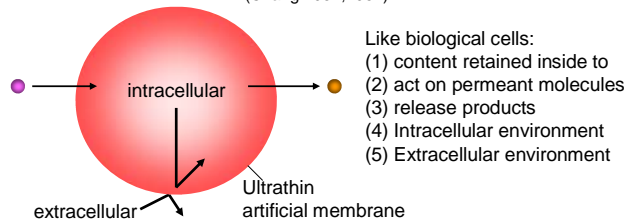


WHAT ARE ARTIFICIAL CELLS?

“Artificial Cell is not a specific physical entity. It is an idea involving the preparation of artificial structures of cellular dimensions for possible replacement or supplement of deficient cell functions. It is clear that different approaches can be used to demonstrate this idea” (From Chang 1972 Monograpy). Since that time, the idea of artificial cells has progressed way beyond this 1972 prediction (Figure 1).

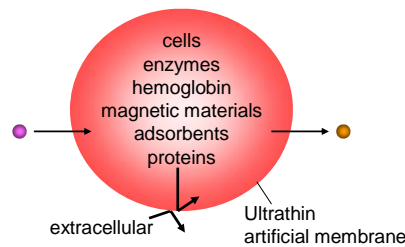
Basic principle of early Artificial Cells

(Chang 1957,1964)



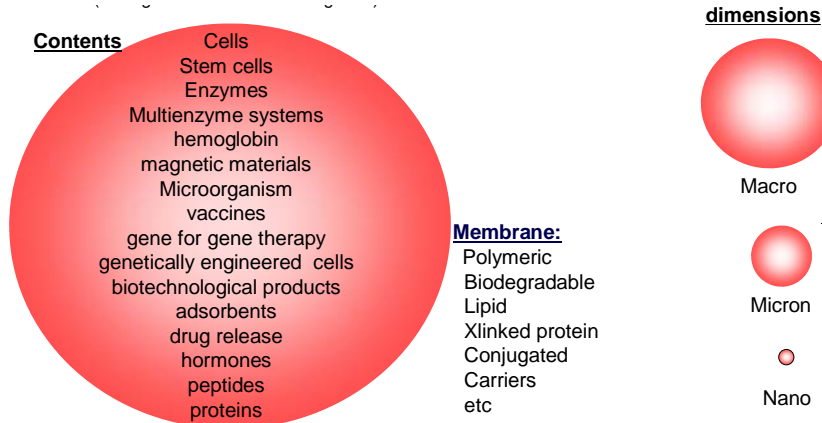
Types of early Artificial Cells

(Chang 1957 to 1966)



Present status of Artificial Cells

(Chang 2005 Nature Rev Drug Disc)



While an undergraduate at McGill, Chang prepared the first artificial cell (Chang, honors Physiology research report, McGill Medical Library 1957). He continued this work while in medical school, and Ph.D., and showed in more detail the potential of artificial cells and published the first paper on this topic (Chang, **Science**, 1964). After his Ph.D.(1965), he continued on his research (Chang & Poznansky, **Nature**, 1968; Chang, **Nature**, 1971 and Chang, **1972 Monograph on Artificial Cells** 1972). The initial research on artificial cell (Chang, 1957, 1964) forms the basic principle that has been extended for use in many areas by many groups (Chang **Nat.Rev.Drug Disc.** 2005; Chang **2007 Monograph on Artificial Cells**; and www.artcell.mcgill.ca 2012). This is already (1) in routine patient use as a miniature device for the treatment of severe acute poisoning (2) approved for routine use in patients for transfusion in South Africa to avoid HIV contaminated blood and in Russia to booster blood supply (3) In a number of drug delivery system in patients. It is also being extensively developed around the world for many other areas of applications. These include treatment for diabetes, liver failure, kidney failure, genetic diseases, endocrine diseases, cancer.; biosensors etc. Nonmedical uses include agriculture, industry, aquatic culture, nanocomputers and nanorobatics

Each major progress in other areas has led to stepwise progress in artificial cells. First there is the coming of age of polymer chemistry and biomaterial. Then there is increasing interest in biotechnology and nanobiotechnology. Then there are ongoing important progress in molecular biology and genomics. Examples of the ongoing development and extension of “artificial cells include nanoparticles, nanotubule, lipid vesicles, liposomes, polymer tethered lipid, polymersome, microcapsules, bioencapsulation, nanocapules, nanosensor, macroencapsulation, red blood cell mimicks, polyhemoglobin, conjugated hemoglobin, synthetic cells and others. One can expect that there will be other future important progress in developments and extensions.

