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NEW GENERATION LIPOSOMES STAY IN THE BLOOD

MONTREAL—New developments in liposome design may provide the way to overcome the obstacles posed by their short serum half-life. Almost since Alec Bangham coined the term liposomes, they have been studied as carriers for targeted drug delivery. But central to any therapeutic use is the ability to manipulate their pattern of *in vivo* clearance. In general, this has been a rather daunting task since liposomes are rapidly sequestered by the reticuloendothelial system (liver and spleen). And while this natural hepatic sequestration has been spectacularly exploited to deliver antimonial drugs to treat visceral leishmania—their efficacy is increased 80-fold—it has impeded realizing the wider potential applications of liposomal delivery systems.

Speaking at the Fourth International Congress of Cell Biology here in August, Dimitri Papahadjopoulos (University of California, San Francisco) described a series of recent experiments, done in collaboration with Alberto Gabrizon (Liposome Technology Inc., Menlo Park, CA), which may offer a general solution to this hitherto intractable problem. Terry Allen (University of Alberta), who chaired the session, has independently obtained many of the same results.

As explained by Papahadjopoulos, three factors contribute to increasing the stability of liposomes in the circulation—reducing their size, increasing the rigidity of the lipid bilayer, and modifying the bilayer composition to contain a small percentage of hydrophilic groups. Passing the liposomes through a Nuclepore membrane by high pressure exclusion results in uniform vesicles of slightly less than 1,000 Å in diameter. When this is done with standard liposomes composed of phosphatidyl glycerol (PG), phosphatidyl choline (PC), and cholesterol (Chol), their distribution in the circulation—after four hours—increases from less than one percent to approximately five percent. But a change of the minor PG component to the hydrophilic ganglioside, GM-1, makes a dramatic difference. Circulating liposomes increase to 34 percent, and levels in the liver and spleen decrease from 70 to 32 percent.

And finally, substituting distearyl-phosphatidyl choline (DSPC)—a rigid lipid with a high phase transition—for PC gives the most promising liposome the researchers have produced. A unilamellar, 1000 Å liposome composed of GM-1:DSPC:Chol (1:10:5) has a reticuloendothelial to blood ratio of 0.7 after 24 hours.

Based on model building and experiments in which numbers of hydrophilic lipids were utilized, Papahadjapoulos thinks that the key factor in conferring plasma stability is that the negatively charged groups in GM-1 (and phosphatidyl inositol, which also enhances stability) are shielded behind carbohydrate hydroxyls and therefore are not well recognized by clearance proteins.

Are such liposomes improved vehicles for delivering drugs to non-hepatic targets? The answer from preliminary experiments is an emphatic yes. When injected into Balb/C mice implanted with lymphomas, the second-generation (GM-1:DSPC-containing) constructions were 30-fold more concentrated in the tumors than were standard liposomes.

—**Harvey Bialy**