Radiolabelling and in vivo imaging to assess regional drug distribution after lung administration

Jordi Llop Roig

jllop@cicbiomagune.es

San Sebastian, March 2017

CIC biomaGUNE

CIC biomaGUNE

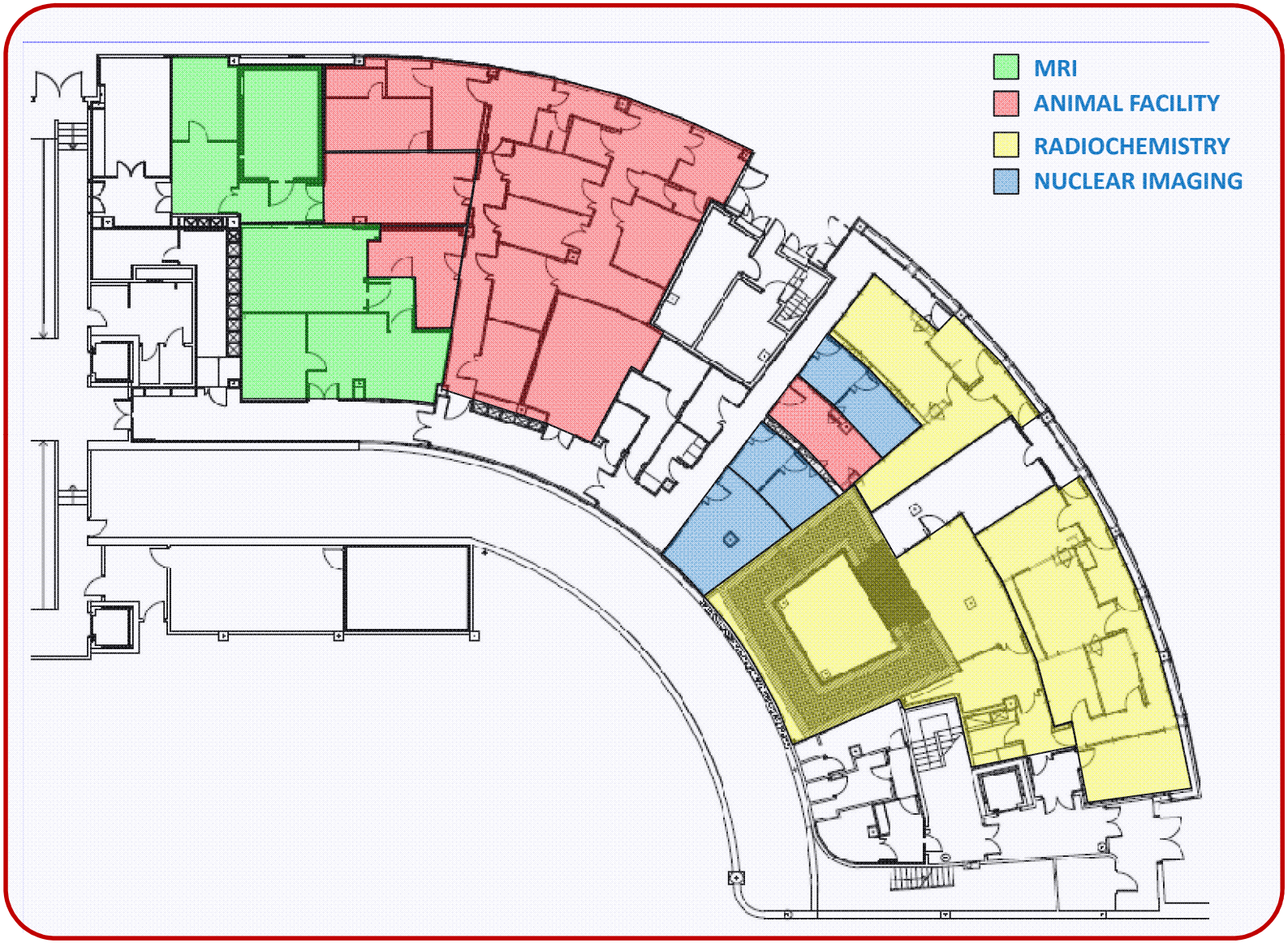
CIC BIOMAGUNE

- BIOFUNCTIONAL NANOMATERIALS
- BIOSURFACES
- MOLECULAR IMAGING UNIT

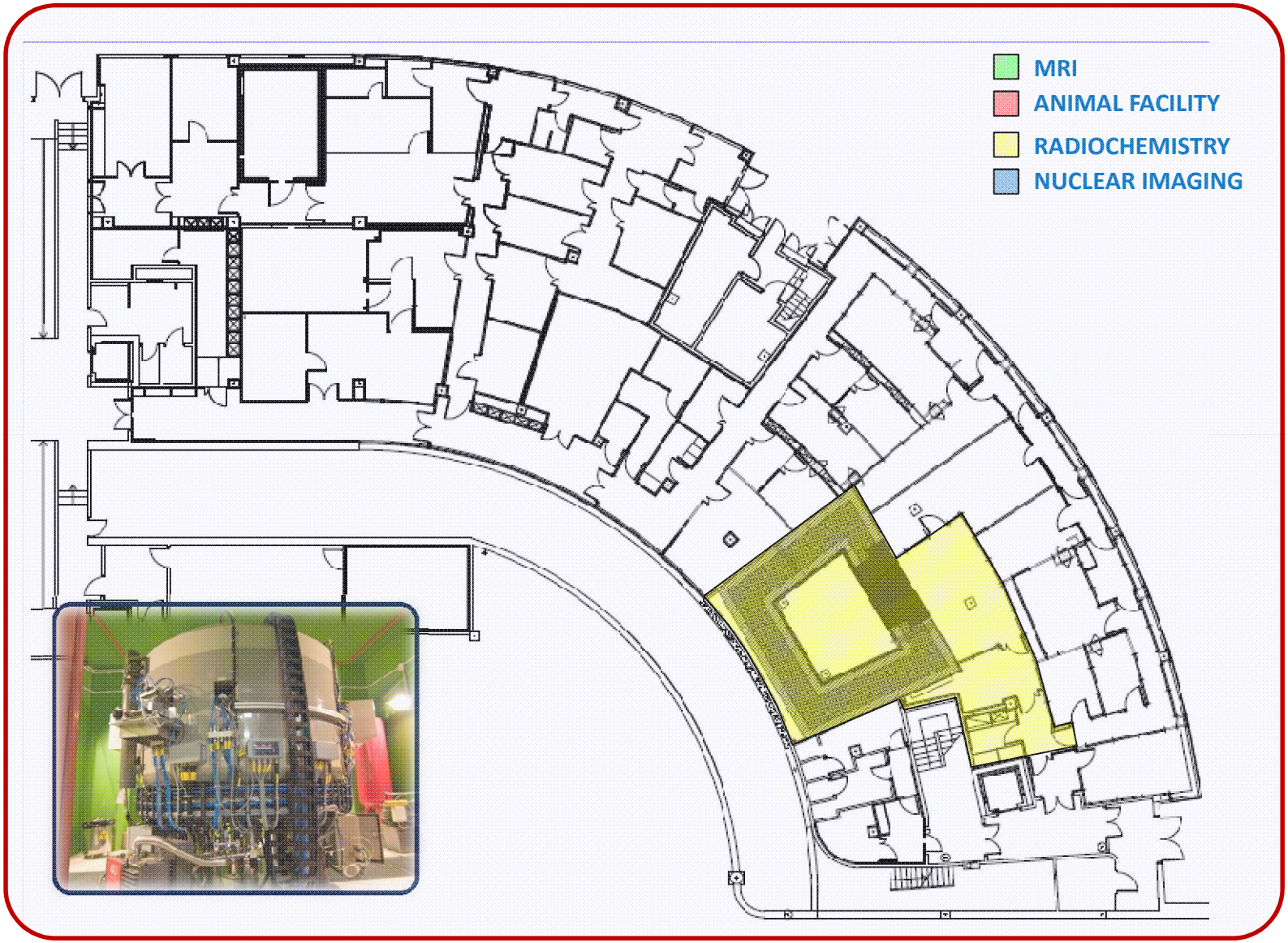
4000 m²
Yearly budget: 10 M€

PERSONNEL	121
Research	
Principal Investigators	12
Associate researchers	07
Research Assistant	01
Platform Managers	10
Platform specialists	04
Post Doc researchers	21
PhD students	27
Technicians	21
Services	
Administration /direction	10
Support	08

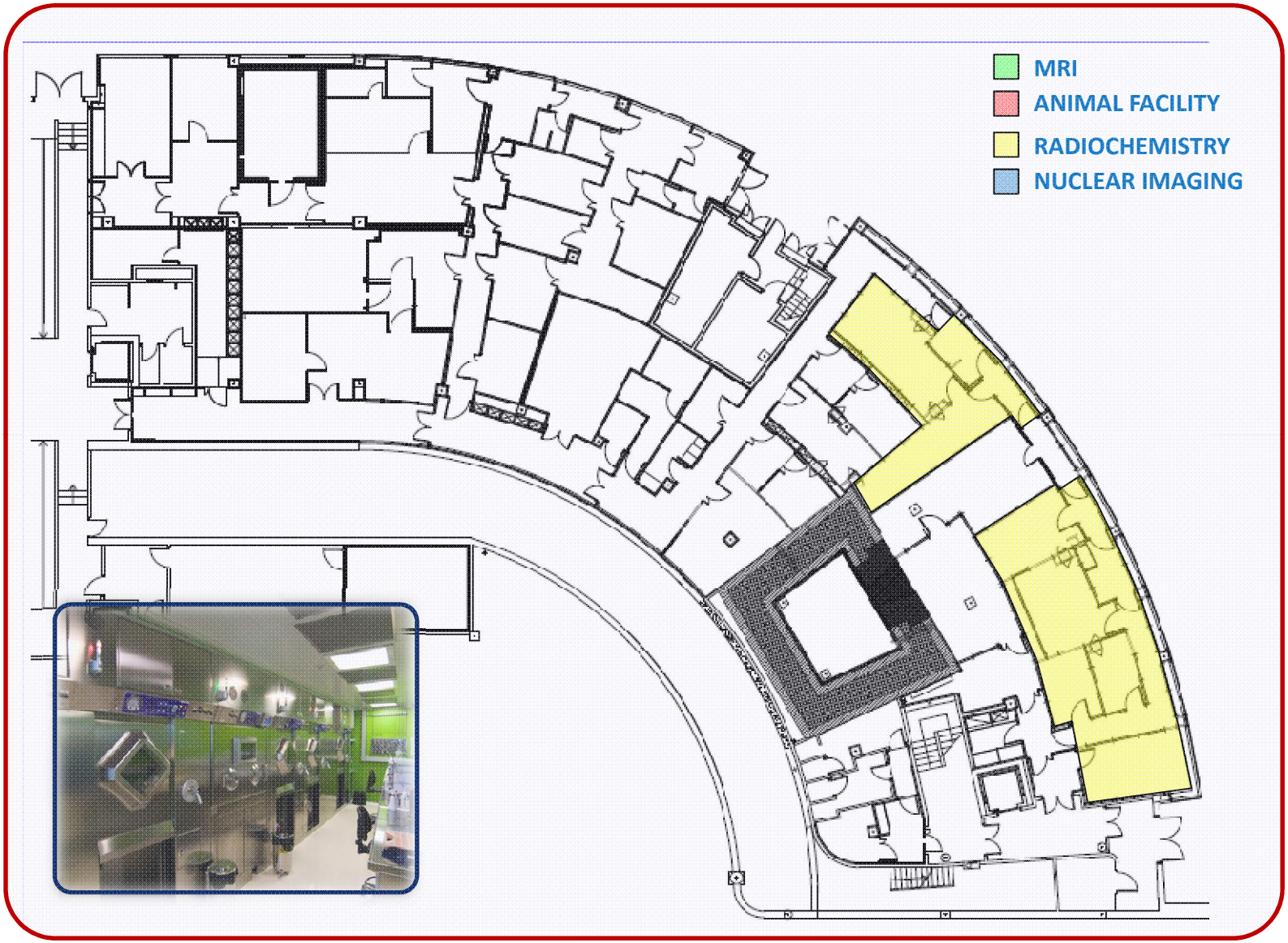
THE MOLECULAR IMAGING UNIT AT CIC biomaGUNE



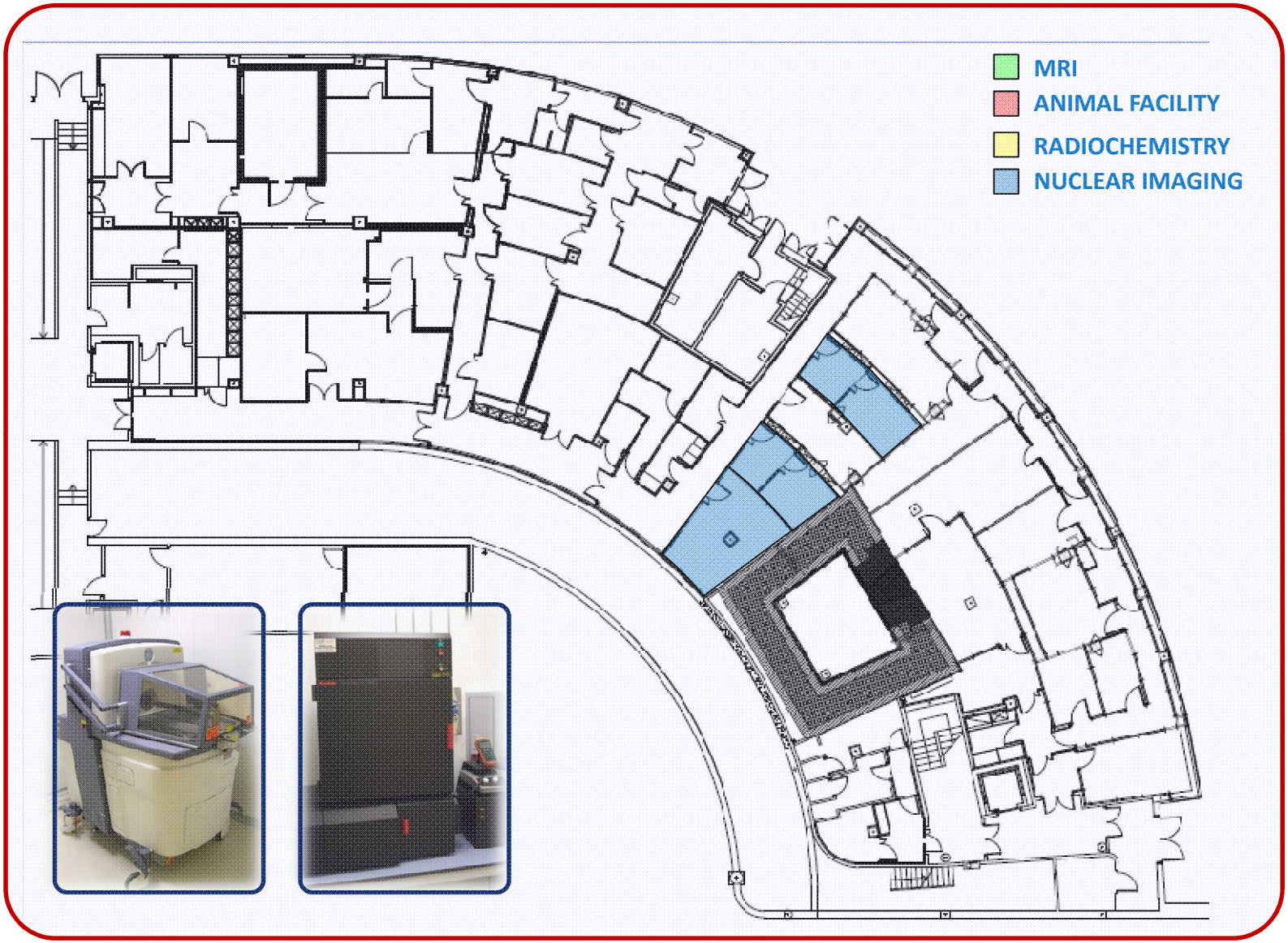
THE MOLECULAR IMAGING UNIT AT CIC biomaGUNE