BASIC FEATURES OF ARTIFICIAL CELLS (figure 1)

- (1) Artificial cells can contain the same biological material as biological cells: including hemoglobin and all red blood cell enzymes, microsomes, cytosol, polymerases, ribosomes and transcription/translational system. In addition, they are more versatile since adsorbents, magnetic materials, drugs, cells, stem cells, enzymes, multienzyme systems, multi-compartment systems, hemoglobin, microorganism, vaccines, gene for gene therapy, genetically engineered cells, hormones, peptides, and many other materials can also be included separately or in combination.
- (2) In addition to being of cellular dimensions in the micron range, they can also be in the macro range, in the nano range or in the nanobiotechnological range
- (3) Membrane of artificial cell separates its content from the outside, but at the same time the membrane can be prepared to selectively allow different types of molecules to cross. For example, one can prepare artificial cell membranes that selective allow the movement of molecules according to molecular size, lipid solubility, affinity to carrier mechanisms etc. By selecting the proper membrane material, the permeability can range from membrane that does not allow any molecules to cross to those that allow even very large molecules like proteins to

cross. The membrane material includes polymer, biodegradable polymer, lipid, crosslinked protein, lipid-polymer complex, lipid-protein complex and membrane with transport carriers.

- (4) Surface properties of artificial cell membrane can be varied by (1) incorporation of negative or positive charge; (2) incorporation of albumin to increase blood compatibility; (3) incorporation of antigens to bind antibodies or antibodies to bind antigen; (4) incorporation of polysaccharide like heparin or polyethylene glycol (PEG) to increase compatibility or retention time in circulation.
- (5) The artificial cell membranes can be ultrathin and yet strong. There is a large surface area to volume relationship. For example 10 ml of 20 μm diameter artificial cells has a total surface area of 2,500 cm^2 that is the same as that in an artificial kidney machine. Since the artificial cell membrane is also 100 times thinner, permeant molecules can potentially move across 10 ml of 20 μm diameter artificial cells 100 times faster than that across the artificial kidney machine [Chang, 1966]. In addition, the microscopic size of artificial cells allows material to diffuse rapidly inside the artificial cells.

POSSIBLE USES FOR ARTIFICIAL CELLS

TABLE I: ARTIFICIAL CELL: applications

Chang (2005) Nature Review: Drug Discovery
Chang (2007) Artificial Cell Monograph
Chang (2009) www.artcell.mcgill.ca

Hemoperfusion
Drug delivery
Blood Substitutes
Enzyme & gene therapy
Cell & Stem Cell Therapy
Biotechnology & Nanobiotechnology
Nanomedicine
Regenerative medicine
Agriculture, Industry, Aquatic culture
Nanocomputers and nanorobatics
Nanosensors etc

Initially, as biotechnology was not yet an area of world interest, Chang used the feature in (5) above. This is the use of nanotechnology of ultrathin polymeric membrane to developed artificial cells containing adsorbents for hemoperfusion for the treatment of poisoning. His clinical trials in patients resulted in FDA approval. This has been a routine treatment for acute poisoning, especially in regions where these are much less costly than dialysis. Terman and later Yu and others have extended this to hemoperfusion using immunosorbents.

Many groups have also extended artificial cells for use in drug and gene delivery systems calling these artificial cells by different names of microcapsules, microparticles, nanocapsules, nanoparticles, liposomes, polymersomes, etc. Chang's original research on artificial cells containing magnetic material has also been developed by other groups for drug delivery, biosensors and bioreactor.

The HIV epidemic and concerns over contaminated blood have stimulated a number of groups to develop Chang's earlier idea of blood substitutes, including nanobiotechnology based polyhemoglobin. Others have developed his principle of polyhemoglobin for clinical trials. The high incidence of HIV in South Africa has led this country to approve the routine clinical use of polyhemoglobin in patients. Russia has most recently approved the routine patient uses of this Polyhemoglobin blood substitute. For more wide spread use in other countries, we and other groups are extending this using nanobiotechnology to develop second generation and third-generation blood substitutes.

His basic research on bioencapsulation of enzymes and cells has been developed by him and others around the world for diabetes, liver failure, kidney failure, genetic diseases, endocrine diseases, cancer. Further research is needed to allow for more than one year of function after implantation. His group has recently shown that only 2 weeks of function is needed, when using artificial cells containing bone marrow stem cells for liver regeneration. This way, one implantation results in the regeneration of liver and recovery of rats with 90% of liver resected. Another recent approach is his group's use of artificial cells containing enzymes or cells for oral administration. This way, each artificial cell works as a microdialyser/bioreactor as it travels down the intestinal tract. We have used this for enzyme replacement therapy. We also study the use of oral administration of artificial cells containing cells to remove unwanted metabolites. Other groups are developing our basic findings for clinical trials in patients.

These and other areas of applications including agriculture, industry, aquatic culture, nanocomputers, nanorobotics being developed by others are summarized in Table I:

Further readings:

This centre's McGill University Website: www.artcell.mcgill.ca for **free complimentary access to**

*Chang 1972 Monograph on Artificial Cells

*Chang 2007 Monograph on ARTIFICIAL CELLS: biotechnology, nanotechnology, blood substitutes, regenerative medicine, bioencapsulation, cell/stem cell therapy.

* Review articles, video interview etc