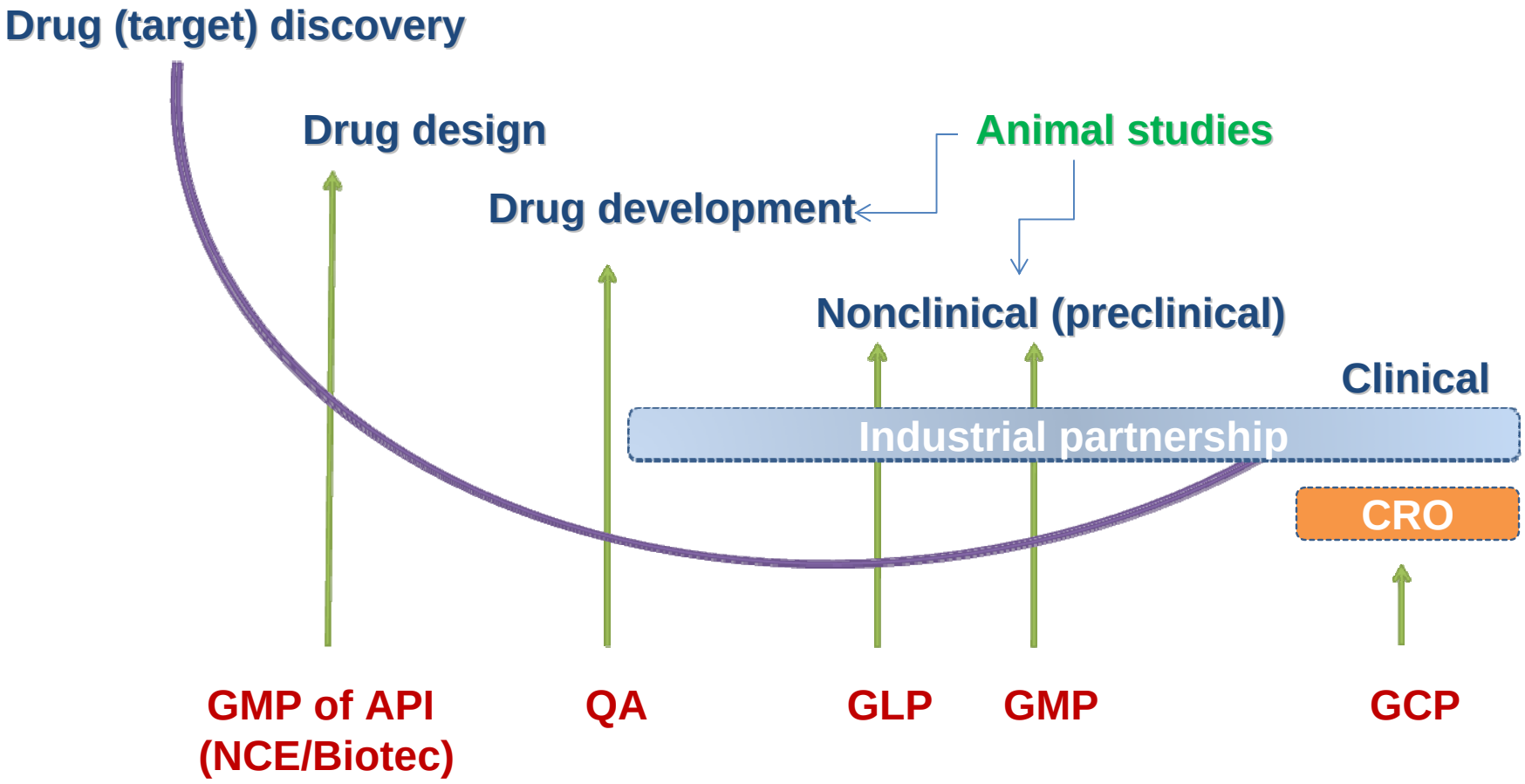
- Are nanopharmaceuticals gaininig access to tissues and cells normally bypassed by larger similar particles?
  - **If so,**
    - **What effects do they have on cellular and tissue functions (transient and/or permanent)?**
    - **How long do they remain there?**
    - **How are they cleared from tissues and blood?**

# Current gaps and how to fill them…

**(A)DME Considerations**

- **What are differences in the (A)DME profile, for nanopharmaceuticals versus larger particles of the same drug?**
  - **Toxicity issues versus biocompatibility of materials**
- Are there methods for measuring levels of nanopharmaceuticals in blood and tissues?
  - Limit of detection, distinction between nanopharmaceuticals and aggregates or between intact nanopharmaceutiacls and metabolized nanopharmaceuticals
  - Accuracy of mass balance studies, for drugs administered at very low levels or targeted products?
- **How is clearance of targeted nanopharmaceuticals accurately assessed?**
  - **Specific methods for assessment of metabolism of materials**
- **How are nanopharmaceuticals appropriately labeled for (A)DME studies?**

# Quality Management Systems and challenges in transfer lab to clinic



# Innovative task force (ITF, EMEA)

**Emerging therapies include:**

- gene therapy products, cell therapy and engineered tissues, new targeted therapies, nanomedicines, novel routes of administration and delivery systems – e.g. ex vivo, by surgical implant.

**Emerging technologies include:**

- new development strategies (e.g. use of genomics or proteomics surrogates), new definitions of target populations in therapeutic fields (e.g. pharmacogenomics), new manufacturing approaches (e.g. use of transgenic plants and animals).

**Borderline therapeutics include:**

- combination of pharmaceuticals and devices, medicinal products borderline to nutrition supplements.