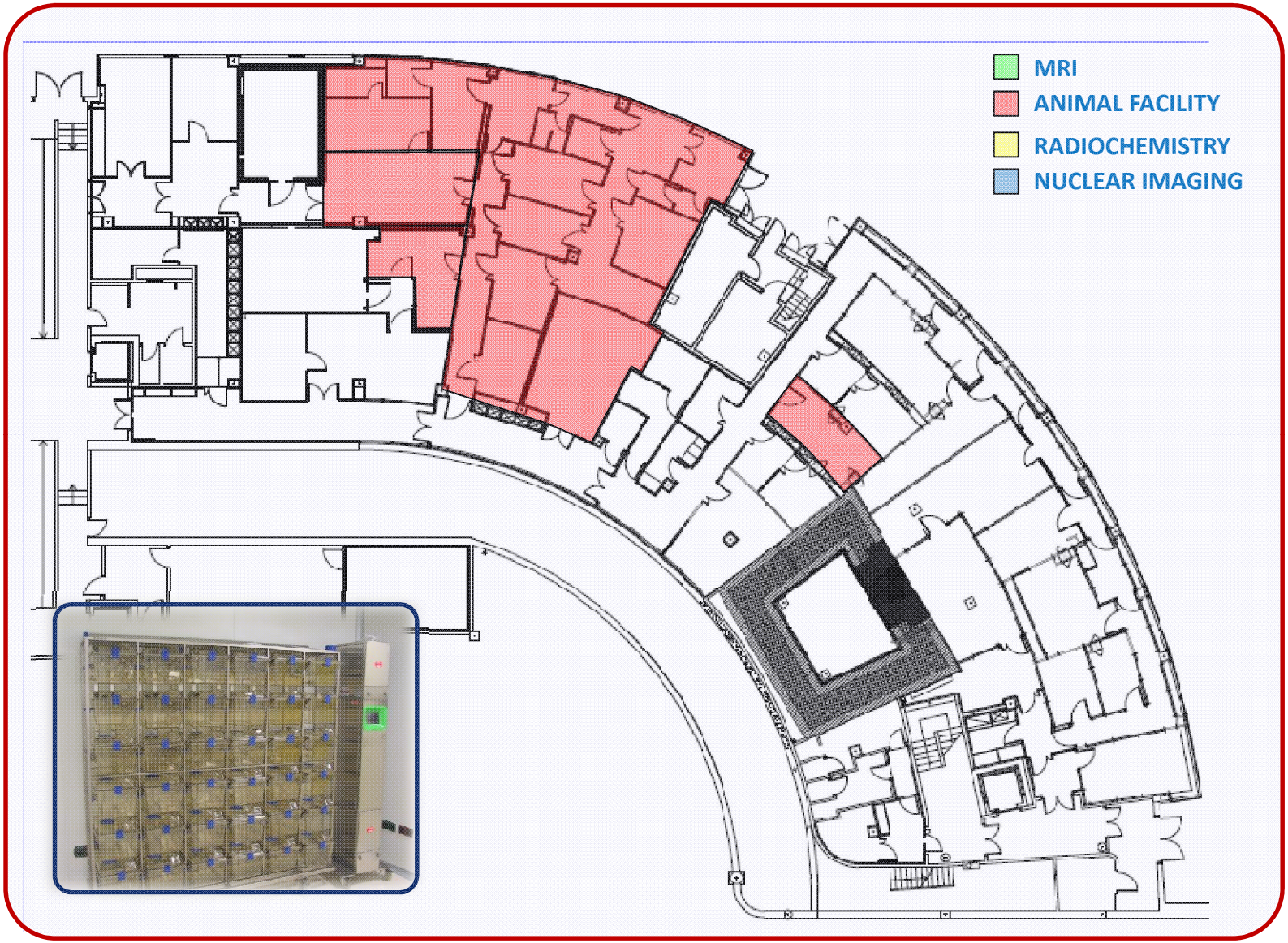
THE MOLECULAR IMAGING UNIT AT CIC biomaGUNE



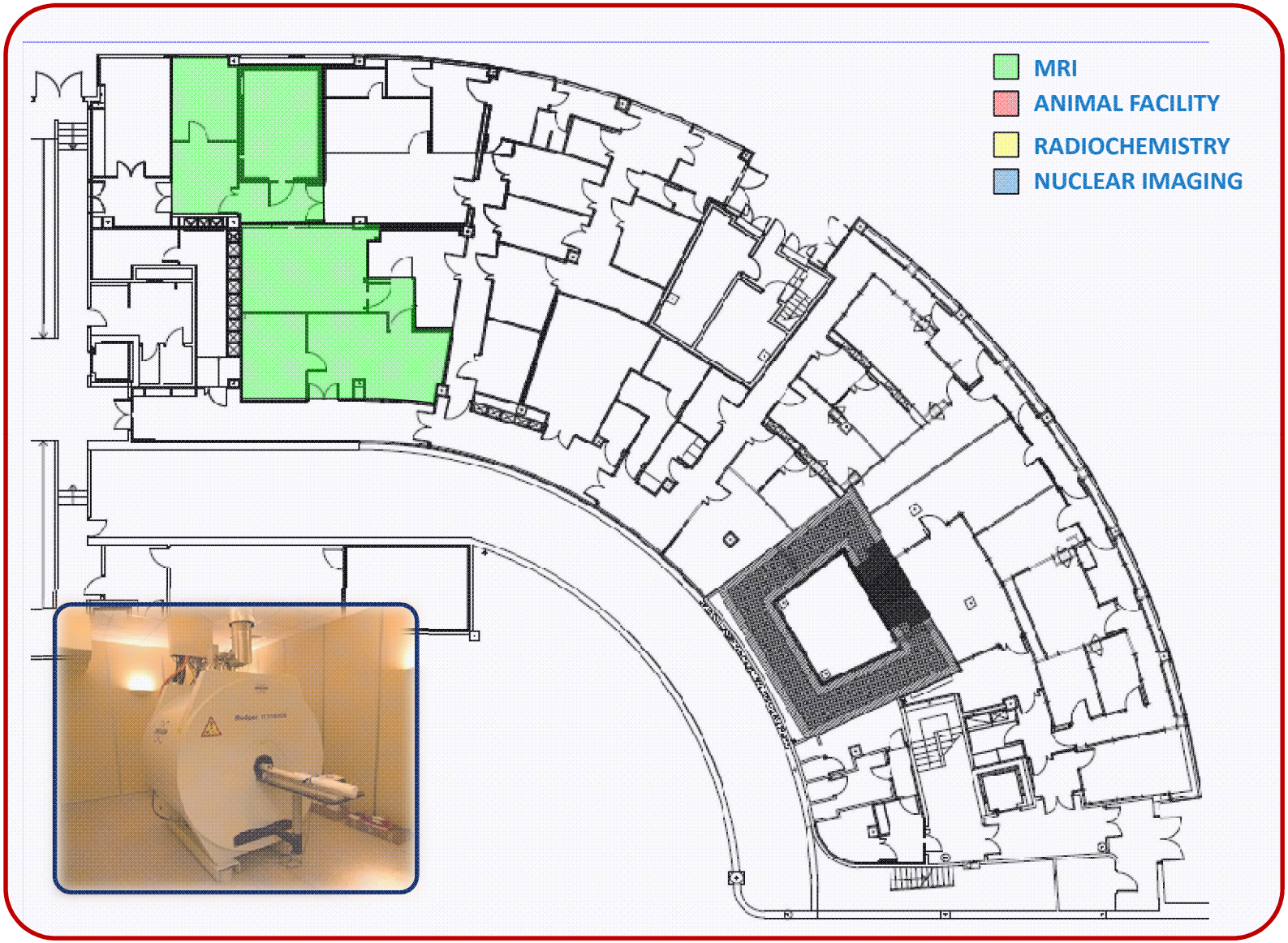
THE MOLECULAR IMAGING UNIT AT CIC biomaGUNE



THE MOLECULAR IMAGING UNIT AT CIC biomaGUNE



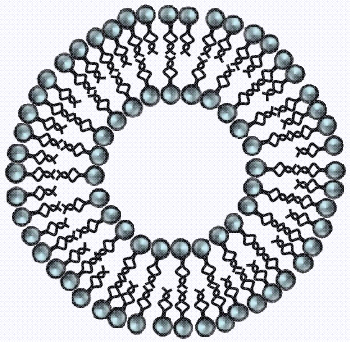
THE MOLECULAR IMAGING UNIT AT CIC biomaGUNE



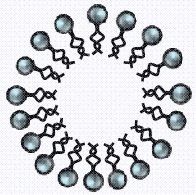
THE MOLECULAR IMAGING UNIT AT CIC biomaGUNE

INTRODUCTION

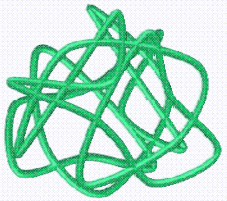
NANOSYSTEMS FOR NANOMEDICINE



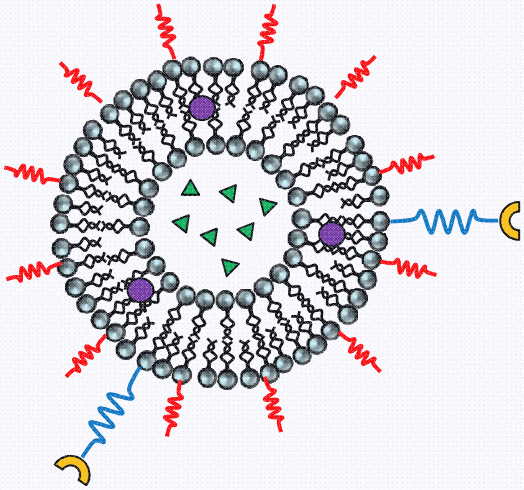
Liposomes



Micelles

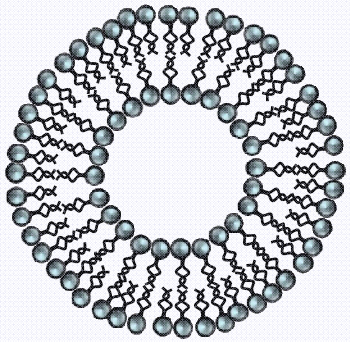


Polymeric NPs

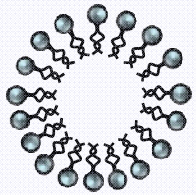


INTRODUCTION

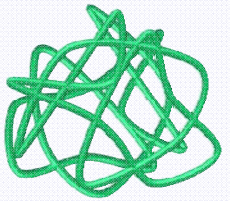
NANOSYSTEMS FOR NANOMEDICINE



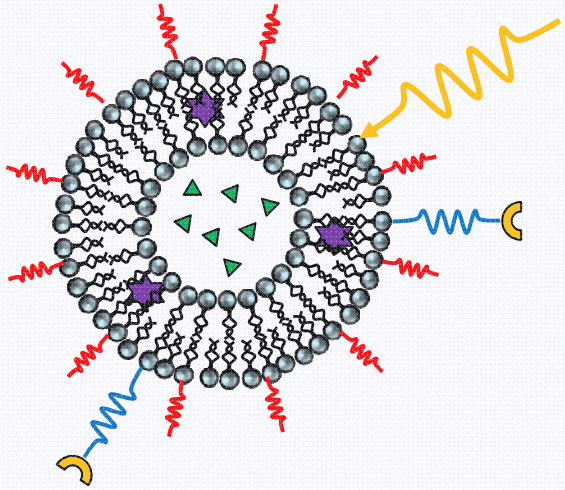
Liposomes



Micelles

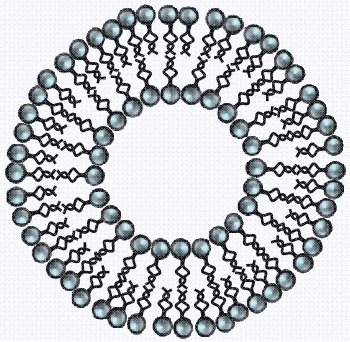


Polymeric NPs

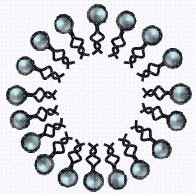


INTRODUCTION

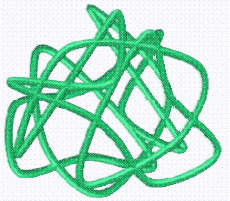
NANOSYSTEMS FOR NANOMEDICINE



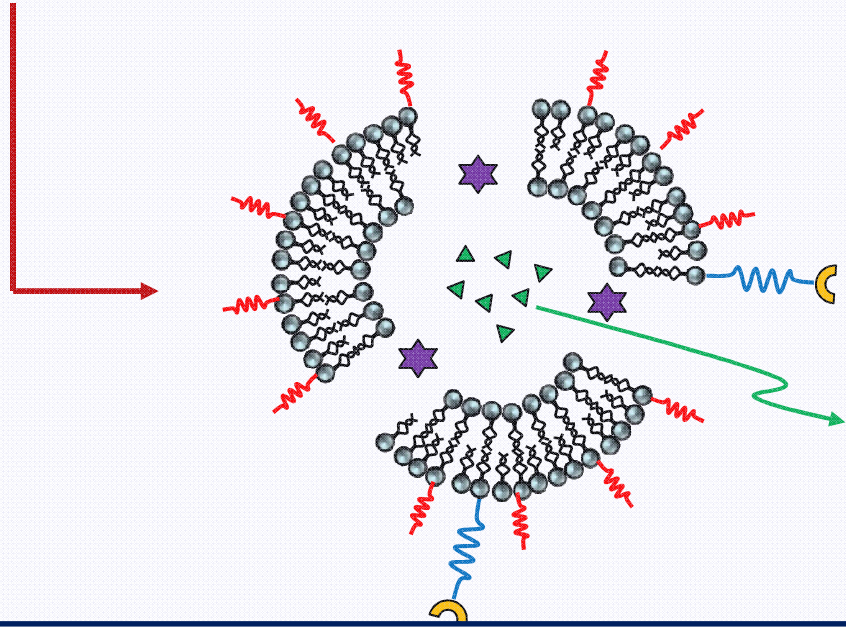
Liposomes



Micelles



Polymeric NPs



INTRODUCTION

Prolonged circulation of drugs – better targeting

- More selective
- More efficient
- Higher efficacy
- Less off-target side effects

NANOMEDICINE IS VERY PROMISING!!

