Professor Chang has been called the “**Father of Artificial Cells**”. While an honours B.Sc. student at McGill University, he invented and prepared the first artificial cell (Chang, Hon B.Sc. research report, 1957 http://www.medicine.mcgill.ca/artcell/514.pdf). He continued this research in medical school then Ph.D. (Chang **Science** 1964, **Nature** 1971, **monograph** 1972 http://www.medicine.mcgill.ca/artcell/1972bookcovercr.pdf)..

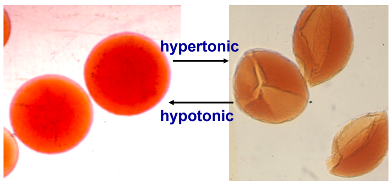
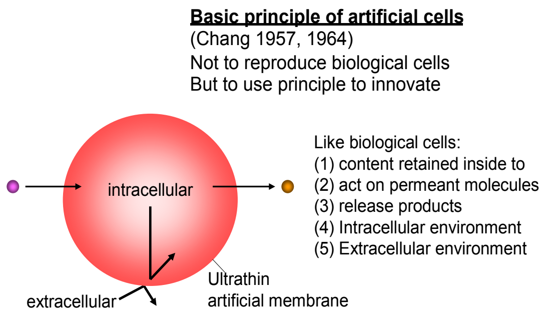


Figure on left from Chang, **Science** 1964 published in B/W showing ulthrathin polymeric membrane artificial red blood cells with hemoglobin and enzyme system of red blood cells.



HOWEVER, right from the beginning he emphasizes that he is not trying to reproduce biological cells since nature and cell culture can do a much better job. His aim is to use this as a basic principle to innovate and go outside the box – especially there can be unlimited variations in the content, dimensions and membranes.

He now has more than 546 full papers and 29 books. He and researchers around the world has since expanded the basic principle of artificial cells into very large areas of uses around the world.(Table I). A few examples are as follows.

1. Nanomedicine: is one of the many areas that came from his invention of artificial cells (Artificial Cells: the beginning of Nanomedicince http://www.medicine.mcgill.ca/artcell/nanobk_ch1.pdf) He was the first to use nanotechnology and nanobiotechnology to prepare artificial cells containing biologically active material with 10-20 nanometer membrane thickness polymers, crosslinked proteins or other membranes. He was also the first to prepare soluble nanobiotechnological complexes. Nanomedicine is now a large area and extensively developed around the world. His peers name him honorary president of the Int Soc Nanomedical Sciences.

2. Micro based miniature device: Hemoperfusion: While waiting for world interest in biotechnology, Chang first used nanotechnology of ultrathin polymeric membrane artificial cells containing adsorbents for hemoperfusion. His clinical trials in patients resulted in FDA approval. This has since been used routinely in patients for acute poisoning and detoxification around the world especially where the cost is reasonable. Extensions have resulted in immunosorbent hemoperfusion for immunological diseases like Lupus etc. http://www.medicine.mcgill.ca/artcell/hpbk_ch1.pdf

ARTIFICIAL CELLS IN 2017

Chang (2005) ***Nature Review: Drug Discovery***
Chang (2007) ***Artificial Cell Monograph***
Chang (2010) ***WIRE Nanomedicine & Nanobiotechbology***
Chang *(2013)* ***in Selected topics in Nanomeidicine***
Chang (2014) ***opening chapter in Blood Substitutes***

- Micro and nano based miniature devices
- Drug delivery:
- Blood Substitutes and oxygen therapeutics:
- Enzyme and gene therapy:
- Cell & Stem Cell Therapy:
- Biotechnology & Nanobiotechnology
- Nanomedicine
- Regenerative medicine
- Agriculture, Industry, Aquatic culture
- Nanocomputers and nanorobatics
- Nanosensors etc

3. Blood substitutes: HIV contaminated blood in the 1980s led many groups to develop his basic research on nanobiotechnology based polyhemoglobin as blood substitutes. http://www.medicine.mcgill.ca/artcell/2014kimgrb.pdf This has been developed by 2 groups and tested clinically in the U.S. and is now approved for routine use in South Africa and Russia where there is still problem related to H.I.V. contaminated donor blood. His group is now working on a more complete 3rd generation system with enhancement of all 3 functions of red blood cells. In animal study in a 90 min sustained severe hemorrhagic shock model this is superior to whole blood http://www.medicine.mcgill.ca/artcell/translation.pdf Peer recognition has resulted in his being appointed the Honorary Symposium President of the biannual International Symposia on Blood Substitutes including the most recent ones: 2011 XIII Harvard, Boston, 2013 XIV Blood Transfusion Institute, China , 2015 XV Lund Sweden and 2017 XVI Montreal. http://www.medicine.mcgill.ca/artcell/meetings.pdf

