Cellular Manipulation

The nucleation sites that initiate cavitation represent a key feature in any cavitation phenomenon. Consequently, in recent years there have been significant potential advances in therapies that involve the introduction into the target region of nuclei that will promote and/or control cavitation. For example in HIFU therapies, the controlled and confined introduction of nuclei to the target region prior to the HIFU bombardment, can lead to more tightly controlled treatments and reduced collateral damage.

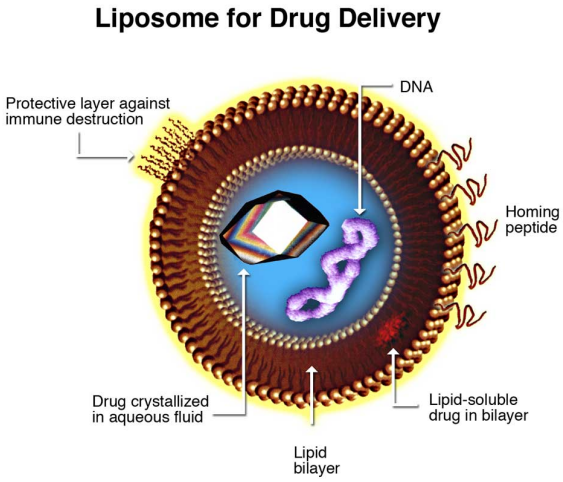

Figure 1: General structure of a liposome for drug delivery.

Most evident in this emerging new aspect of the use of cavitation in medicine is the deployment of liposomes or injected microbubbles in conjunction with focussed ultrasound. A liposome is a very small spherical structure (up to $10\mu m$ is size) formed from the same material as a cell membrane. As illustrated in figure 1 they can be manufactured with a variety of contents, structures and appendages in order to carry drugs to desired sites, to preferentially attach to desired cells or sites or to include a gaseous interior so that respond (explode) when bombarded with ultrasound. This technology (for a comprehensive review see Ibsen *et al.* (2013)) has created a whole new spectrum of possible therapies in which liposomes or special microbubbles (see, for example, figure 4) are devised to transport drugs to specific sites where ultrasound is then used to deposit the drug at its intended target in a procedure known as *sonoporation* (Blomley *et al.* (2001)).

A wide spectrum of special purpose liposomes have been designed and a idea of the variety can be gauged from the selection shown in figure 3. In the example shown in figure 4 gas-filled microbubbles have been designed with drug and gas loaded interiors. A stabilising coating surrounds the bubble which may be targeted to specific tissue by incorporating protein ligands on the surface. Drugs can be incorporated by themselves or, if insoluble in water, in an oil layer. Perhaps the most exciting of these therapies is the possibility of the delivery of genetic material to a chosen site (see, for example, Blomley *et al* (2001), Price *et al* (1998), Taniyama *et al.* (2002)) as illustrated in figure 5. Focussed ultrasound is then used to cavitate the gene-loaded microbubble and the shockwaves or microjets thus generated cause the genetic material to be injected into the surrounding cells. Even more remarkable are the recent efforts to manipulate individual microbubbles using optical trapping (Prentice *et al.* (2005)) or by embedding magnetic particles in the liposome so as to move them electromagnetically (Stride *et al* (2009)). The liposomes or microbubbles can

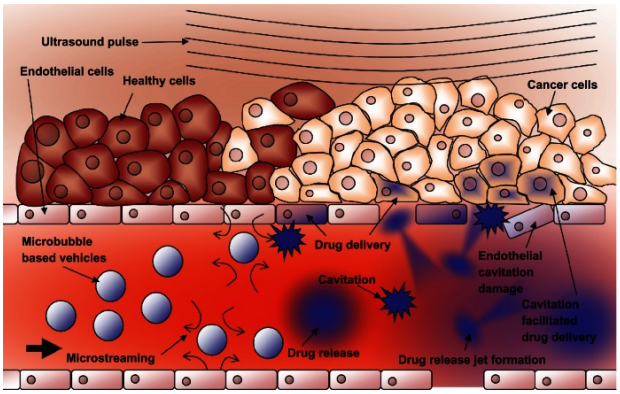

Figure 2: Schematic of cancer treatment with liposomes and ultrasound (from Stride *et al.* (2009)).

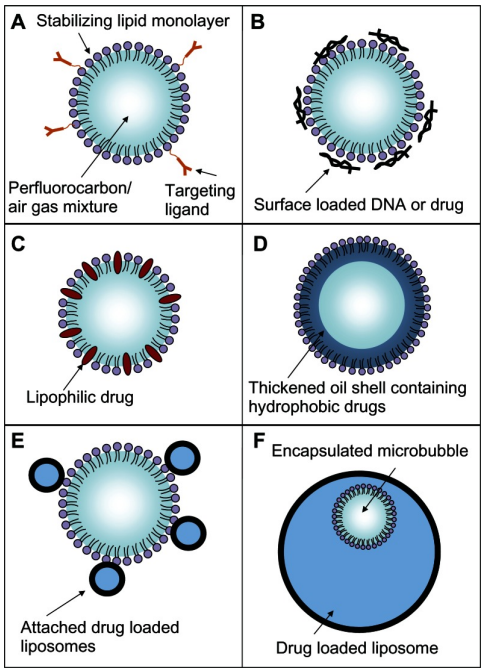

Figure 3: Some of the various designs of special purpose liposomes from Stride *et al.* (2009).

then be placed in an optimal location next to the targeted cell or tissue, even to the extent of injecting new DNA without destroying the target cell (Prentice *et al.* (2005)).

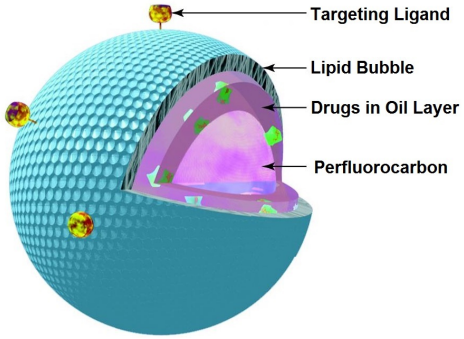

Figure 4: Example of a liposome or microbubble constructed for drug delivery by sonoporation (from Blomley *et al* (2001)).

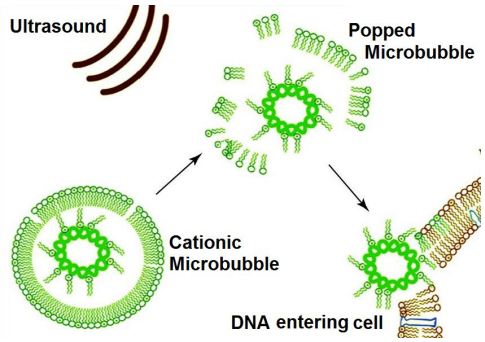

Figure 5: Gene delivery using ultrasound and microbubbles (from Blomley *et al* (2001)).