FDA + ALLIANCE *for* NANOHEALTH

# Scientific Workshop:

# FDA/ANH Nanotechnology Initiative

## *March 10-12th, 2008*

**Event Summary:**

*The Alliance for NanoHealth (ANH) and the Food & Drug Administration (FDA) are co-sponsoring a scientific workshop being held in Houston, Texas on March 10-12th, 2008. This workshop, called the FDA-ANH Nanotechnology Initiative Scientific Workshop, is an invitation-only event dedicated to obtaining feedback from stakeholders in an attempt to identify key scientific and translational challenges in nanoengineered medical product development. In this regard, we have assembled ~50 key stakeholders from industry, Federal government, and academia. A main deliverable of this workshop will be the development and publication of a short list of existing translational gaps and a the key elements that will be needed to bridge these gaps. It is hoped that by implementing joint projects, having these key elements, we can work with stakeholders to overcome R&D hurdles, inform regulatory review of nanoengineered biomedical products, and ultimately, benefit patients. The results of the Workshop will be made available in the public domain.*

**The University of Texas M.D. Anderson Cancer Center**
**Frank E. Anderson Conference Hall (R11.11)**
**1515 Holcombe Blvd., Houston, Texas 77005**

## Breakout Session Groups

| | Preclinical | Clinical | Manufacturing |
|---|---|---|---|
| Co-Chair | George Q. Mills, MD, M.B.A. | Mark N. Melkerson | Vicki Colvin, Ph.D. |
| Co-Chair | Abigail Jacobs, Ph.D. | David Feigal, M.D. | Lucinda Buhse, Ph.D. |
| Presenter | Mark N Milton, Ph.D. | Gabriel Lopez-Berestein, M.D. | Neil Desai, Ph.D. |
| Presenter | Martin Philbert, Ph.D. | Daniel C. Sullivan, M.D. | |
| Rapporteur | Paul C. Howard, Ph.D. | Daya Ranamukhaarachchi, Ph.D. | Katherine M Tyner, Ph.D. |
| Rapporteur | Chekesha S. Clingman, Ph.D. | Viju Bhadkamkar | |
| | Chris Anzalone, Ph.D. | Mostafa Analoui, Ph.D. | James V.A. Abbey |
| | Susan Blaney, M.D. | Hugh C. Cannon | May G. Akrawi, Ph.D. |
| | Ferdy Bremmer | Diana Shu-Lian Chow, Ph.D. | Stephen Barry, Ph.D. |
| | Al Lin Chun, Ph.D. | Rabih O. Darouiche, M.D. | R. Steven Conlan, Ph.D. |
| | Jack Coats | Omid C. Farokhzad, M.D. | Dr. Sergio Dompe |
| | Roland A. Fleck | Bambi Grilley | Anthony J. Elam |
| | Rogerio Sa Gaspar, Ph.D. | Placido Grino, M.D. | Dr. Gordon France |
| | Henry A. Havel, Ph.D. | James C. Hamilton, M.D., M.B.A. | Stephen H. Friend, M.D., Ph.D. |
| | Maha Khaled, Ph.D. | June Kaplow, Ph.D. | Randal K. Goodall, Ph.D. |
| | Amit Kulkarni, Ph.D. | Luigi Manzo, M.D. | David G. Gorenstein, PhD |
| | Kathleen Matthews, Ph.D. | Massoud Motamedi, Ph.D. | Tony Huang, Ph.D. |
| | Alexander J. (Sandy) McEwan, MD. | Larry A. Nagahara, Ph.D. | Annette T. Kolodzie, J.D., Ph.D. |
| | Scott E. McNeil, Ph.D. | Nakissa Sadrieh, Ph.D. | J. Donald Payne |
| | Joseph Mlone Ph. D | Jan Simak, Ph.D. | Mark W. Shumbera |
| | Robert Powell, Pharm.D. | Clifford Stephan, Ph.D. | Larry Tamarkin, Ph.D. |
| | Sally Tinkle, Ph.D. | Barbara Trautner, M.D. | Subhas G. Malghan, Ph.D. |
| | Donald A. Tomalia, Ph.D. | | Sean Murdock |
| | | | John Weiner |

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# U.S.A. versus E.U. trends


**FDA Critical Path**

- Biomarkers & disease models
- Clinical trial streamlining
- Bioinformatics
- Manufacturing
- Develop products of urgent public health need (e.g., anthrax Rx)
- At risk populations- pediatrics

**EU Innovative Medicines Initiative**

- Prediction of Safety
- Early indication of Efficacy
- Knowledge Management
- Education & Training

# An agenda for Europe (EMEA) ?

- Integrated discussions (QWP, SWP, Sci.Advice, ITF, experts in nanotechnology)?
  - AdHoc/ Institutional ?
- Need for new set of guidelines?
  - Not necessarily, need better integration in existing regulatory frame
  - “Nano-hype” dangerous and comparable to “Nano-scare”
- Cross-regulatory issues
  - Critical issues in Quality, PK/PD (existing liposomes and nanoparticles versus “generic versions”, fluid micelles versus rigid micelles, “biosimilars” and impact of different pegylation strategies), toxicology of new engineered nanostructures (mostly inorganic but also dendrimers, quantum dots, carbon nanotubes and others), safety in non-clinical studies, biomarkers for cellular pathways and links to events (both safety and efficacy)
- Cross-Atlantic interactions
  - Opportunity for building an European expert group (EMEA) that could interact with existing FDA (and FDA/ANH) initiatives (need for global regulatory response)