4. Delivery systems: Many groups have also extended his idea of artificial cells for use in nanomedicine based drug delivery systems and they call these artificial cells as microcapsules, microparticles, nanocapsules, nanoparticles, liposomes, polymersomes etc. Artificial cells can now be prepared in the micro, nano or soluble nanodimension complexes. His earlier work on biodegradable polymeric peptide delivery system www.medicine.mcgill.ca/artcell/1976changbiodegr.pdf has now been developed around the world especially in the nano dimensions. Jiang's group in Peking University uses the basic principle for biodegradable polymeric growth factor release conduit connect a branch of C7 on the normal side to the C7T1 trunk on the paralyzed side, resulting in neural connection and function on the limb of the paralyzed side resulted from stroke or brain trauma in patients (Zhang et al Jiang, Art Cell, Nanomed & Biotech. Online then Dec issue of 2017 – to receive Best 2017 paper award for this journal)

5.Bioencapsulation of cells/stem cells/genetic engineered cells followed his original research on cell encapsulation. This is being investigated around the world for potential clinical uses in liver failure, kidney failure, genetic diseases etc http://www.medicine.mcgill.ca/artcell/510.pdf http://arwww.medicine.mcgill.ca/artcell/511.pdf

6. Other areas: Advances in molecular biology, biotechnology, nanotechnology and other areas have led to rapid developments in the use of his invention of artificial cells for nanomedicine, bioencapsulation, gene therapy, enzyme therapy, cell/stem cell therapy, regenerative medicine, blood substitutes, liver/kidney support systems and even in agriculture, aquatic culture, fermentation industry, food industry, nanorobotics, nanocomputers and other areas.(Table I). More details are summarized in http://www.medicine.mcgill.ca/artcell/2005NatureRev.pdf . and in more details in his 2007 monograph http://www.medicine.mcgill.ca/artcell/2007%20ebook%20artcell%20web.pdf

Why the basic principle of artificial cells can have such wide range of applications?

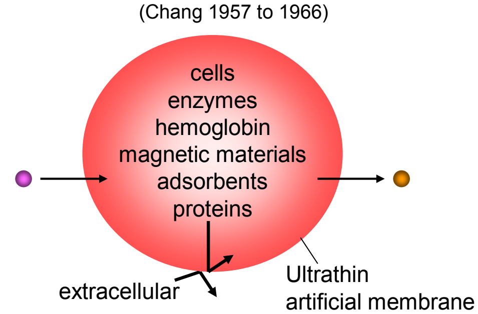
The unlimited possible variation in the content, dimensions and membrane materials for artificial cells as shown in the figure below is the reason why many uses are possible.

*(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/translation system. In addition, they are more versatile s adsorbents, magnetic materials, drugs, cells, stem cells, enzymes, *(2)*multienzyme systems, multi-compartment systems, hemoglobin, microorganism, vaccines, gene for gene therapy, genetically *(3)*engineered cells, hormones, peptides, and many other materials can also be included separately or in combination.