INTRODUCTION

Application of drugs in therapeutic and preventive medicine is marred by indiscriminate drug action and inability of drugs to reach areas in need of treatment. On the other hand, development of new, more selective drugs is very expensive, lengthy and often uncertain. Recently, much attention has been given to an alternative approach, namely the use of drug delivery systems which are expected to optimize the action of drugs already in existence. One of the more promising systems is liposomes, microscopic spheres made of natural materials (lipids) and able to accommodate large amounts of drug. Fifteen years of liposome

The types of polymer used for controlled release can be biodegradable, non-biodegradable, non-biodegradable and soluble As drug-carriers, these polymers exist in the form of microspheres, matrices and membranes They can be administered via the parenteral, implantation, oral, insert and transdermal routes Several of these devices have been successfully commercialized, some are in clinical trials, and many promising ones are in the experimental stage Controlled release technology has been a success from the scientific, clinical and economic standpoints

INTRODUCTION

6. Conclusion and future challenges

The ability to precisely control tubular dimensions and differentially functionalize the inner and outer surfaces of nanotubes using the template synthesis method makes these constructs promising for drug delivery, bioseparation and imaging applications. Much needs to be done to explore the full potential of these structures in nanobiotechnology. Their biocompatibility is largely unexplored. Nanotube interaction with cells and their subcellular fate based on geometry and surface functionality need to be studied. Full exploitation of the large inner void of nanotubes for increasing drug loading capacity will require development of new capping techniques (such as the one described recently [11]) for reversible "on–off" release in response to local environmental stimuli. Despite these challenges, the unique ability to control shape, size, functionalization and composition provided by template synthesis can potentially open new avenues for controlled release applications.

Silica nanoshell

A fundamental limitation of molecular imaging is the signal to background ratio caused by non-specific adhesion of bio-imaging agents to surfaces [13] making it difficult to identify a low intensity signal. A molecular imaging agent that only lights up following a particular molecular event is ideal for *in vivo* tissue pathology. With well-developed silane chemistry, various surface modifications of silica nanoparticles can easily be realized and are widely performed. Silica nanoparticle-based bio-imaging agents are promising in nanomedicine as bioimaging agents [14].

INTRODUCTION

2014

Another promising nanotechnology used to improve the aqueous solubility of lipophilic drugs pertains to polymeric micelles (PMs), a type of self-assembly nanostructure formed by the aggregation of polymeric amphiphiles [55–57], that have been assessed by different administration routes such as parenteral [58–60], oral [61,62], intranasal [63, 64] and ocular [65,66]. A number of PM-based products for the treat-

These nanomedicines are very promising to replace the current daily administration regimen by one single administration every 7–10 days. This would also facilitate the implementation of a Directly Observed Treatment, Short Course (DOTS), leading to greater adherence levels. Even though these developments were not primarily conceived for children, any successful bench-to-bedside translation would be beneficial for the pediatric population. At the same time, additional clinical trials in children are mandatory to comply with the PIP regulatory rule.

5. Perspectives

According to the market forecasting company BCC Research, the global nanomedicine market has been growing steadily, reaching a value of $72.8 billion in 2011, with anticancer agents as the market leader [275]. The market is expected to increase at an annual growth rate of 12.5% until 2016, reaching a value of $130.9 billion. In this global context, nanomedicine emerges as a promising tool to also optimize the therapy of pediatric diseases [276]. An expression of this potential and vision was the development of the pioneering NanoPediatrics Program

2014

working to develop new approaches for early stage detection of CTCs to help physicians treat patients and predict cancer progression [11–25]. Although CTCs have been known since 1869, they can only be detected in patients with advanced stage tumors [26–40]. Because CTCs are present at extremely low levels, accounting for only a few cells/10^6 peripheral blood mononuclear cells, it is a challenge for early detection. To overcome this problem, effective separation and enrichment is highly crucial [22–24,39,41–56]. Recent reports show that use of nanomaterials as contrast agents and therapeutic actuators is one of the most promising methods, although this is still at an infant stage [25,26,28,34,35,37,40,42,48,49,51,57–66]. Because nanoparticles exhibit unique optical, magnetic, and

INTRODUCTION

2017

Synthesis and Functionalization of Dextran–Based Single–Chain Nanoparticles in Aqueous Media

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

R. Gracia,[a] M. Marradi,[a] U. Cossío,[b] A. Benito,[a] A. Pérez-San Vicente,[a] V. Gómez-Vallejo,[b] H.-J. Grande,[a] J. Llop[b] and I. Loinaz[a,*]

Water-dispersible dextran-based single-chain polymer nanoparticles (SCPNs) were prepared in aqueous media and mild conditions. Radiolabeling of the resulting biocompatible materials allowed the study of lung deposition of aqueous aerosols after intratracheal nebulization by means of single-photon emission computed tomography (SPECT), demostrating their potential use as imaging contrast agents.

Advances in engineering polymer chains at the molecular level[1] have pushed the development of synthetic strategies for the controlled compaction of single polymer coils into unimolecular soft nano-objects, named single-chain polymer nanoparticles (SCPNs).[2-4] SCPNs based on synthetic polymers benefit from the possibility of a controlled construction of the precursors in order to prepare tuned SCPNs with desired size and functionality.[3] Additionally, a wide variety of biocompatible, non-toxic and ready-to-use natural polymers are available. Consequently, SCPNs have gained interest as potential mimetics of biomacromolecules such as proteins[5,6] and for application in different fields including nanomedicine.[7-9] Among natural polymers, polysaccharides can be envisaged as natural analogues of polyethylene glycol (PEG). For of pre-functionalized polymers through covalent, dynamic covalent, and non-covalent bonding.[15,16] Most of the covalent strategies are performed in organic solvents and require highly diluted polymer solutions (usually <1 mg/mL), high temperatures and/or the presence of metal catalysts. The preparation of SCPNs through "continuous addition" avoids ultra-dilution conditions, which is beneficial for multigram scale preparations.[17] Recently, it has been described that the presence of oligo(ethylene glycol) brushes as side-chains allows to achieve SCPNs at high polymer concentrations (100 mg/mL).[18] However, the development of general procedures to obtain functionalizable SCPNs in aqueous media, mild conditions and scalable conditions is still a challenging issue.

Our group reported a strategy to generate structurally defined and water-dispersible poly(methacrylic acid)-based SCPNs.[19] In pursuit of novel types of biocompatible polymeric nanoparticles based on readily available and easily functionalized materials, we here present a novel and straightforward synthetic methodology to obtain small (approximately 13 nm) dextran (DXT)-based SCPNs through the intramolecular crosslinking (compaction) of single polysaccharide chains by means of a homobifunctional cross-

INTRODUCTION

Where is the gap?

Production

- Reproducibility
- Scalability
- Quality control
- Can it be produced under GMP?

Biology

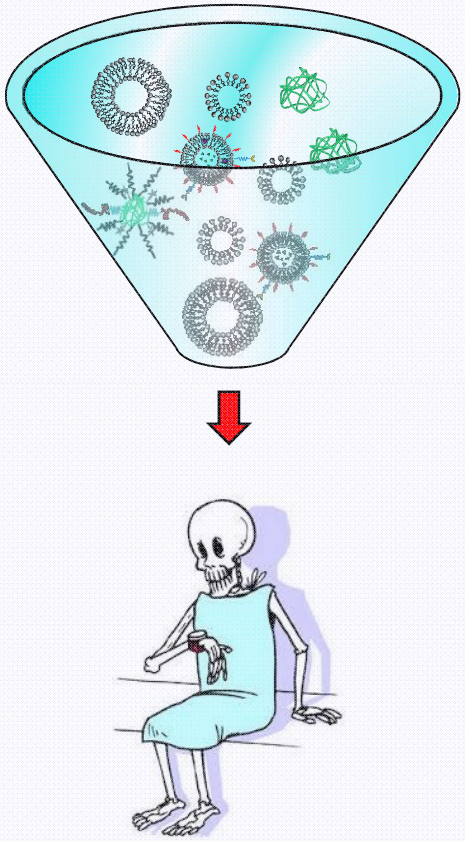
- Which is the biodistribution of the NSs?
  and the in vivo stability?
  and the biological fate?
  and the toxicity *in vivo*?
  and the efficacy?

More Biology

- Is the NP working in more than one model?
- Is it more efficacious than the drug alone?

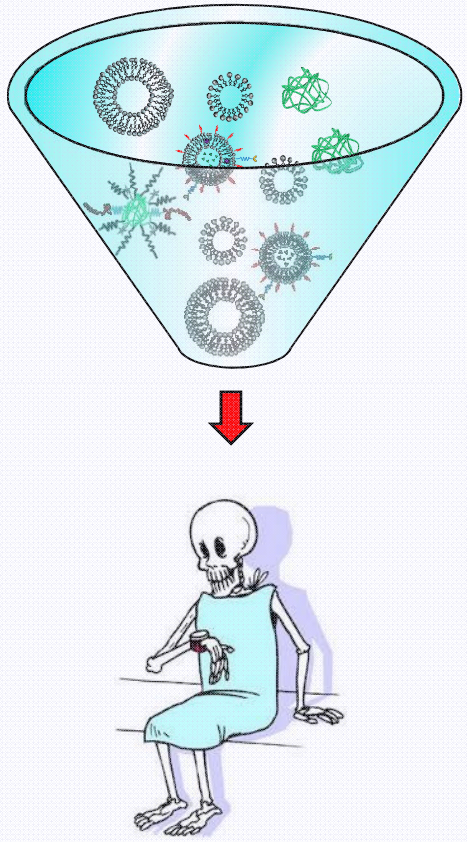
Others

- Patenting issues

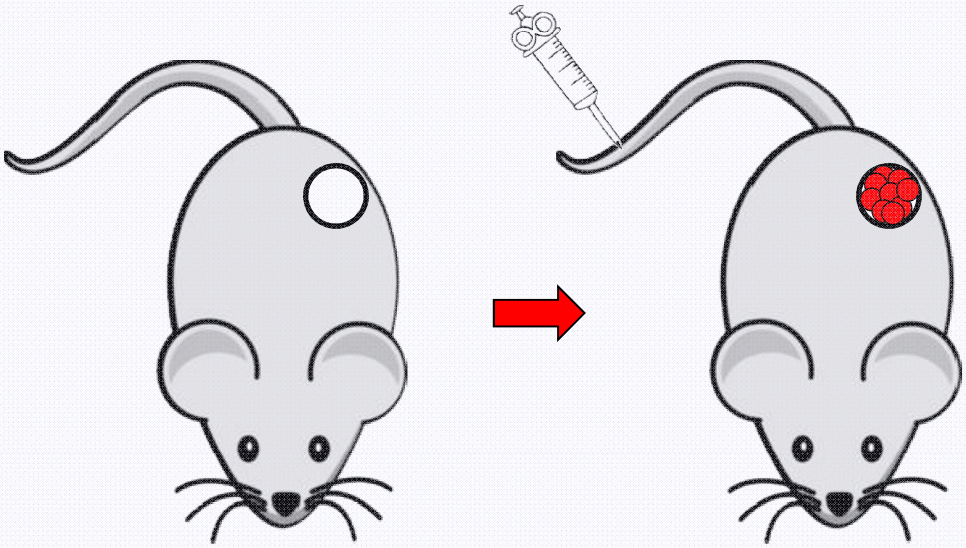


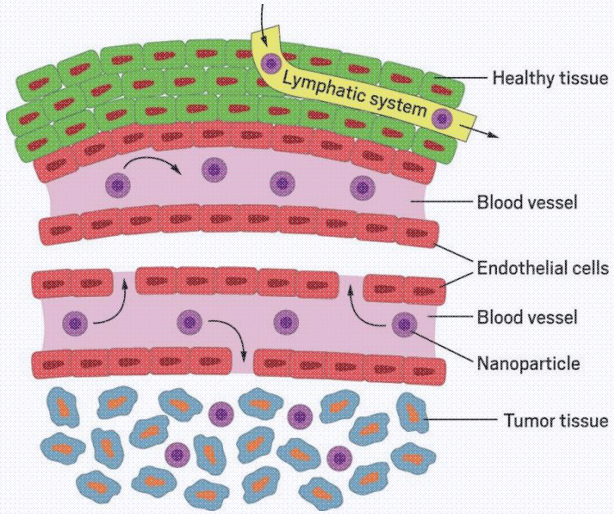
INTRODUCTION

Are we using the correct administration route?

