PNEUMONP

Introduction to the subject

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Nanomedicine is expected to gain more and more importance in the future thanks to its enormous potential, and is seen as a major driver for the European pharmaceutical industry, **helping to maintain Europe's competitiveness** and market volume in this important **commercial and scientific discovery sector.** The delivery of nano-sized biomolecule drugs, based on nucleic acids and proteins, is going to be **indispensable for the future health of European citizens,** as it represents a pre-requisite for the development of **novel efficient therapies** for diseases such as cancer and infectious diseases. In this respect, the **development of adequate nanocarriers (NCs) to transport macromolecules will be essential** in order to be able to meet future health-priority objectives. Currently, several nanopharmaceuticals are available on the market, especially for cancer treatment. However the full range of possibilities opened by the use of nanoparticles in health care systems has not yet been fully realized. Specifically, the following characteristics of nanoparticles can be manipulated to generate enormously versatile drug-carrying systems:

i) targeted delivery of drugs, thereby enhancing the therapeutic efficiency of drugs, decreasing the risk of patients suffering from potential side-effects;
ii) **enabling the transportation of a wide range of biological drugs** across a range of biological barriers;
iii) facilitating the **internalization of a drug** or even the internalization of a combination drugs;
iv) acting as carriers of imaging agents that can **increase the diagnostic accuracy and sensitivity of disease detection;**
v) **allowing drugs** (and drug combinations) **to bypass multi-drug resistance mechanisms** by facilitating the delivery of drugs within the cellular environment.

1. Antibiotic Resistance

From recent surveys, international stakeholders from the healthcare sector consider **antibiotic resistant Gram-negative bacterial infections** as one of the major global health threats currently facing the world. This is due to the lack of effective treatments available against multidrug and extremely antibiotic resistant Gram-negative bacteria. The global, and largely unrestricted, use of **broad spectrum antibiotics has generated bacterial strains** that cannot be treated with the help of standard, or even extended, antibiotic treatments. Specifically, in many countries of the world, Gram-negative bacterial infections are increasingly becoming isolated with resistance to a wide range of antibiotics, including beta-lactam, aminoglycoside, fluoroquinolone and even carbapenem antibiotics. Many of these infections are associated with **pneumonia bacterial infections, caused by organisms such as *Klebsiella pneumonia*.**

Although the increasing problem of global mutli-antibiotic resistant bacterial infections has been known for at least a decade, the development of new antibiotics by pharmaceutical companies has been very slow, mainly due to the fact that manufacturing antibiotics is not as profitable as manufacturing drugs used in the treatment of with chronic diseases. Therefore at the moment there is a **gap between global bacterial treatment requirements and active principle antibiotic discovery programs.** To address this issue, the European Union continues to fund programs scientific research and business development related to the introduction of new antibiotics, including close collaboration with large pharmaceutical companies, for example the Innovative Medicines Initiative.

PneumoNP is one of the projects chosen to be funded by the EU, which is designed to help overcome the gap between the current global bacterial infectious disease burden and the rapidly diminishing antibiotic therapy is available to treat these infections. In this respect, the objective of the PneumoNP project is to **develop a new theragnostic system for a rapid identification of bacterial respiratory tract infections and targeted treatment of the infected area with a selective therapeutic nanosystem (NS).**

The project will mainly address **multidrug resistant Gram-negative bacteria generated infections of the lungs,** using *Klebsiella pneumoniae* (*K. pneumoniae*) as proof-of-concept. The information and experience gained will act as proof-of-concept for future projects involving testing of NCAMP combinations in respiratory tract infections caused by other difficult-to-treat bacterial pathogens, including MRSA and *Mycobacterium tuberculosis.* A radically new nanotherapy will be developed, based on **antimicrobial peptides coupled to a nanosystem delivery vehicle,** which will be inhaled directly to the affected area. The use of fellow systems to deliver antimicrobial peptides (AMPs) and API Meropenem, as in this PneumoNP project, will enhance the effectiveness of antibiotic treatment regimens by improving the transportation and concentrated delivery of antibiotics to the site of bacterial infcetion. The AMPs have been chosen for their targeting efficiency towards Gram-negative bacteria, which will also increase the safety of the treatment. These peptides have already been tested against *K. pneumoniae* in pneumonia, urinary tract infection and bacteremia in animal models[6].