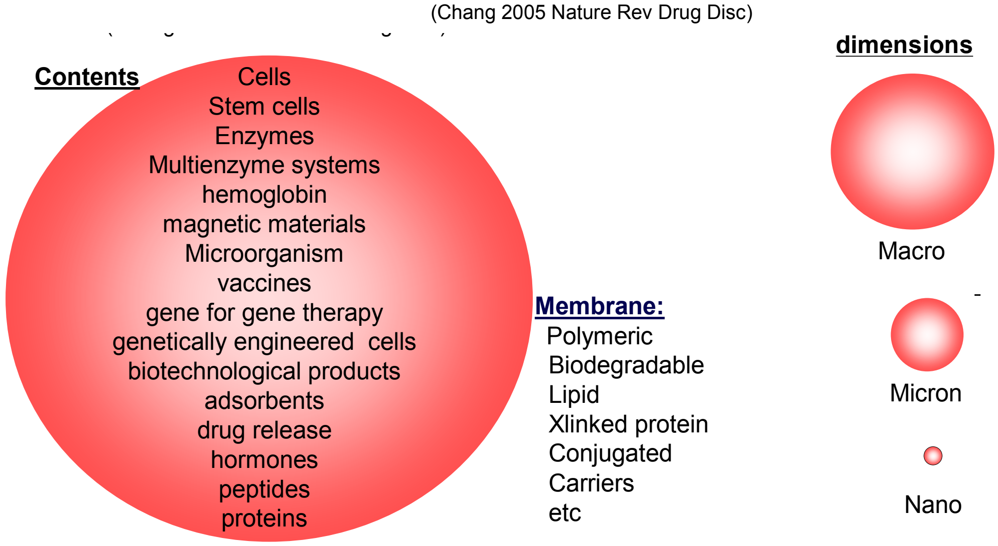
*(4)*In addition to being of cellular dimensions in the micron range, they can also be in the macro range, in the nano range or in the soluble nanobiotechnological range

*(5)*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

Types of early Artificial Cells
(Chang 1957 to 1966)



Present status of Artificial Cells
(Chang 2005 Nature Rev Drug Disc)



Appointments: Medical Research Council of Canada (MRC) awarded him “MRC scholar (junior career)” (1965-68), then the MRC career investigator award (1968- until after 65 age limit 1999). At McGill, He rose from assistant professor (1966) to associate professor (1969) to full professor (1972). In 2007 he asked to be appointed emeritus professor to allow him to have more flexibility in international activities. He continues to be the Director (since 1979) of McGill’s Artificial Cells & Organs Research Centre, an http://www.medicine.mcgill.ca/artcell/CentreChart.pdf His other international activities include for examples: Honorary Professor, Peking Union Medical College of the Chinese Academy of Medical Sciences (CAMS), Honorary Professor, Blood Transfusion Institute (CAMS), Honorary Professor, Nankai University, Honorary Professor. Shantou University Medical College. Honorary President, International Society (network) Artificial Cells, Blood Substitutes & Biotechnology;

Editor in chief Artificial Cell, Nanomedicine and Biotechnology, an international journal, Francis & Taylor Publisher, U.K., Reuter impact factor 5.605 , ranks 4th Biomedical Engineering journals (77)

Awards: His awards start with the 1969 “Inaugurate First Incentive Lecturership” given in Sweden at Karolinska Institute, Lund Univ and Gothenburg Univ Hospital, then others including Clemson Award, Silver Medal Award of Bologna Univ, First Julius Silver Lectureship of Technion, Confederation Medal Award, Queen Elizabeth 25th Jubilee Medal, ISBP Annual Award, Virage Award, ISBS life time achievement award, first “Outstanding Research Award” of the Int Academy of Nanomedicine, Q.E. Diamond Jubilee Medal,. He also received the highest Canadian civilian decoration of Order of Canada. In 2011 he was voted the Greatest McGillian out of 700 nominee in McGill’s 190 years history http://www.medicine.mcgill.ca/artcell/voting%20result.pdf .Other details on his public service website: http://www.medicine.mcgill.ca/artcell and C.V.: http://www.medicine.mcgill.ca/artcell/changpub.pdf

Detail C.V. including publications and books http://www.medicine.mcgill.ca/artcell/changpub.pdf

Detail review: Monograph on Artificial Cells

“ARTIFICIAL CELLS: biotechnology, nanotechnology, blood substitutes, regenerative medicine, bioencapsulation, cell/stem cell therapy” by TMS Chang, World Scientific Publisher/Imperial College Press 435 pages. Free online access: http://www.medicine.mcgill.ca/artcell/2007%20ebook%20artcell%20web.pdf

> *Book reviewed by A Gerson Greenburg, MD, PhD, Professor Emeritus of Surgery, Brown University, U.S.A. “This volume is the most comprehensive review of the field of artificial cells and associated fields published to date. It refreshes the knowledge of the experts while informing the naive of the history and promise of the future. Written in a conversational style and very well illustrated for fact and emphasis, it is an easy and informative read. Presented in easily accessible form are the underlying theories and concepts of artificial cells, blood substitutes, nanomedicine, regenerative medicine and stem cell therapy in the context of specific clinical situations ranging from general to very specific diseases. Basic science observations support the tested or proposed clinical applications in an exact manner. This volume contains a near encyclopedia quantity of information, carefully and logically assembled and presented. Future developments in the field will depend on the essential information presented here. An essential read for anyone interested in this field, the vision and foresight of this senior scientist and leading statesman of the field makes the topic accessible and understandable.”*