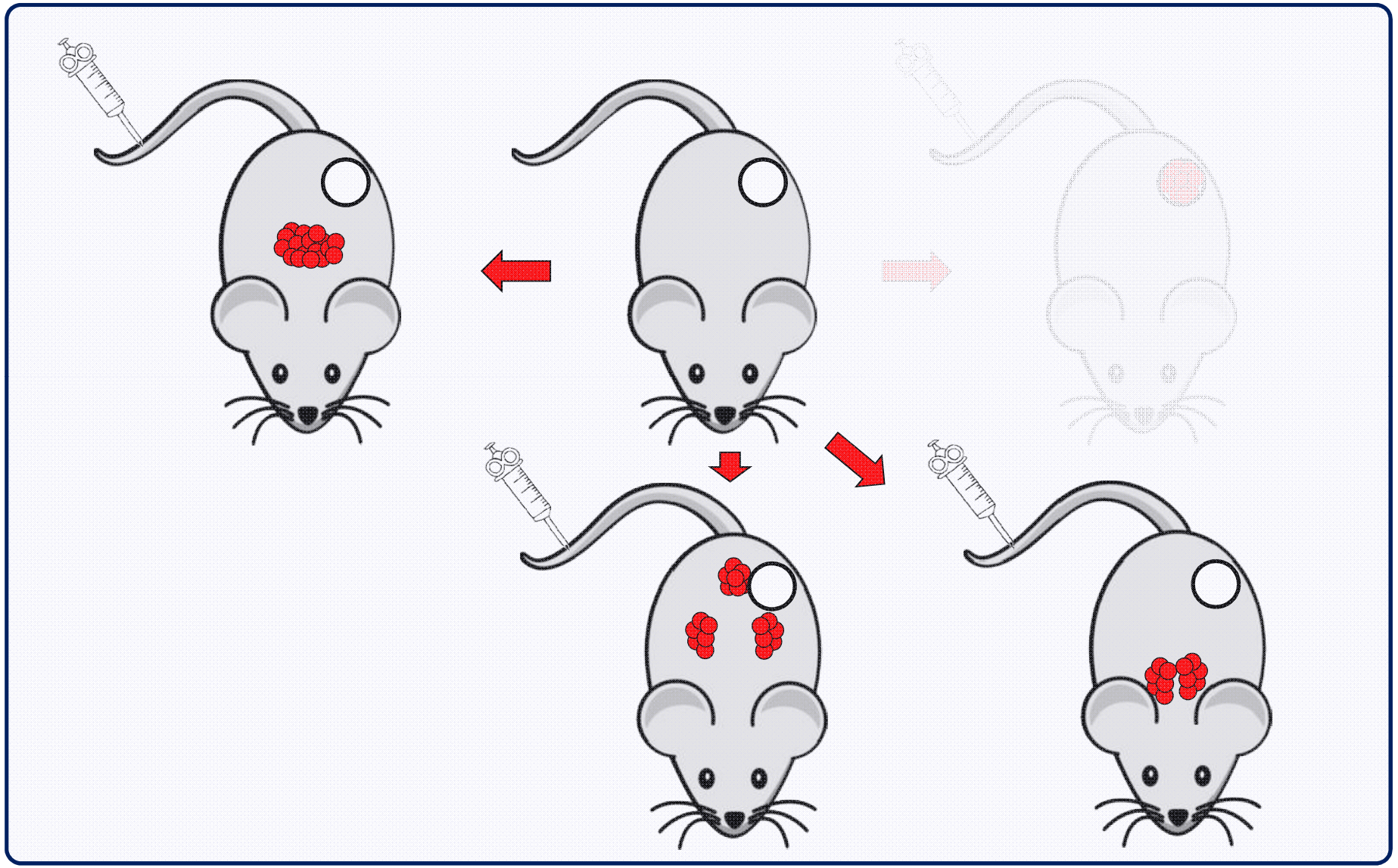


INTRODUCTION





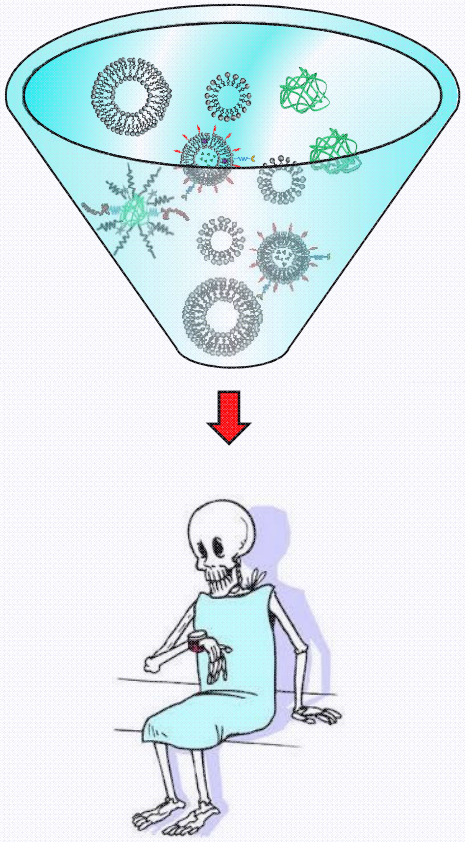
INTRODUCTION



INTRODUCTION

Lung administration can be an option when the lung is the target organ

- Lung cancer
- Lung infection



NANOMEDICINE FOR LUNG INFECTION

PNEUMONP

SEVENTH FRAMEWORK PROGRAMME

NANOMEDICINE FOR LUNG INFECTION

A 'nightmare bacteria' resistant to all US antibiotics has killed a Nevada woman

STAT

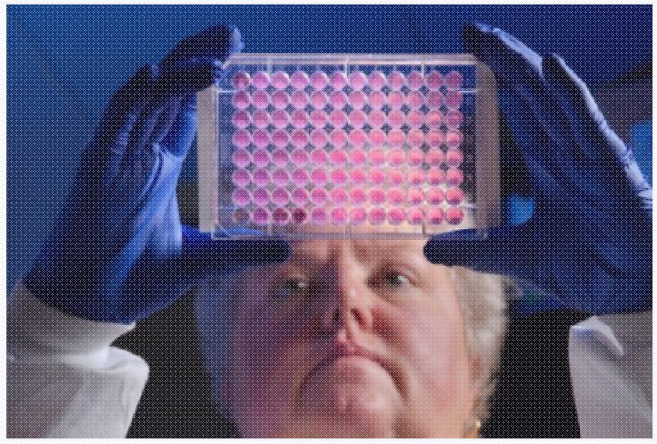
Helen Branswell, STAT

Jan. 13, 2017, 2:06 PM 8,305

FACEBOOK LINKEDIN TWITTER EMAIL PRINT

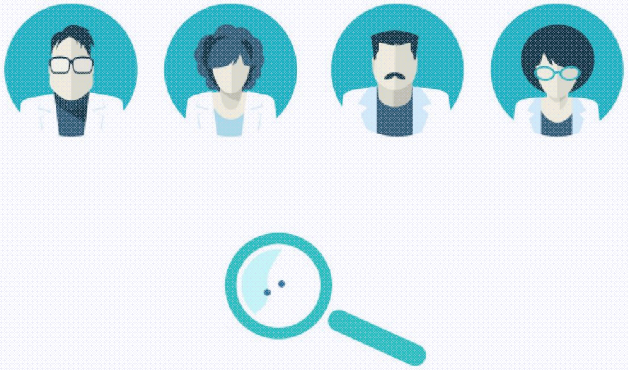
If it sometimes seems like the idea of antibiotic resistance, though unsettling, is more theoretical than real, please read on.

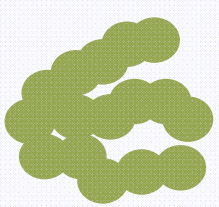
Public health officials from Nevada are reporting on a case of a woman who died in Reno in September from an incurable infection. Testing showed the superbug that had spread throughout her system could fend off 26 different antibiotics.

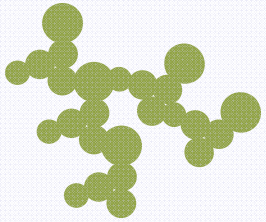


A CDC researcher holds up a experiment testing for drug-resistant

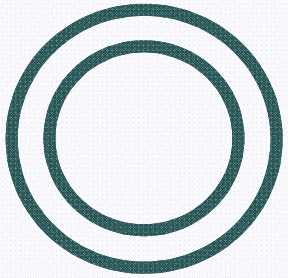
NANOMEDICINE FOR LUNG INFECTION





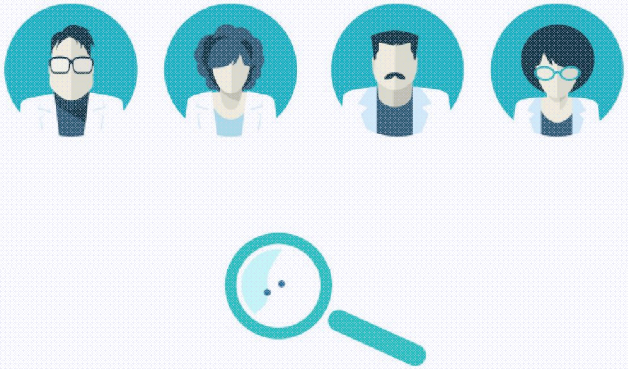


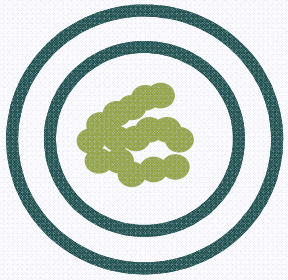
Antimicrobial peptides (AMPs)



Nanocarriers

NANOMEDICINE FOR LUNG INFECTION

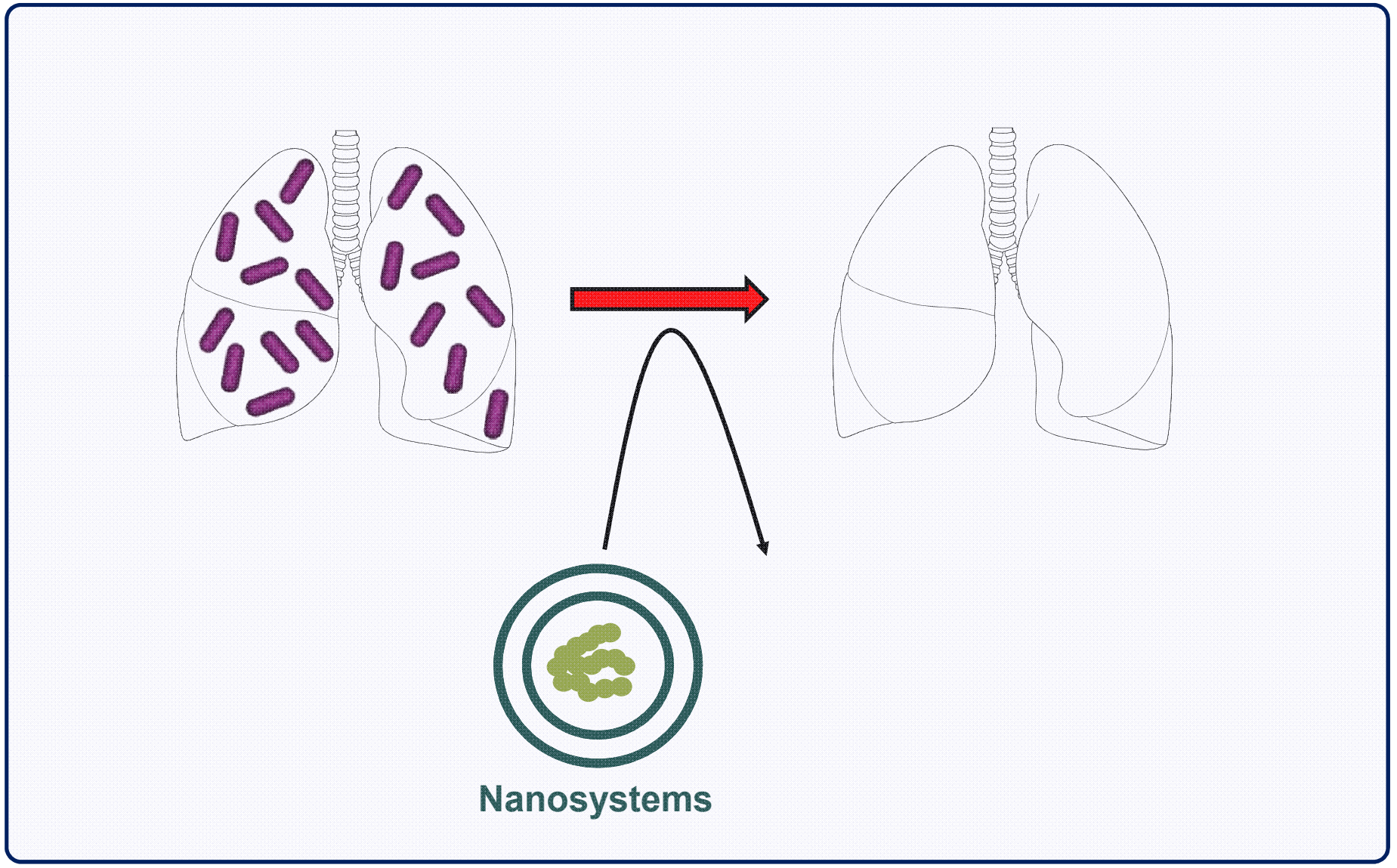




Nanosystems

Higher residence time
Higher stability
Higher efficacy

NANOMEDICINE FOR LUNG INFECTION



NANOMEDICINE FOR LUNG INFECTION

Some questions

Lung administration…

- Which is the best way to administer the NSs in the preclinical setting to mimic administration in humans?
- Which the dose actually reaching the lungs?
- Is it uniformly distributed within the lungs?
- PK properties? (distribution, residence time, elimination…)
- Biological fate/stability? Are the NCs and the drugs staying together?
- Therapeutic efficacy?
- Toxicity *in vivo*?

NANOMEDICINE FOR LUNG INFECTION

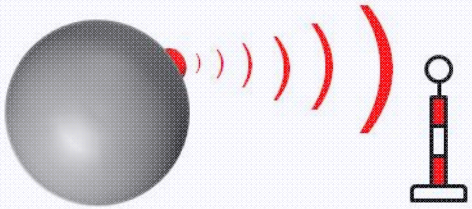
Some questions

Lung administration…

- Which is the best way to administer the NSs in the preclinical setting to mimic administration in humans?
- Which the dose actually reaching the lungs?
- Is it uniformly distributed within the lungs?
- PK properties? (distribution, residence time, elimination…)
- Biological fate/stability? Are the NCs and the drugs staying together?
- Therapeutic efficacy?
- Toxicity *in vivo*?