2. Nanosystems

Ideally, any nanosystems (NSs) used to treat patients should be biocompatible, biodegradable or easily removable and specifically designed to obtain an appropriate biodistribution, so that they specifically reach a defined target site. The differing nature of nanoparticle delivery vehicles allows the delivery of drugs, including antibiotics, to be adapted to the intended site of use.

The NSs are going to **target the lungs**, which is an attractive route for non invasive administration of a drug, offering the following advantages for NC systems:

i) Avoidance of first-pass metabolism;
ii) **Direct delivery** to the site in respiratory infections;
iii) The possibility to achieve relatively **uniform distribution** in the intrathoracic respiratory track:
iv) **Non-invasive** alternative for systemic delivery.

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3. Single chain polymer NPs (SCPNs)

Intramolecular cross-linking or collapse of single polymer chains has emerged as an efficient alternative for the synthesis of well-defined polymer NPs. This technique allows the generation of particles of around 20 nm in size, though it can be fine-tuned by controlling the molecular weight of the precursor polymer chain and the quantity of intramolecular bonds generated in the collapse. Additionally, the surface can be easily tailored according to the chemical and physical properties required through straightforward and widely used chemistry (i.e. peptide coupling).

K. pneumoniae infections are characterized by the formation of thick and blood-tinged sputum, for which the **transmucosalproperties of Polyacrylic acid (PAAc) nanoparticles** could be interesting, with the negative charges and easy elimination of these SCPNs fulfilling all of the conditions necessary to be considered good candidates for pulmonary delivery.

4. Liposomes

Liposomes are usually artificial vesicles formed by one or more lipid bilayers enclosing aqueous compartments. They have been investigated extensively as drug carriers for a variety of indications to increase the therapeutic index of the encapsulated drug. They have proven to be able to accommodate a wide variety of agents with different characteristics. **Their liposomal physicochemical properties** (like size, charge, bilayer fluidity) **can be adapted:**

1) to optimize their passage through biological barriers:
2) to optimise pharmacokinetics;
3) to enhance retention at the site of administration.

Optimal liposomal properties depend on the administration route: large-sized liposomes show good retention upon local administration (e.g subcutaneous administration), **nano-sized liposomes are better suited to achieve passive argeting upon intravenous administration.** Pulmonary administration of liposome-encapsulated drugs, can help maintain relatively high concentrations of drug in the lungs for a prolonged period of time compared to pulmonary administration of the free drug, thereby providing a sustained benefit of significant therapeutic value in the treatment of bacterial infections localised in the lungs.

Also, liposomes have proven to be well tolerated, which is in line with their (semi)natural, biodegradable nature. However, despite these advantages, only few liposomal products have entered the market, with as leading examples Caelyx and Myocet, both liposomal doxorubicin formulation, and Ambisome, liposomal amphotericin B, mostly focused in cancer treatment. Relatively little effort has been made to develop liposomes for the treatment of infectious diseases, with the commercial Ambisome formulation as the early and only exception. However, the growing, problem of antimicrobial resistance and lack of effective treatment regimens for this type of infections there is an urgent need for new antibiotics and novel pulmonary drug delivery systems.

Liposomes are formed by a **mixture of phospholipids** requiring knowledge of 5 key parameters in order to generate suitable liposomes for a particular target. These 5 key parameters are:

i) **Selection of phospholipids** for optimal pulmonary delivery;
ii) **Rigidity/fluidity of liposomal bilayers** affecting drug release kinetics;
iii) Superficial charge of the carriers to allow optimal peptide loading efficiency as well as required drug release characteristics;
iv) **Size of liposomes** impacting liposomal drug deposition pattern in the lung;
v) **Attached surface moieties** to promote cellular uptake and targeting.

5. PNEUMONP PROJECT

PNEUMONP

PneumoNP is a collaborative research program funded under the **Seventh Framework Programme**, with a **€5.7 million grant**. Starting in 2014, it is aiming at the **development of a theragnostic system for the treatment of Gram-negative bacterial infections of the lung**, with focus on *Klebsiella pneumoniae*caused infections.

Visit www.pneumonp.eu for more information on the project and regular updates on the project progress.