Comments by his peers

Greatest McGillian in the university’s 190 years history *A 2011 world wide poll voted the inventor of artificial cells, Chang, as the “Greatest McGillian” out of 20 finalists from 700 nominee in McGill University’s 190 years history.* http://www.medicine.mcgill.ca/artcell/votingresult.pdf

The Canadian Academy of Health Sciences "Dr. Chang’s original ideas were years ahead of the modern era of nanotechnology, regenerative medicine, gene therapy, stem cell/cell therapy and blood substitutes. Evidence of his stature within the international scientific community was confirmed by 2 nominations for the Nobel Prize".

United Kingdom journal, New Scientist: In 1957, Thomas Chang was completing his final year as an undergraduate at McGill University in Montreal. … He would make the first artificial cell...... has grown into a dynamic field....worldwide. …. artificial cells is now a sophisticated marriage of microbiology, chemistry and biotechnology, the concept remains as straightforward as Chang's original notion. Theoretically, an artificial cell can contain virtually anything: oxygen, drugs, enzymes, antibodies, cell extracts and even cells themselves.... can now create artificial cells with roughly 30 different polymers, as well as several kinds of proteins. ......in 1961(Bangham) also added lipids to the list …."liposomes"

Journal of the British Royal Society of Chemistry , "Chemistry in Britain": Professor Tom Chang ……when he started work in the 1950's he was ploughing a lone furrow. Chang is credited with inventing microencapsulation, …….. can emulate both in vitro and in vivo the behaviour of some natural cells. "Artificial cells" already have many medical applications..... chronic renal failure, drug poisoning, liver failure, enzyme therapy and metabolic function replacement. He told Chemistry in Britain: "When I first started work it was considered too far-fetched, but by 1966 when I demonstrated the value of artificial cells in hemoperfusion and detoxification there was a surge in interest and curiosity. … interest in artificial cells and especially modified hemoglobin as a blood substitute has taken off".

"American Medical News(American Medical Association)" (Mark Moran):
"For nearly 40 years, Dr. Chang has pursued the development of artificial blood, and his work has laid the foundation for products that may be available in coming years. These products, however, are not true red blood cells but modified hemoglobin molecules for short-term transport of oxygen .... Today, Dr. Chang is working on products that more closely resemble nature's own creation........."

"Blood Weekly",U.S.A.: "The conference (VI International Symposium on Blood Substitutes) coincides with the 40 year anniversary of Chang's initial efforts back when he was a student at McGill University. This started … the modern approach of red blood cell substitutes……. McGill University, where Chang and his colleagues have been instrumental in advancing the field of blood substitute research".

Modern Drug Discoveries, ACS Publications: "The first encapsulated cells were developed as far back as the 1960s, when T.M.S. Chang and colleagues first reported the ….. microencapsulation of cells. The vision of using these cells for therapeutic purposes was present from the start…….. Several polymeric encapsulation systems have been developed or are currently being tested in clinical trials…. Many …. are examining the use of biocompatible .. membranes to surround the encapsulated cells"

Nature Medicine, "Cell encapsulation: promise and progress" G. Orive et al
"In 1964 Chang (Chang. **Science** 146(3643):524-525) proposed the idea of using ultrathin polymer membrane microcapsules for the immunoprotection of transplanted cells and introduced the term "Artificial Cells" to define the concept of bioencapsulation. Since then …bioencapsulation has provided a range of promising therapeutic treatments for diabetes, hemophilia, cancer and renal failure".

From 50th Anniversary Special Gold Edition of the Official Journal of The American Society for Artificial Internal Organs The 1966 paper by Chang is one of the 25 landmark papers selected for this Gold edition. The editorial comments "…Chang is the originator of artificial cells…for medical applications such as related to the artificial kidney, artificial liver, detoxification, enzyme therapy etc… in addition… he is also recognized for his work in the artificial blood field on hemoglobin type products. (Others included Kolff, inventor of artificial kidney; Scribner for chronic hemodialysis; Gibbon on heart-lung machine; Cooley first human implant of artificial heart; Kantrowitz on intra-aortic balloon pumping; Kolobow on oxygenator)
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