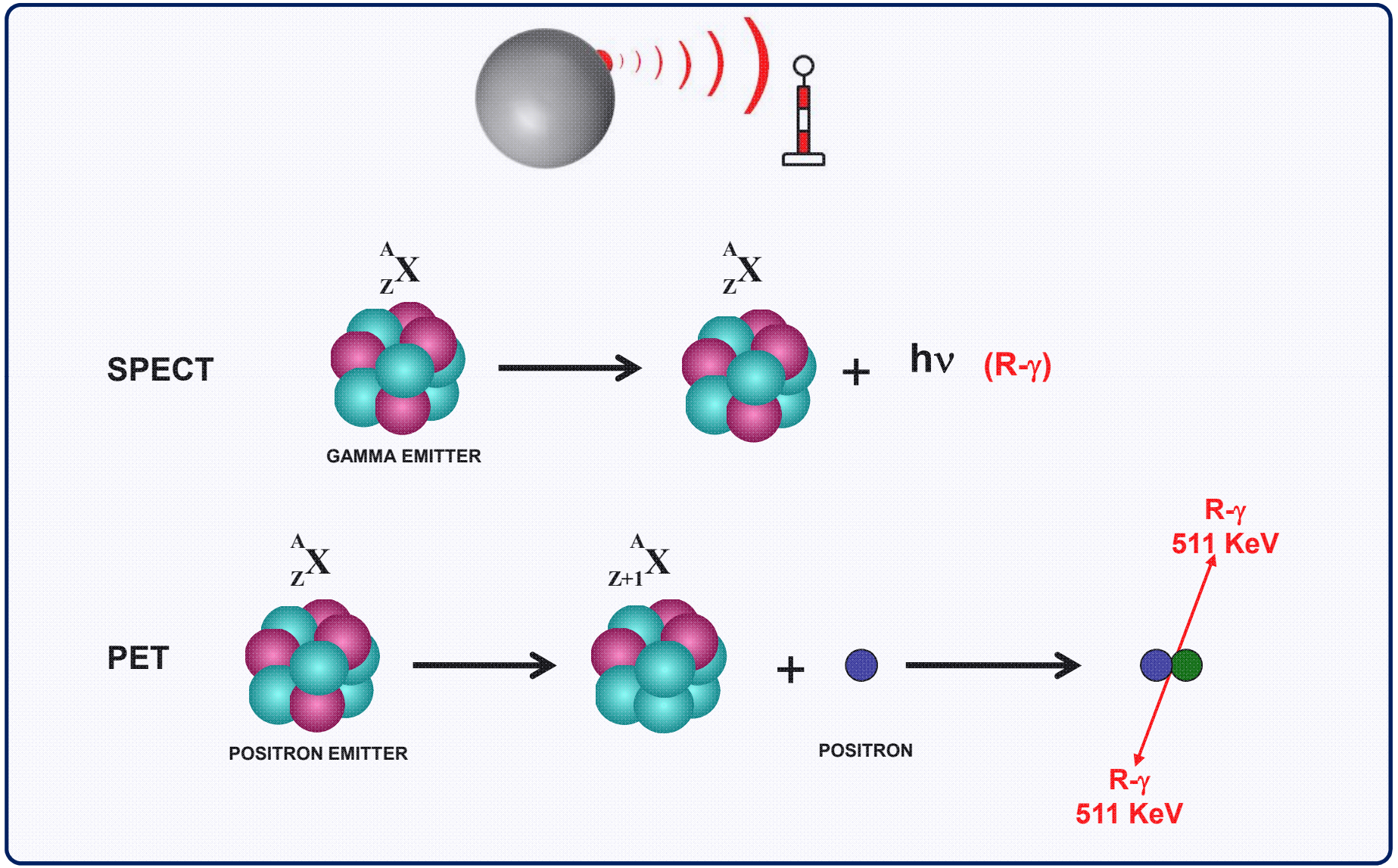
IN VIVO IMAGING

NANOMEDICINE FOR LUNG INFECTION

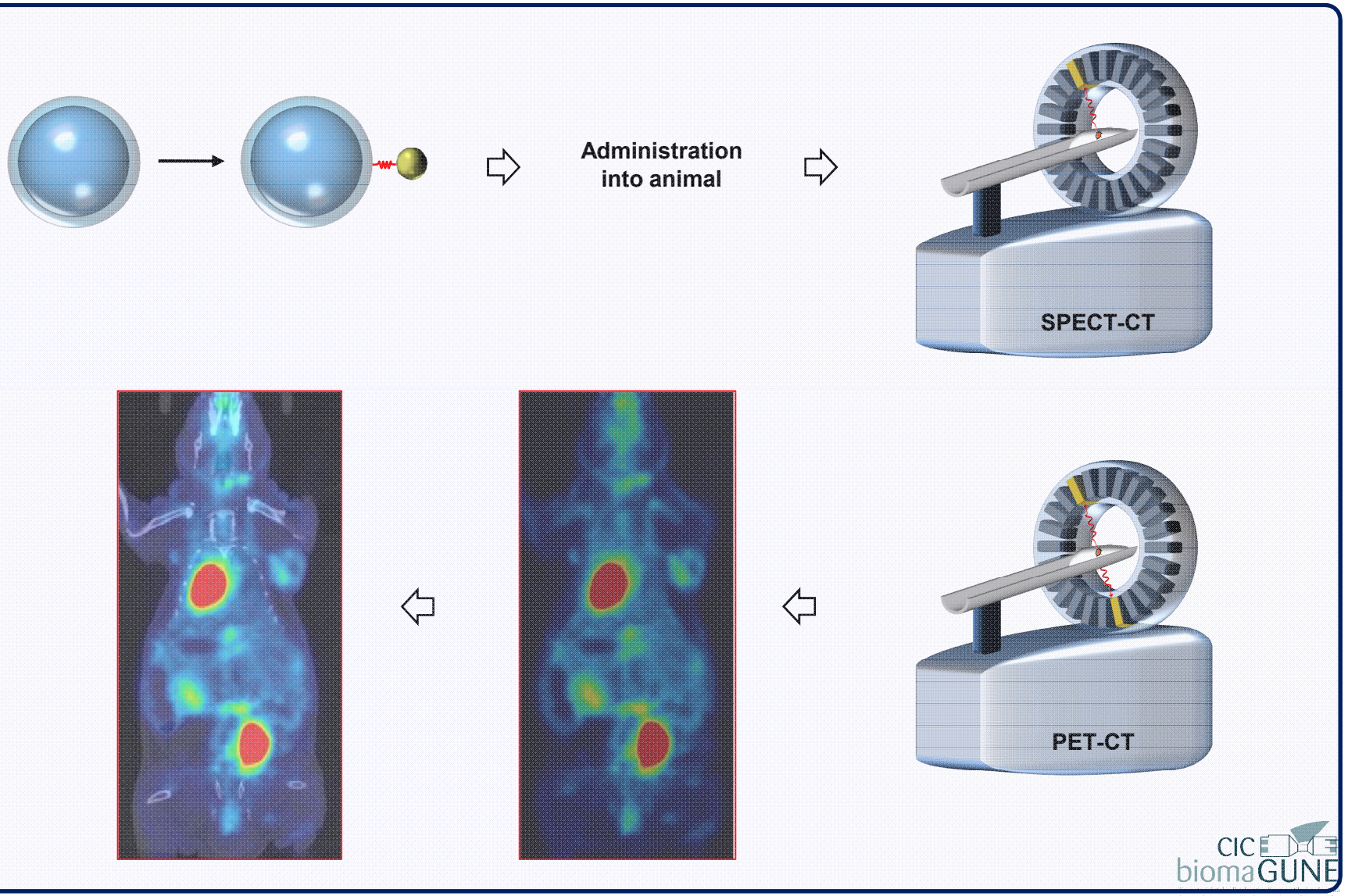


Emitter	Technique
Positron emitter	PET
Gamma emitter	SPECT

NANOMEDICINE FOR LUNG INFECTION

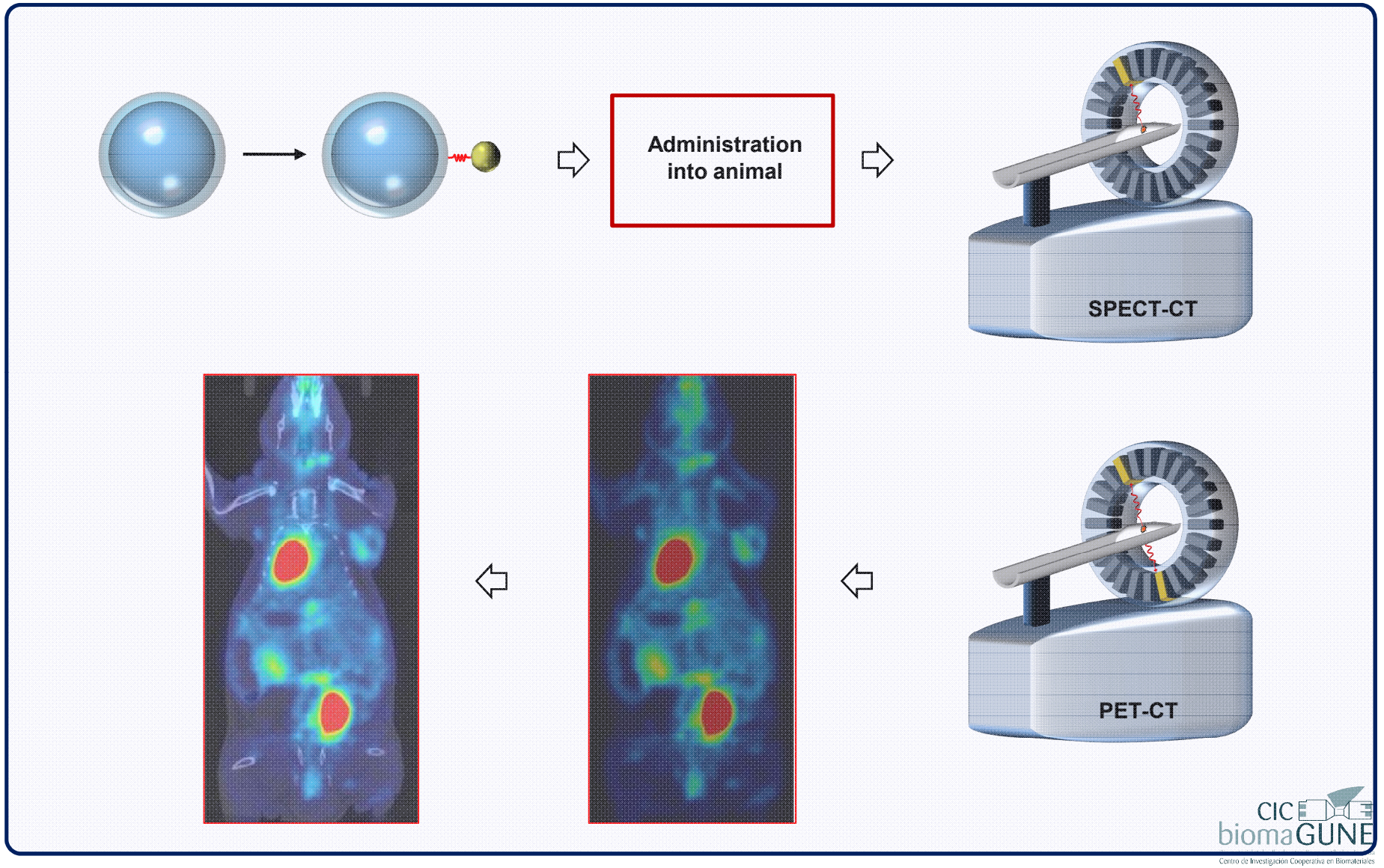


NANOMEDICINE FOR LUNG INFECTION



CIC biomaGUNE
Centro de Investigación Cooperativa en Biomateriales

NANOMEDICINE FOR LUNG INFECTION



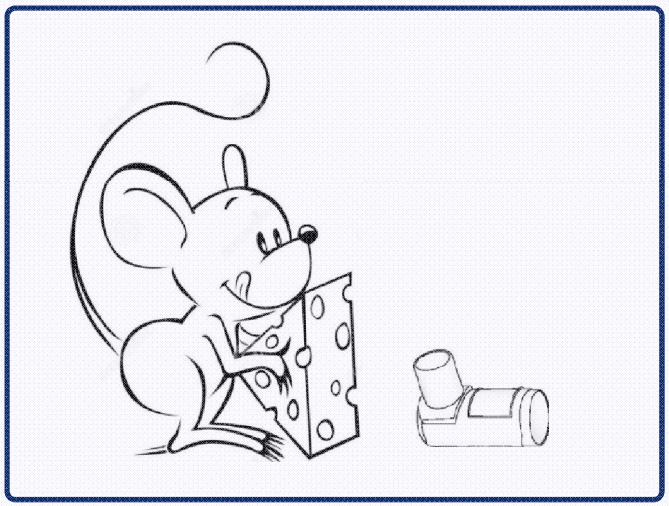
CIC biomaGUNE
Centro de Investigación Cooperativa en Biomateriales

NANOMEDICINE FOR LUNG INFECTION

Administration way: Regional distribution

HUMANS

RODENTS



NANOMEDICINE FOR LUNG INFECTION

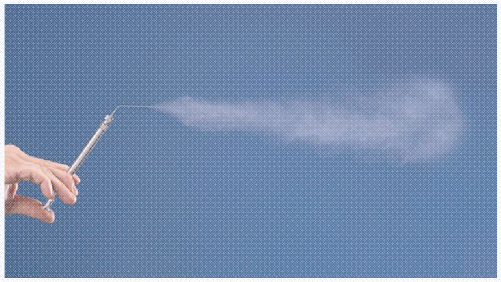
Administration way: Regional distribution

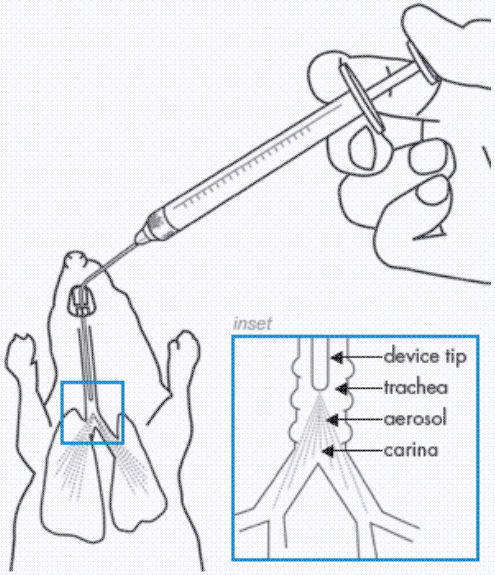
How can we mimic administration by aerosol inhalation in rodents?

NANOMEDICINE FOR LUNG INFECTION

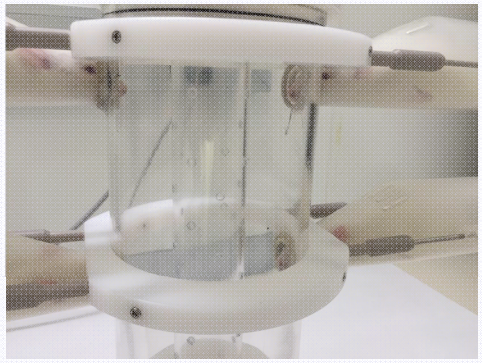
Administration way: Regional distribution

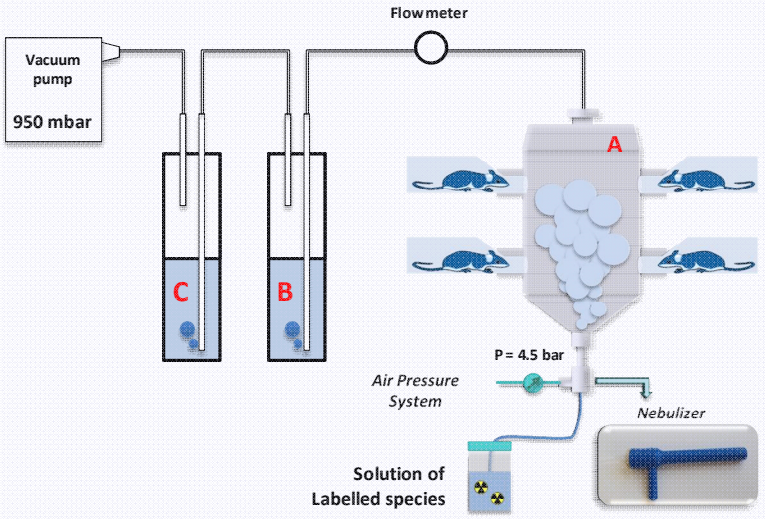
Intratracheal nebulization





inhalation





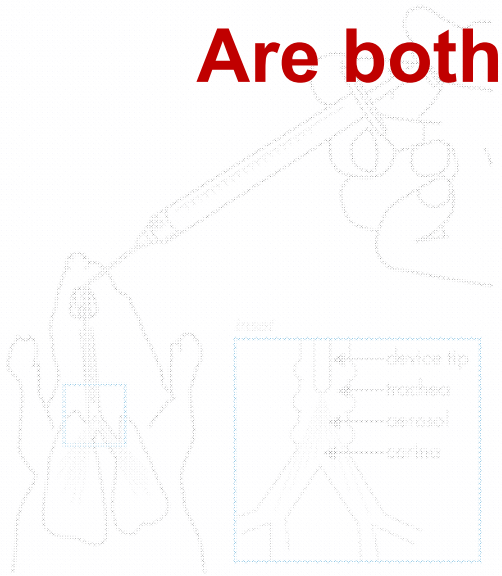
NANOMEDICINE FOR LUNG INFECTION

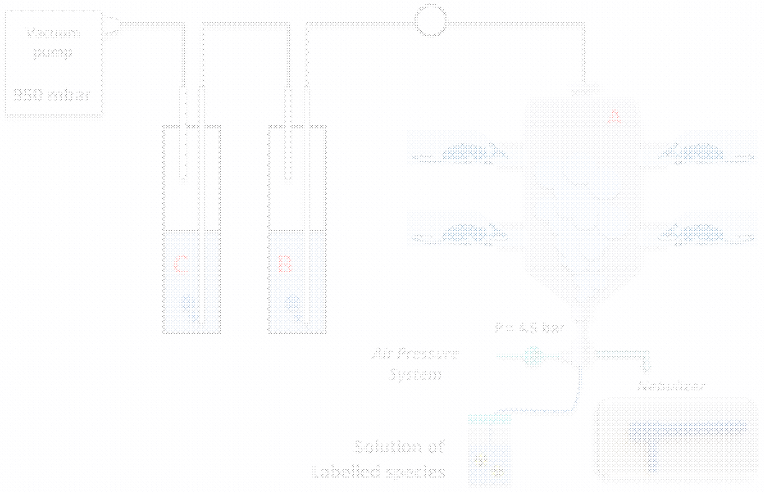
Administration way: Regional distribution

Intratracheal nebulization

inhalation

Are both techniques equivalent?

