Obituary

Demetrios Papahadjopoulos (1934–98)

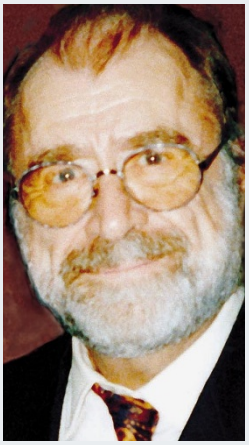
Innovation in liposomes

Demetrios Papahadjopoulos, who died in San Francisco on 21 September, was a pioneer in the development of liposomes and their applications. One of these is their use as a system for the efficient, targeted delivery of drugs and vaccines, leading to optimal pharmacological action.

Papahadjopoulos was born on 24 August 1934 in Patra, which has been one of Greece's western gates for more than 2,500 years. He obtained a BSc in chemistry from the University of Athens and a PhD in biochemistry from the University of Washington in Seattle, under D. J. Hanahan. His interest in phospholipids and their role in blood coagulation (the subject of his thesis) brought him in 1966 to A. D. Bangham's laboratory at the Institute of Animal Physiology, Babraham, Cambridgeshire, where liposomes had just been discovered. His fascination with them was to remain undiminished throughout his life.

Liposomes had originally been recognized as closed, semipermeable bilayers of phospholipids (very similar to cell membranes) that can entrap water and solutes. Some of Papahadjopoulos's work, both in Babraham, and later on at the Roswell Park Memorial Institute in Buffalo, New York state, dealt with the development of novel, reproducible methods for making liposomes of a defined vesicle-size distribution. He was thus able to study bilayer permeability to ions, which was found to reach a maximum at the liquid crystalline transition temperature of the phospholipid. This research greatly contributed to the understanding of the physical nature of liposomes (and, indirectly, of cell membrane biophysics) in terms of their structure, the stability of the bilayer and mobility of the lipids within it, their interaction with proteins, and membrane fusion. Liposome research had made the transition from art to science, and Papahadjopoulos's contribution to it was decisive.

In the early 1970s, liposome research branched into biology and therapeutics when it was shown that liposomes could be a way to deliver entrapped drugs and vaccines to cell targets *in vivo*, thus avoiding many of the problems associated with direct drug use. At Roswell Park Memorial and, from 1978, at the Cancer Research Institute of the University of California at San Francisco, Papahadjopoulos and his group were quick



to appreciate the significance of this new angle. Among the central questions they addressed was that of how liposomes are taken up by cells. Their elucidation of the mechanisms concerned, by observing the migration of gold-containing vesicles from the coated pits on the cell's membrane to the cell organelles known as lysosomes, was particularly influential. These studies were much facilitated by the development in the Papahadjopoulos laboratory of a method for the efficient entrapment of solutes in liposomes, the so-called reverse-phase evaporation technique. This allowed the encapsulation of substantial amounts of material in the liposomes' aqueous phase.

Soon after the study of liposome uptake by cells, Papahadjopoulos started investigating the possibility of using liposomes for DNA transfer. In 1981, two papers appeared (one from Papahadjopoulos's laboratory) reporting on their use for the transfer of DNA into cultured cells. Initially, however, transfection efficiency was low, and much work was done in his laboratory to improve efficiency by manipulating the lipid composition of liposomes and the conditions under which they were incubated. In 1983, the first reports of liposome-mediated gene transfer *in vivo*, and of successful expression of those genes, began to appear independently. This line of research has culminated in a potentially effective clinical approach to gene therapy and genetic immunization.

Another aspect of the drug-carrier concept of liposomes that captured the imagination of many a liposomologist was the prospect of using them for the ligand-mediated targeting of drugs to selected cells. The approach consists of attaching to the liposome surface molecules, or fragments of molecules, that have a particular affinity for other, specific molecules on the target-cell surface. This too was an area where Papahadjopoulos excelled, with several of his techniques on the conjugation of cell-specific antibodies to the liposomal surface being widely adopted.

The capacity of liposomes to deliver relatively large amounts of drug, with the help of only a few molecules of ligands, is an advantage over the use of ligands conjugated to the drugs themselves. But there were several drawbacks to the approach, mainly related to the immune reaction prompted by the ligand and further potentiated by the liposomal carrier. Moreover, targeted, as well as conventional, liposomes are relatively rapidly cleared from the blood circulation and intercepted by cells of the reticuloendothelial system (mostly fixed macrophages) before they can reach their intended targets.

Papahadjopoulos and co-workers tackled the latter problem, and to some extent circumvented it, first by the use of gangliosides added to the liposomal surface; and, later (independently with several other groups), with polyethyleneglycol in the same role. His group dominated this second approach and was able to produce liposome formulations that persisted in the circulation long enough to deliver therapeutic doses of drugs to tumours. The approach led eventually to the liposome-based drug Doxil, licensed for clinical use and marketed by Sequus Pharmaceuticals (of which Papahadjopoulos was a co-founder).

Demetrios Papahadjopoulos — Demetri, to his friends and colleagues — was justifiably proud of the many young people he trained, not only in his chosen branch of science, but also in scientific integrity, the need for precision and reproducibility in experimentation and, above all, in what Pasteur defined as the origin of scientific creativity: ***Savoir s'étonner à propos*** (to know when to be astonished). His was a multifaceted personality, for he was also artistically sensitive (and part-owner of an art gallery), and with a high degree of historical, political and philosophical awareness. For those qualities, and his intellect and warmth, Demetri will be sorely missed — by his many friends and colleagues, and by his wife Brigitte Sternberg-Papahadjopoulos, and three sons from a previous marriage.

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