Science LETTERS | Lifesome Therapeutics, December 2023

Nano-based drug delivery: an evolving landscape

by **Jean-Marie Ruysschaert**

As a PhD student, I had the privilege to meet Alec Bangham showing us a milk-like suspension that he obtained by exposing phospholipids to water. The turbid suspension was made of vesicles in which an aqueous volume is entirely enclosed by a bilayer made of lipid molecules. I did not realize that this was a unique moment in the landmark of biomembrane history and a milestone for drug delivery. **Liposomes were born.**

Their exclusive properties of rapidly sequester small and large molecules and being easily decorated with specific targets, opened the way to a novel and extraordinary drug delivery concept never achieved before. Liposomes allow site-targeting, sustained and/or controlled release, protection of drugs from degradation and clearance, superior therapeutic effects and lower toxic side effects. Experiments carried out on animals were quite promising and clinical tests were of course, the final objective. Altogether with our team in Brussels, we demonstrated that liposomes can be safely injected intravenously in patients and interestingly, liposomes allow the administration of water-insoluble material[1,2]. Intravenous injection in patients, was a new crucial step and opened nanomedicine as a new way to envisage treating patients. Consequently, several liposomal drug products were successfully approved and used in clinics over the last decades. The next step was to extend the Trojan horse concept initiated by Gregory Gregoriadis, towards the encapsulation of genetic material (DNA and RNA). Although encapsulation was possible, the yield was extremely low. Figuring out how to deliver these nucleic acid therapies -either DNA or RNA- into cells, was a major challenge and required something more sophisticated than a conventional liposome. The landscape changed completely with the discovery of a DNA-transfection protocol that makes use of a synthetic **cationic lipid**. Small unilamellar liposomes containing cationic lipids interacts spontaneously with DNA to form lipid–DNA complexes with a 100 % entrapment of the DNA[3]. Since then, several companies contributed to the development of new cationic lipids as cellular *in vivo* transfection agent.

The invention of cationic liposome-forming lipids (which are non-existent in nature) triggered a boom in the area of gene therapy during the 1990s. **Cationic liposomes** emerged as valuable alternative to viral transfection vectors, gene therapy companies were founded and numerous clinical trials have been conducted. Indeed, cationic lipids were absolutely essential for COVID-vaccines, since fragile mRNA molecules used in COVID-19 vaccines can't get into cells on their

own. Without these lipid shells, there would be no mRNA vaccines neither lipid nanoparticles (LNPs) would be going into millions of arms over the course of the years. Undeniably this established an unprecedented success for the lipid field, a consequence of course of the hard work carried during the last 50 years.

Nevertheless, nanomedicine is still in its infancy and there is an urgent need to explore new competences with the aim of advance in the development of new therapeutic modalities.

As a participant throughout this fascinating technological revolution and as a team member of Lifesome Therapeutics, I feel enthusiastic and honoured to contribute to the development of the only one market-available therapeutic nanocarrier made of a single lipid compound, that can be decorated with any active molecule and safely administered as nanotube or liposome, among other possible structural conformations. I am convinced that this will lead to promising advancements in oncotherapy, in the battle against antibiotic resistance and potentially among many other therapeutic areas.

(**1**) Coune A., Sculier J.P., Hildebrand J., Frühling J., Strijkmans P., Brassine C., Ghanem G., **Ruysschaert J.-M.** and Atassi G. IV administration of a water-insoluble antimitotic compound entrapped in liposomes. Preliminary report on infusion of large volumes of liposomes to man. *Cancer Treat. Rep*., 67(11): 1031-1033 (1983).

(**2**) Sculier J.P., Coune A., Brassine C., Laduron C., Atassi G., Frühling J. and **Ruysschaert J.-M.** Intravenous infusion of high doses of liposomes containing NSC251635, a water-insoluble cytostatic agent. A pilot study with pharmacokinetic data. *J. Clin. Oncol.*, 4(5): 789-797 (1986).

(**3**) Lonez C, Vandenbranden M, **Ruysschaert J.-M.** Cationic lipids activate intracellular signaling pathways. *Adv Drug Deliv Rev*. 64(15):1749-58 (2012).

About the author

Jean-Marie Ruysschaert received his Master degree and Ph.D. degree in Chemistry from the Free University of Brussels. He was collaborating during his PhD work with the Nobel Prize Laureate, Ilya Prigogine. He worked as a postdoctoral researcher at the Cambridge University (U.K.), Weizmann Institute of Sciences with E. Katchalski (Israel), and Carnegie Institute with D. Pagano (Baltimore,MD). He then joined the Department of Chemistry at the Free University of Brussels where he created the laboratory for Chemistry and Physics of Macromolecules at the Interfaces and later the Center for Structural Biology and Bioinformatics (Brussels, Belgium) of which he became Director since 2000. He has authored more than 400 articles, reviews and monographies in international journals (h-index:71) and he was awarded the Avanti Lipid Prize in 2017. His research interest is mainly focused on the structures, activities and interactions between membrane components (lipids and proteins) and more recently on the immunology of lipid nanoparticles.