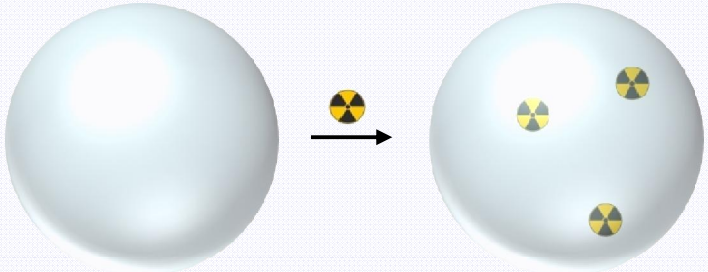


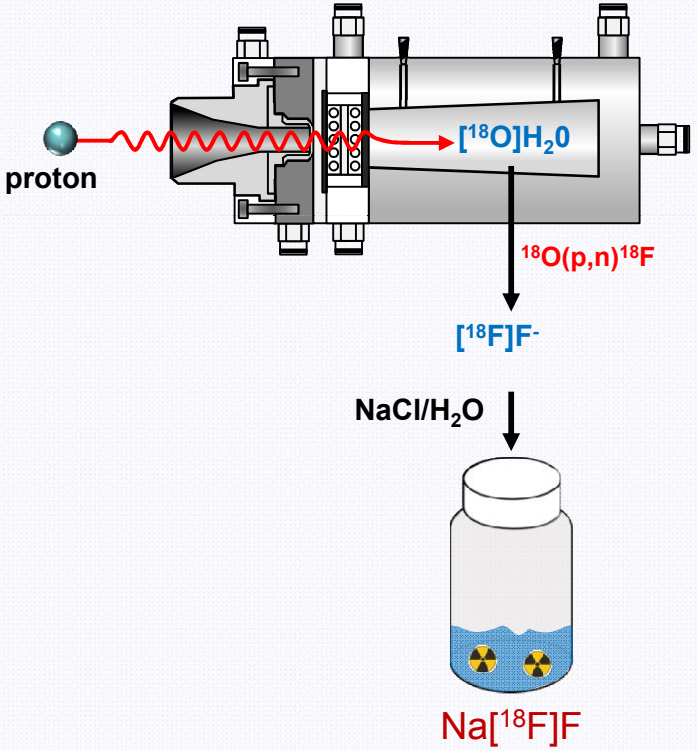


NANOMEDICINE FOR LUNG INFECTION

Administration way: Regional distribution

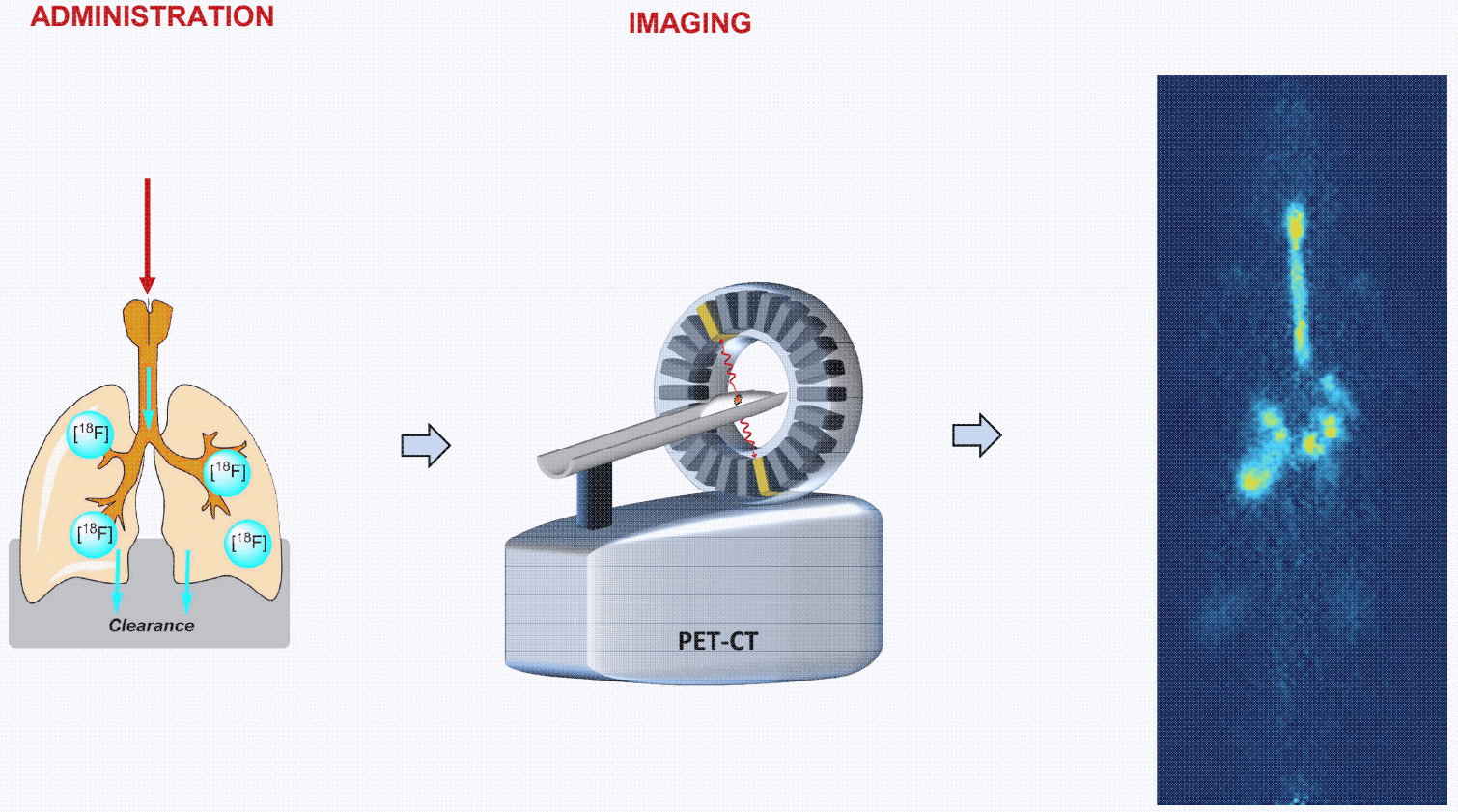
LABEL THE AEROSOL





NANOMEDICINE FOR LUNG INFECTION

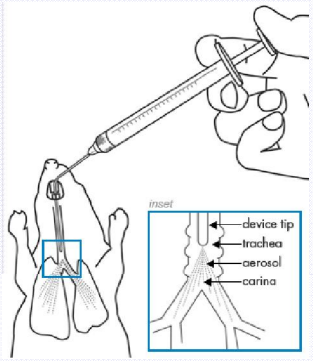
Administration way: Regional distribution

