Project no. 026723-2

NanoBioPharmaceutics

Nanoscale Functionalities for Targeted Drug Delivery of Biopharmaceutics

Integrated Project (IP)
Thematic Priority 3: NMP

Periodic Activity Report
First Period
01.10.2006 – 30.09.2007

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<th>Period covered: from 01.10.06 to 30.09.69</th>
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<td>Start date of project: 1 October 2006</td>
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<td>Organisation name Coordinator</td>
<td>DECHEMA</td>
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Executive Summary

The NanoBioPharmaceutics project aims at the development of innovative multidisciplinary approaches for the design, synthesis and evaluation of molecular, nano- and micro-scale functionalities for targeted delivery of therapeutic peptides and proteins (biopharmaceutics). The development of functionalized nanocarriers and nanoparticle-based microcarriers for P/P delivery is both an important scientific challenge and potentially a business breakthrough for the biopharmaceutical industry. NanoBioPharmaceutics is focused on the development of functionalized nanocarriers for the treatment of various diseases based on targeted, controlled delivery of Protein/Peptide (P/P) drugs. More specifically, NanoBioPharmaceutics addresses the following scientific and technological objectives:

- Design, synthesis and functionalization of novel nanocarriers and nanoparticle-based microcarriers for targeted delivery of P/P drugs via oral, pulmonary and Blood Brain Barrier (BBB) crossing administration routes.
- Toxicological screening of the nanocarriers and investigation of the release profile of P/P drugs under various environmental conditions as well as the assessment of the biocompatibility and biodegradability of the new formulations.
- Novel pulmonary P/P carriers with improved delivery features to overcome the administration difficulties and increase efficiency of protein delivery to the deep lung.
- Oral nanoparticles P/P carrier systems capable of adhering to the gastrointestinal mucosa and also displaying protective and permeation enhancing properties.
- Establishment of an in vitro model for the assessment of nanocarriers permeability through the Blood Brain Barrier (BBB).

The project consists of ten work packages (WP). Two are related to the synthesis and characterisation of new nanostructured particles and their functionalization with P/P drugs

- WP 1: Polymer-Protein/Peptide Complexes and Nanostructures
- WP 2: Novel Nanocarrier-based Systems for Targeted P/P Delivery

One work package focuses on toxicological aspects and one on fundamental aspects related to protein-surface interaction

- WP 3: Toxicity, Immunogenicity and Degradation Testing
- WP 4: Interaction between Cells and Nanostructures

Application aspects are the major issue of the three work packages

- WP 5: Pulmonary P/P Delivery Systems
- WP 6: Oral P/P Delivery Systems
- WP 7: P/P Delivery Systems for Brain Disorders

Management, dissemination, and training aspects are addressed by

- WP 8: Dissemination and exploitation of the Knowledge/Societal Aspects
- WP 9: Training and Education
- WP 10: Project Management

According to the workplan work packages 3, 4, 5, 6, and 9 only started in the second half of the first year of the project, but some partners already initiated preparatory activities. The work packages starting at month 0 have been affected by the delay for the first prepayment transfer that slowed down the effective start of the planned work during the first 6 months period. Nevertheless, the second half of the project year was highly efficient and allowed most of the contractors to make up for lost time. The present status can be described in general as follows:

- In work packages 1 and 2 all groups involved have produced new systems and characterized them in detail. Optimisation presently still relies on internal toxicology testing according to standardized protocols.
- In work package 3 all test systems necessary for the implementation of the tasks have been established. In addition guidelines for the in-house toxicology tests of partners in work packages 1
and 2 have been developed and for the consortium as a whole a toxicology test strategy was established in close cooperation with all project partners.

- Work package 4 is well ahead of the work plan with respect to establishing cell culture based test systems and their testing.
- In work package 5 also nasal delivery is now being addressed in addition to the pulmonary route. This is a result of an expressed new interest of two industrial partners (GSK, LIPOXEN) which intend to administer vaccines in this way.
- WP6 is in time line with the work plan. The initial activities have already generated an increased interest for co-operation by a significant number of additional partners in work packages 1 and 2 that will be actively involved in the next period.
- Work package 7 is well ahead of the work plan and already performed preliminary in-vivo tests.
- Work packages 8, 9, 10 are in time line with the work plan.

It is important to note that meanwhile three groups are addressing HIV issues:

- Partner EPFL is working on new fusion inhibition peptides and their linking to polymers.
- Partner APLA is working on Fuzeon nanoparticle aggregates for crossing BBB.
- Partner GSK addresses nanoparticles loaded with P24.

The toxicological aspects of the synthesised nanocarrier systems play a prominent role within the project and all partners are aware of it. The members of the Advisory/Ethical Board were appointed according to their toxicological and ethical expertise. The most important strategic decision is that toxicological test requirements will be determined before performing animal studies. There requirements are defined by a close interaction of the respective producers of the nanocarriers with the leaders of work packages 5, 6, or 7, advised by the experts in toxicology in work package 3. For each nanocarrier this group will judge and advise to complete the toxicological data file before starting any further in-vivo testing. Accordingly, a scheme describing the test procedure has been established.

In work package 3 and 4 there is a delay with respect to the analysis of new P/P loaded and unloaded particles due to prolonged in-house toxicology test of partners in work packages 1 and 2. The underlying issues have clearly identified by the Steering Committee and corrective actions have been taken. The delays are expected to be caught up within the next 6 month. Therefore no effects on the application oriented work packages and hence no interference with the long term objectives of the project are envisaged.

From a management point of view, all main planned tasks have been correctly handled and all partners have signed the Consortium Agreement before the start of the project. All operational bodies are successfully established in time and working in a co-operative atmosphere. A strong and active management of the NanoBioPharmaceutics Consortium is ensured by a good interaction of the Management Team, the Steering Committee and the General Assembly.

The kick-off meeting in October 2006, the half year meeting in May 2007, numerous technical meetings of the work packages and visits of the Management Team members at some partner facilities allowed a good progress of the consortium building process leading to a detailed update of the necessary tasks and activities. A modus for cooperation has been established by each work package and an adjustment of the role of each partner has been done.

The co-leadership of work packages 3 and 5 has been transferred from partner GSK to partners MM and Lipoxen, respectively. Due to the strong overlap in work packages 1 and 2 with respect to the synthetic approaches and to the partners involved, the two work packages will be merged to a work package 12 in the next reporting period. In addition the activities of work package 12 will be closely linked to the R&D activities in the application oriented work packages.

The communication between the partners synthesising and modifying nanocarriers with P/P drugs and the partners of the application oriented work packages was enhanced significantly during the meetings in the first year. One important step was the preparation of the position papers of the application oriented work packages (5, 6, and 7) and their presentation by the work package leaders at the work package 1/2 meeting in April 2007. The position papers describe the state of the art of the respective delivery routes and the requirements for the nanocarriers which have to be synthesised by the work package 1 and 2 partners.
The project partners already actively started the dissemination of the results by publishing of scientific papers and presentation at relevant conferences. A leaflet has been prepared and distributed at the first NanoBioPharmaceutics conference. The project has been successfully presented at a large European conference.