EMERGING RESEARCH FRONTS - 2009

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Terry M. Allen & Pieter Cullis talk with *ScienceWatch.com* and answer a few questions about this month's Emerging Research Front Paper in the field of Pharmacology & Toxicology. The authors have also sent along images of their work.

Article: Drug delivery systems: Entering the mainstream
Authors: Allen, TM;Cullis, PR
Journal: SCIENCE, 303 (5665): 1818-1822, MAR 19 2004
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SW: Why do you think your paper is highly cited?

The paper summarizes the state of the art, in 2004, for drug delivery systems (DDS) and provides examples of several DDS that have received clinical approval. At that time, there was increasing publicity about, and interest, in nanomedicines, and the field was in a stage of exponential growth. It appears to have appealed to a captive audience, or maybe we could say that we were fortunate that it was "the right paper at the right time."

Within a few pages, it summarized the major background information on the mechanism of action of DDS, and attempted to provide the know-how on how to select appropriate drugs, to design DDS with appropriate characteristics such as size, stable drug retention, and appropriate release rates, and to select applications where the DDS have a higher chance of success.

Does it describe a new discovery, methodology, or synthesis of knowledge?

The paper is basically a synthesis of the knowledge that was contributed by our laboratories and co-workers, along with our wonderful series of colleagues, too many to mention, that have been working on DDS going back several decades. Indeed, "we stood on the shoulders of giants."

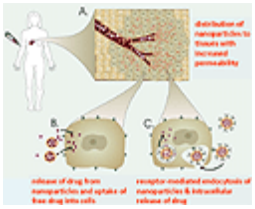
Would you summarize the significance of your paper in layman's terms?

These days, we are beginning to see a number of negative comments in the press concerning the potential hazards of nanotechnology. In some cases, these concerns may be justified. However, all applications of

nanotechnologies are not equal, and the paper clearly shows how the use of nanomedicines—a subclass of nanotechnology—has been of enormous benefit to, in particular, cancer patients, by improving their therapeutic outcome and/or improving their quality of life by reducing the side effects of the cancer drugs.

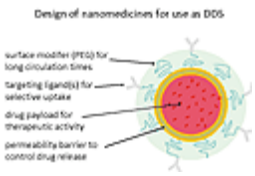
At the time of the writing of the paper, DDS had already experienced thousands of patient-years of use, and over a decade of clinical experience with few or no serious side effects associated with their use. This remarkable record continues to this day, and shows that DDS will have an important role in medicine as we go forward, if applications are chosen judiciously and go through the proper regulatory controls.

Figure 1



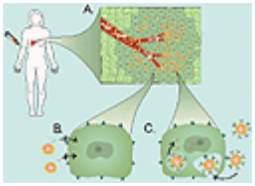
Passive and ligand-mediated...

Figure 2



Design of nanomedicines...

Figure 3



Ligand-mediated targeting...

How did you become involved in this research and were any particular problems encountered along the way?

Theresa M. Allen:

As a young post-doctoral fellow, I worked in a laboratory that was among the first to purify the acetylcholine receptor. I became interested in studying the properties of the purified receptor by reconstituting it in a lipid membrane. This led to a general interest in membrane structure and function, and eventually to a continuing interest in the use of lipid nanoparticles as DDS.

One of the big problems that plagued the field of DDS in the early days was a destruction of the lipidic DDS, because they were seen as "foreign" entities by the body and prematurely taken up into macrophages, which are the body's main defense system.

By studying the surface structure of red blood cells, which the body allows to circulate for many days, we devised a method to "coat" the liposomes with hydrophilic molecules that increased their invisibility to the macrophages. Once the DDS could avoid the macrophages, they circulated long enough to concentrate in diseased tissues such as tumors —leading to their clinical approval.

Pieter Cullis:

I became involved in drug delivery research as a result of my early studies on the roles of lipids in membranes. In that work I employed simple "model membrane" systems consisting of dispersions of lipid in water (also known as liposomes) to gain insight into the potential roles of individual lipid species in biological membranes.

In the 1980s I used the model membrane approach to investigate the influence of trans-membrane ion gradients on the ability of lipids to move across membranes, demonstrating that transbilayer pH gradients can lead to asymmetric trans-membrane distributions of lipids such as are observed in biological membranes. This work required the development of new procedures to generate small liposomal systems in the 100 nanometer size range that exhibited trans-membrane pH gradients.

In order to make these "liposomal nanoparticle" (LN) systems we developed a rapid extrusion procedure whereby aqueous dispersions of lipid are extruded under high pressure through filters with 100 nm pore-size filters to rapidly (10 minutes or less) produce LN systems of 100 nm diameter. This technique is now the preferred method for making LN worldwide.

We then showed that when these liposomal systems were subjected to a trans-membrane pH gradient (e.g., pH 4 inside, pH 7 outside), weak base drugs, which includes many anticancer drugs, could be loaded into the interior of the liposome, achieving encapsulation efficiencies approaching 100% and the stable encapsulation of tens of thousands of drug molecules per LN. This discovery had a major impact in the emerging field of drug delivery using LN as it provided methods, which were previously not available, for rapidly making liposomes and then efficiently loading them with the desired drug.

In the 1990s, we investigated whether nucleic acid-based macromolecules such as antisense oligonucleotides (OGN) and plasmids coding for therapeutic genes could be encapsulated in LN, developing novel and efficient ways of encapsulating such macromolecules into small (~100 nm), well-defined LN systems that exhibited little surface charge.

The development of small uncharged LN systems is vital for *in vivo* applications to reduce toxic side effects and to avoid rapid clearance by the reticuloendothelial system (RES) following i.v administration. LN that avoid rapid clearance are necessary to access non-hepatic tissues in the body. Three kinds of therapeutic are resulting from this work. The first concerns well-defined LN systems containing one plasmid per LN that exhibit long circulation lifetimes following i.v. injection and preferentially transfects tumor tissue with the plasmid gene.

Second, these techniques allow well-defined LN containing thousands of OGN to be made. Subsequent work showed that LN containing OGN that are immunostimulatory (such as those containing CpG sequences) dramatically enhance the innate immune response to the encapsulated oligonucleotides. We are currently investigating the utility of these systems as stand-alone agents to fight disease by stimulating the innate immune system, as agents to enhance the potency of MAb as well their properties as potent adjuvants for vaccine applications.

A third and very exciting area concerns the extension of this work to delivery of siRNA *in vivo*, which is the major focus in my lab currently.

Where do you see your research leading in the future?

Nowadays, promising new therapeutics are coming out of genomics and proteomics. But these new therapeutics, which are mostly macromolecules, e.g., siRNA, can be fiendishly difficult to deliver *in vivo* for a variety of reasons related to their premature destruction and/or elimination from the body, and their difficulties in crossing cell membranes.

In recent years we and others have been researching ligand-targeted DDS, where surface ligands such as antibodies can trigger the internalization of the DDS into the target cells. It is now widely believed that these targeted DDS may represent our best hope for delivering new therapeutics such as siRNA to diseased cells.

Do you foresee any social or political implications for your research?

We have alluded above to the social and political implications of the unfettered application of nanotechnology, and the fear of the unknown in the form of unidentified toxicities associated with the unapproved, unregulated use of products containing nanoparticles.

However, we want to state clearly and unambiguously that nanomedicines, such as the DDS systems currently approved for clinical applications, have been widely examined over many years in both humans and animals, and have been subjected to the stringent guidelines and scrutiny of regulatory authorities such as the FDA. We can be confident that these products are safe and effective.

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