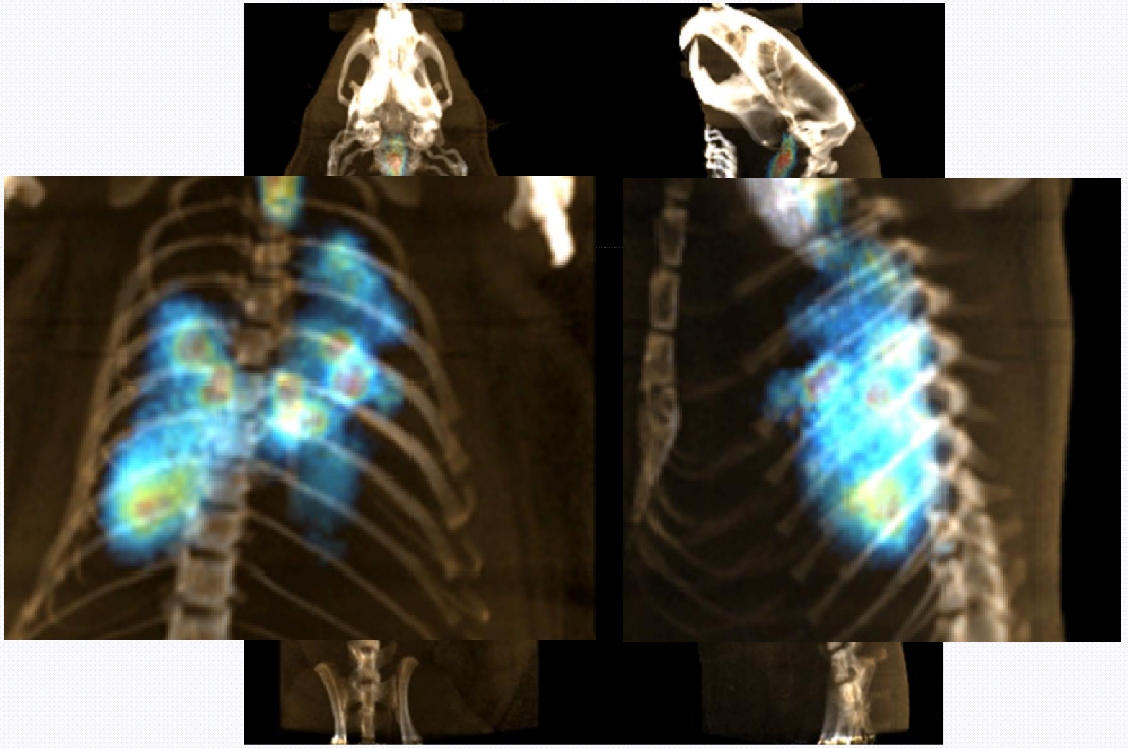


NANOMEDICINE FOR LUNG INFECTION

Administration way: Regional distribution

Intratracheal nebulization

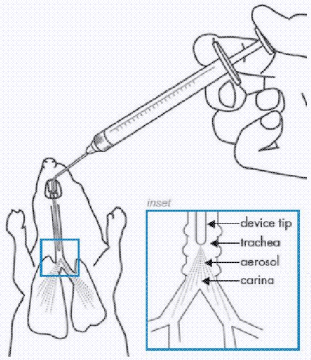


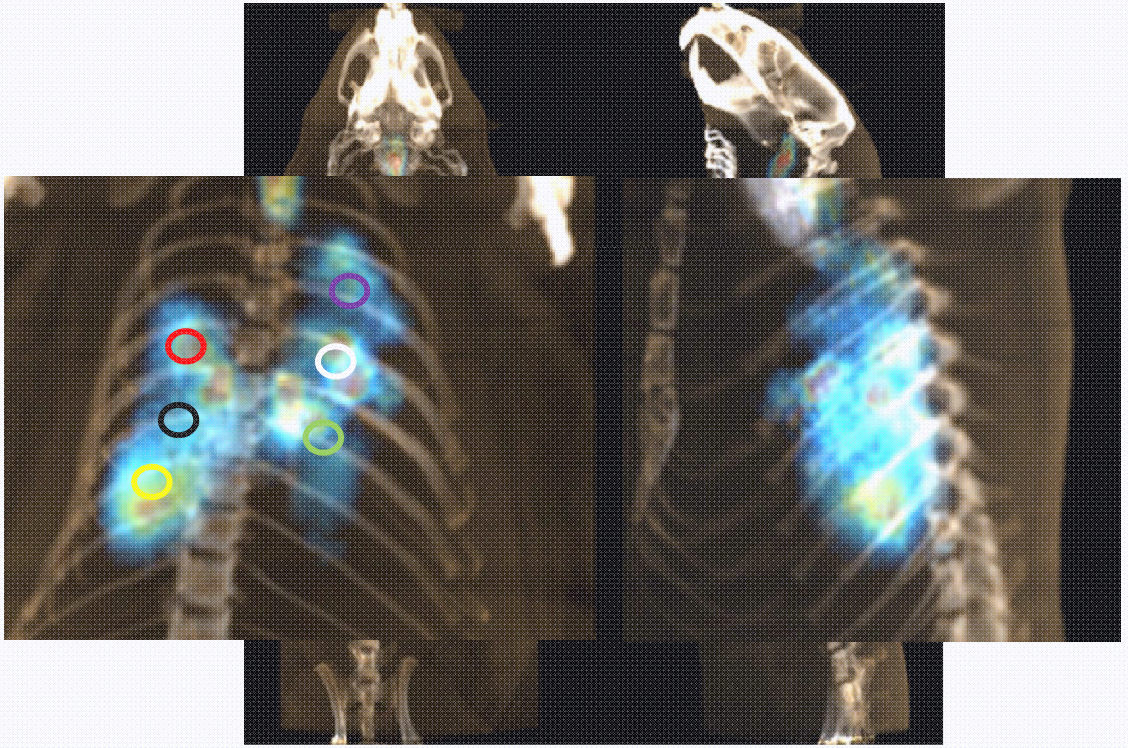


NANOMEDICINE FOR LUNG INFECTION

Administration way: Regional distribution

Intratracheal nebulization

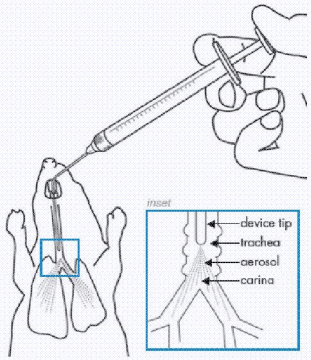


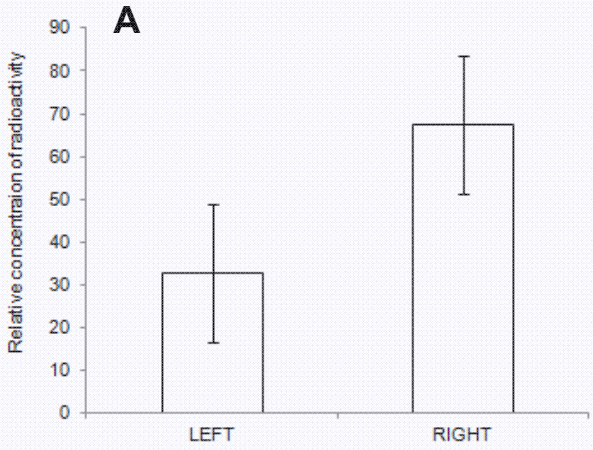


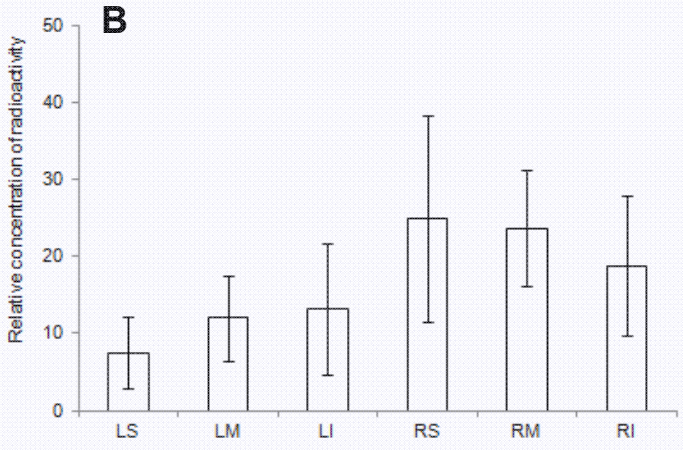
NANOMEDICINE FOR LUNG INFECTION

Administration way: Regional distribution

Intratracheal nebulization



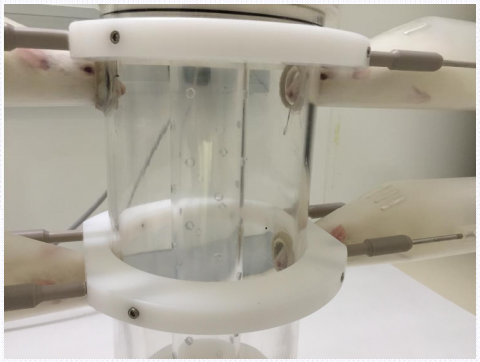


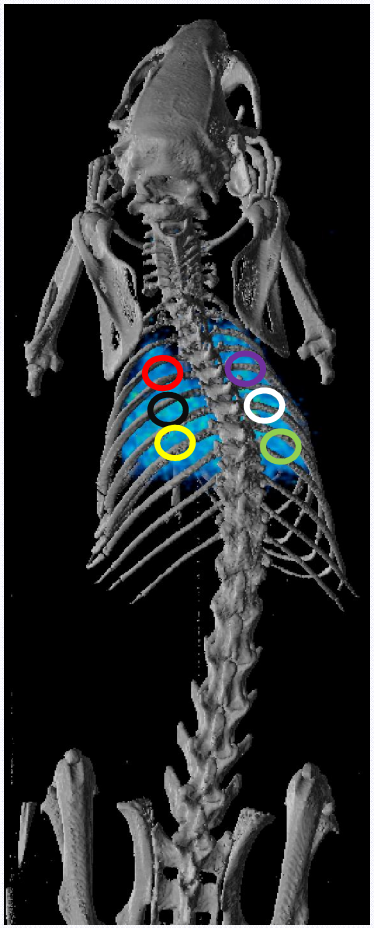


NANOMEDICINE FOR LUNG INFECTION

Administration way: Regional distribution

Inhalation

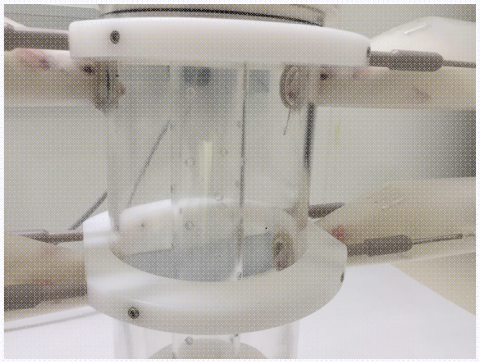




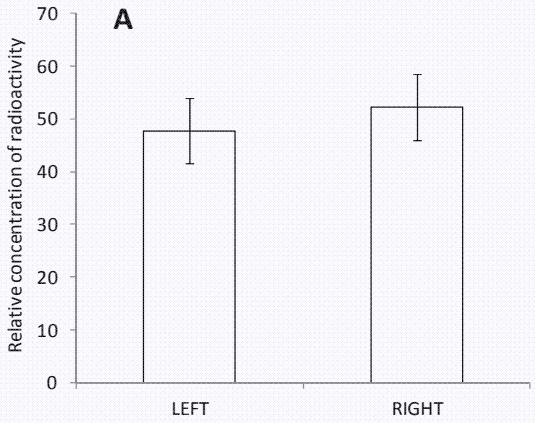
NANOMEDICINE FOR LUNG INFECTION

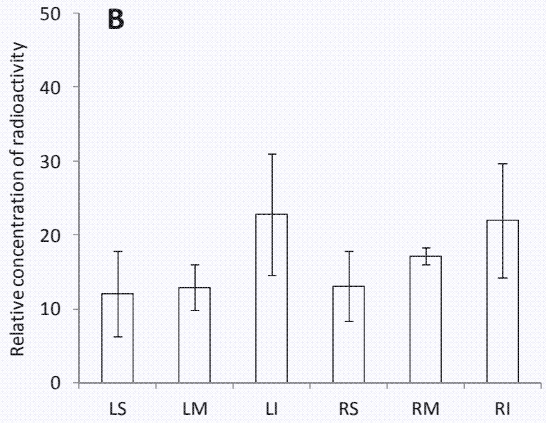
Administration way: Regional distribution

Inhalation



0.1% of the aerosol reaches the lungs





NANOMEDICINE FOR LUNG INFECTION

Administration way: Regional distribution

Intratracheal nebulization

100% in the lungs

Non uniform distribution

Aerosol inhalation

0.1% in the lungs

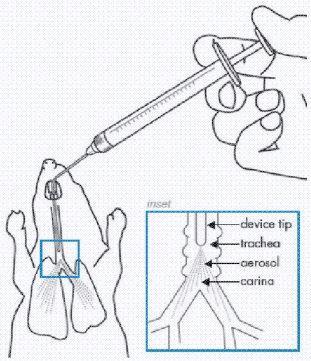
Uniform distribution

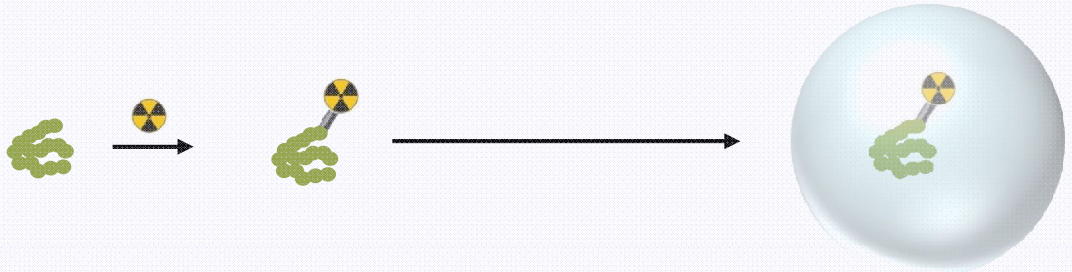
NANOMEDICINE FOR LUNG INFECTION

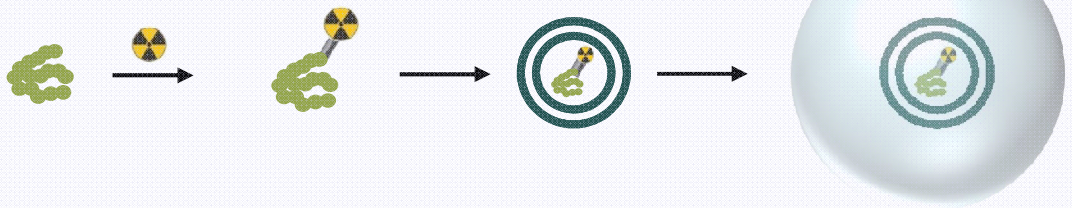
What about the drug?

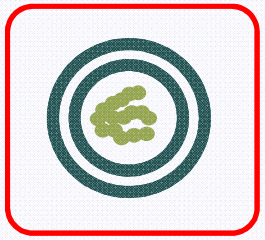
NANOMEDICINE FOR LUNG INFECTION

Residence time of the drug in the target organ?



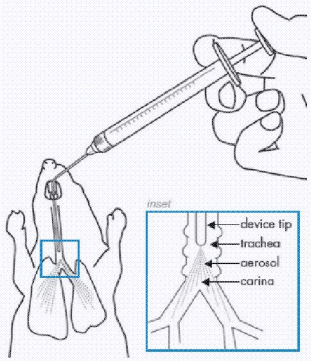


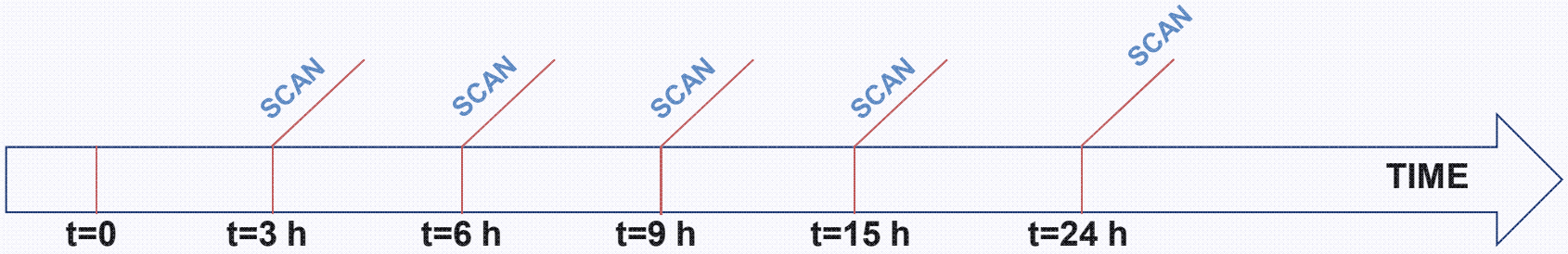




NANOMEDICINE FOR LUNG INFECTION

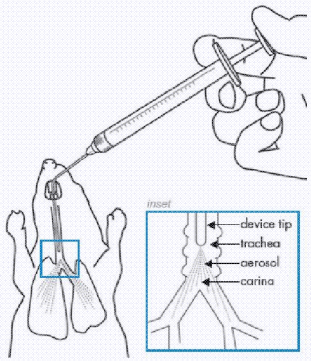
Residence time of the drug in the target organ?

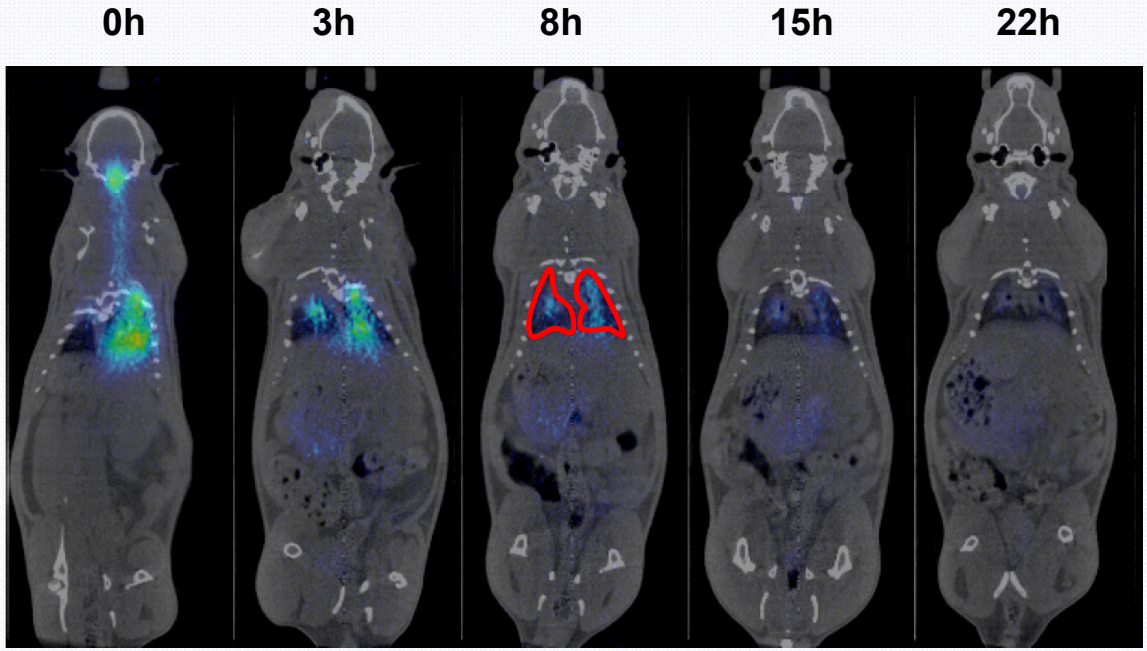




NANOMEDICINE FOR LUNG INFECTION

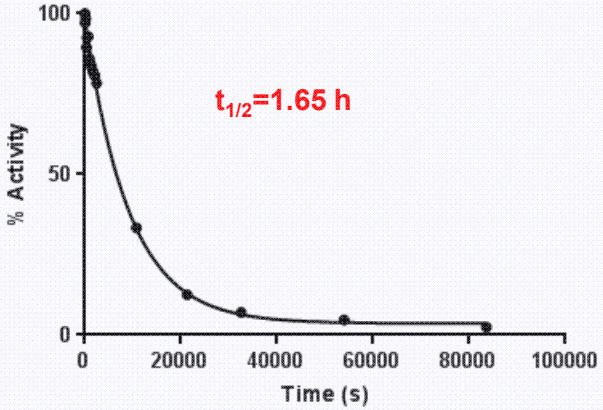
Residence time of the drug in the target organ?

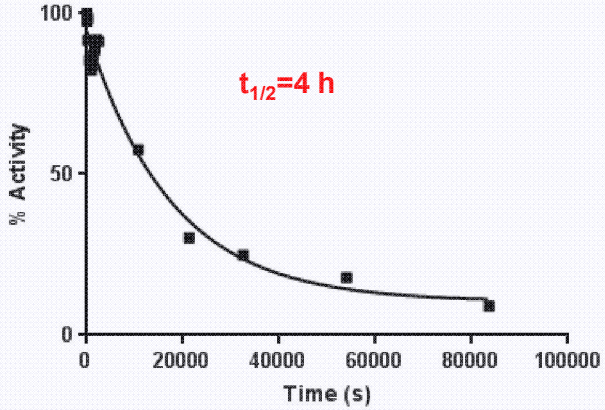




NANOMEDICINE FOR LUNG INFECTION

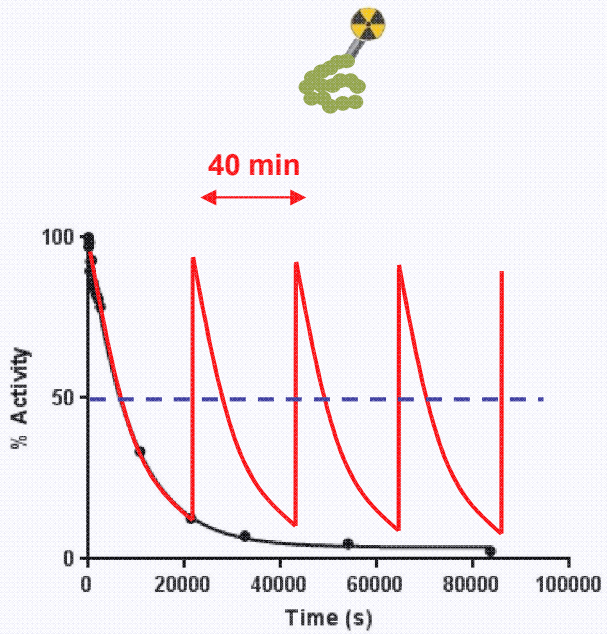
Residence time of the drug in the target organ?

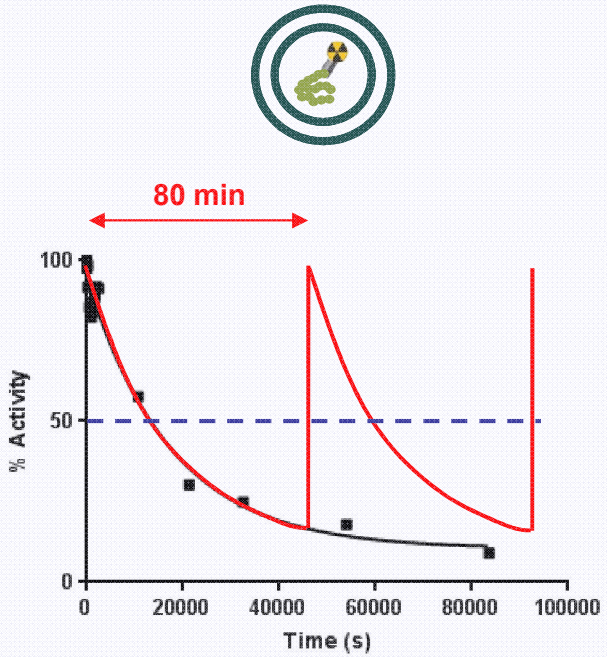




NANOMEDICINE FOR LUNG INFECTION

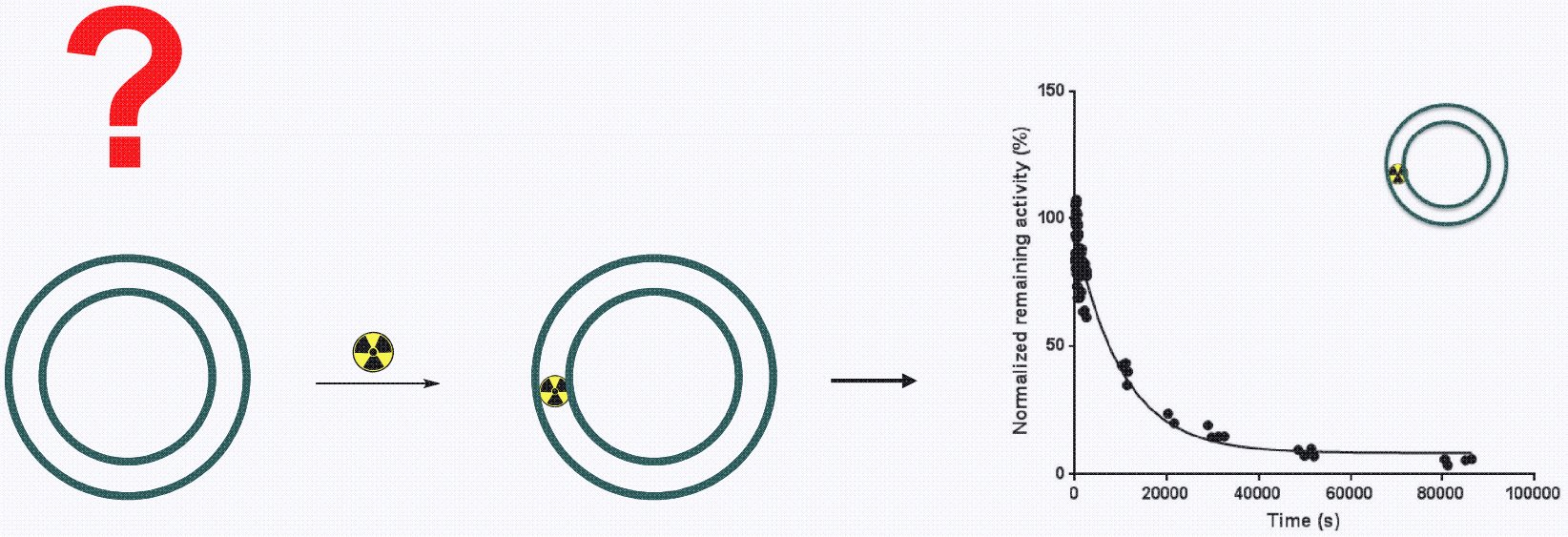
Residence time of the drug in the target organ?





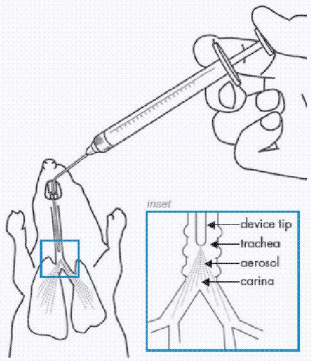
NANOMEDICINE FOR LUNG INFECTION

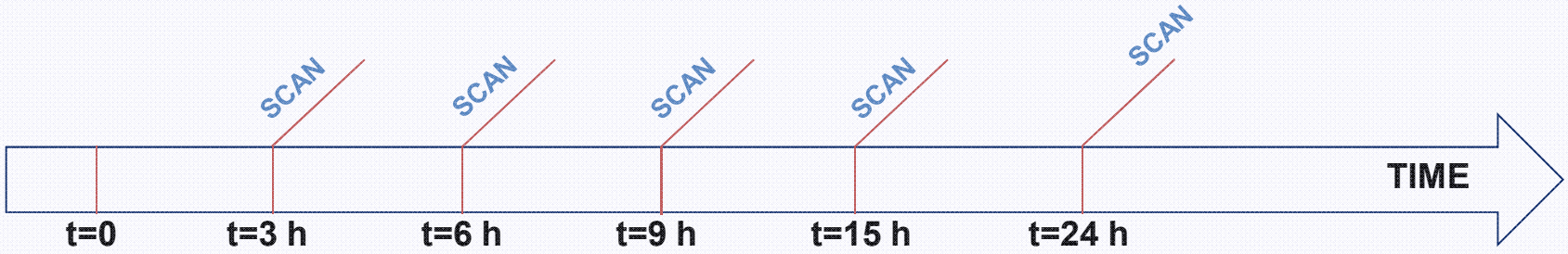
And the carrier?



NANOMEDICINE FOR LUNG INFECTION

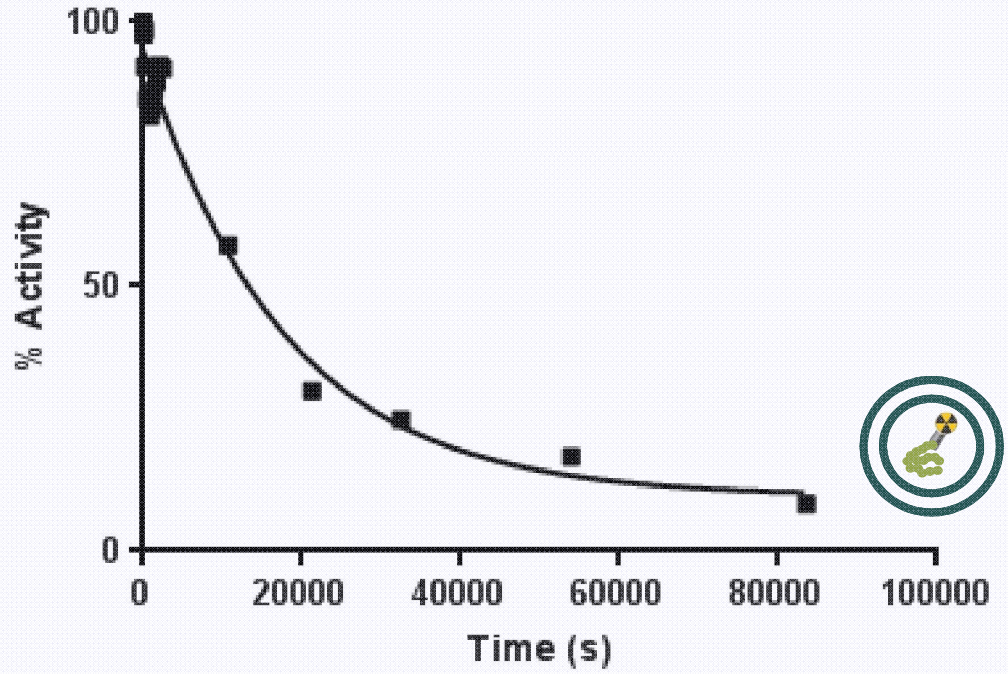
And the carrier?





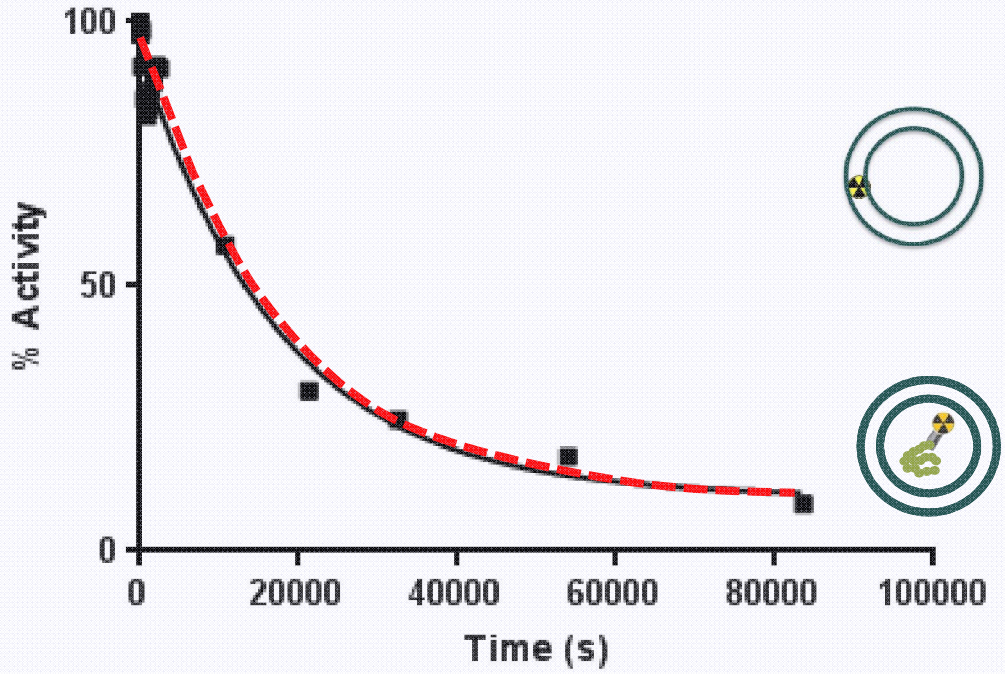
NANOMEDICINE FOR LUNG INFECTION

And the carrier?



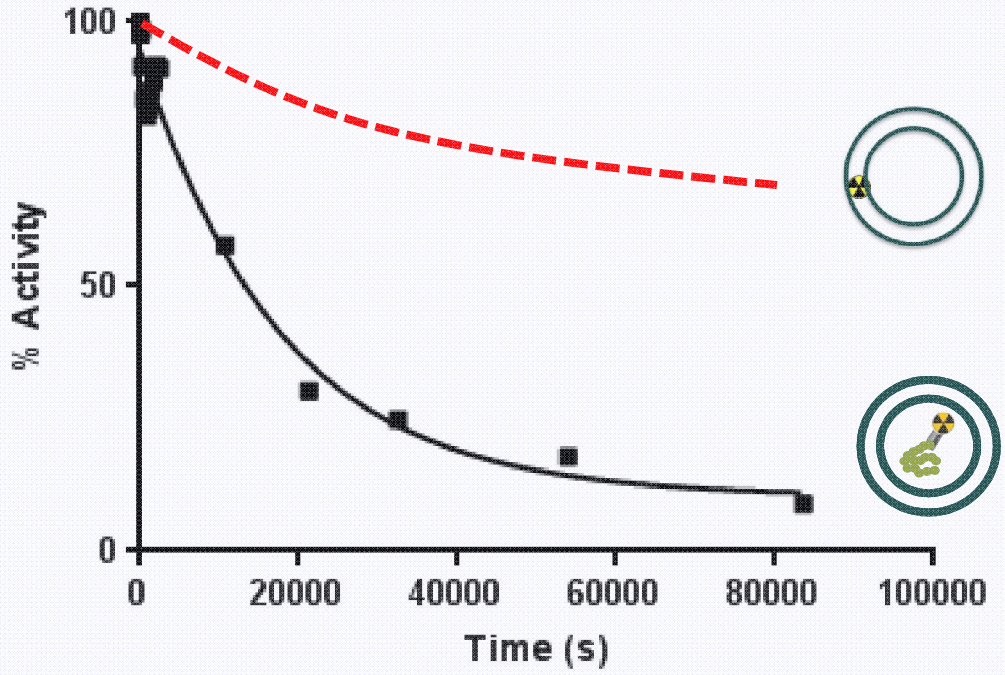
NANOMEDICINE FOR LUNG INFECTION

And the carrier?



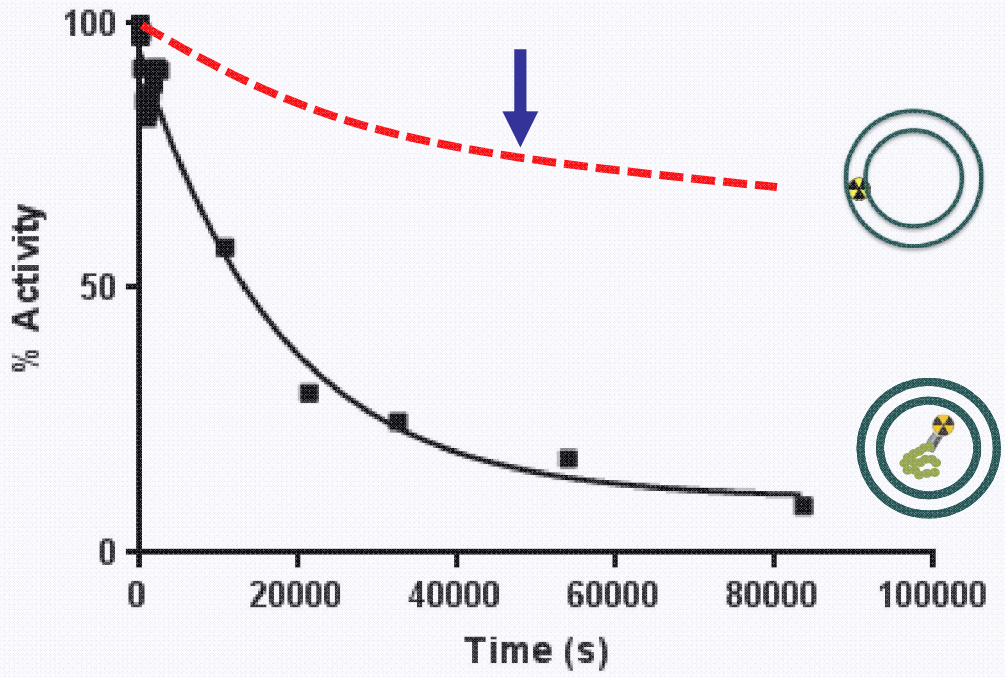
NANOMEDICINE FOR LUNG INFECTION

And the carrier?



NANOMEDICINE FOR LUNG INFECTION

And the carrier?



TAKE HOME MESSAGE

- Pulmonary administration is an alternative when the lung is the target organ
- Administration tools should be considered at the preclinical stage
- Labelling and nuclear imaging can help in:
    - Determining regional distribution
    - Getting PK information

ACKNOWLEDGEMENTS

SEVENTH FRAMEWORK PROGRAMME

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
SECRETARÍA DE ESTADO DE INVESTIGACIÓN, DESARROLLO E INNOVACIÓN

Fundació La Marató de TV3

EUSKO JAURLARITZA GOBIERNO VASCO

Gipuzkoako Foru Aldundia
Diputación Foral de Gipuzkoa


MOLECULAR IMAGING
WORKSHOP 2017
November 20th-23rd, 2017
Donostia - San Sebastian
Thank you!
MOLECULAR IMAGING WORKSHOP
CIC biomaGUNE
Biomaterialetako Ikerkuntza Kooperatiboko Zentroa
Centro de Investigación Cooperativa en Biomateriales