ARTIFICIAL CELLS: EXECUTIVE SUMMARY

The name of “Father of Artificial Cells” has been given to the originator. While an honor B.Sc. student at McGill University, no one took Chang’s proposal for artificial cells seriously. He prepared some preliminary artificial cells on his own in his dormitory room and was then allowed to complete this in the teaching laboratory for his required honor research project (Chang, Hon B.Sc. research report, 1957). He continued this research in medical school then Ph.D. (Chang Science 1964, Nature 1971, Nature 1978. Artificial Cells Monograph 1972) and for the rest of his research career to the present with 560 full papers. (references and full texts available at www.medicine.mcgill.ca/artcell)

Invited Monograph on Artificial Cells (Chang 1972) (Charles C Thomas Publisher), he stated that: “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. My initial attempts were to model the simplest of biological cells, red blood cells. Each of the artificial cells consists of a spherical ultrathin polymer membrane enveloping a microdroplet of hemoglobin and enzymes from hemolysate. The potential of artificial cells in biomedical research and clinical application is only limited by one’s imagination. An entirely new horizon is waiting impatiently to be explored

For a practical demonstration of its potentials he analyzed the effect of the ultrathin membrane and large total surface area of a small handful of microscopic artificial cells. He found to his surprise that the mass transfer is many times that of a standard hemodialysis machine. Based on this he applied ultrathin membrane to microscopic absorbent and designed a small hemoperfusion device. After his in...
vitro studies and animal safety and efficiency studies. He personally carried out clinical trials at McGill's RVH, then help a Montreal company to scale up and personally carrying out clinical trials leading to FDA approval and a successful blood purification device. A large US dialysis company bought the company and removed the product from the market. He had no vote against this since for ethical reason he did not want stocks and no stock no vote.

Jafron Co. One of his past trainees, late Professor YU YT, helped a Jafron Co in China, [http://en.jafron.com](http://en.jafron.com) using Chang’s published method. It now has around 200 researchers and 1800 employees. It is the 3rd largest medical device company in China. Their clinical results support Chang’s earlier clinical finding in acute poisoning, kidney failure, liver failure etc. Their products has since been used routinely in patients in China and 25 other countries. This success has stimulated extensive interest on artificial cells.

**PERSPECTIVES**

**A. Nature (Sept 2018) published a special issue on synthetic cells**
[https://www.nature.com/articles/d41586-018-07285-1](https://www.nature.com/articles/d41586-018-07285-1)

The editorial included "...urges bottom-up biologists to set their sights on definite applications, such as artificial blood". (own note: indeed, Chang’s research has resulted in a simple polyhemoglobin artificial blood approved for use in South Africa and Russia for use to avoid HIV contaminated blood. His group is working from bottom up and just completed a soluble nanobiotechnology complex with enhancement of all 3 red cell functions) In 2017, researchers from 17 laboratories in the Netherlands formed the group Building a Synthetic Cell with €18.8 million (US$21 million) Dutch Gravitation grant. In September, the US National Science Foundation (NSF) announced its first profram on synthetic cells, of $10 million. European investigators, have proposed synthetic cell as one of the European Commission’s Future and Emerging Technologies Flagship Scheme that has funding of €1 billion.

**B. China**

1. "Thomas Ming Swi Chang Artificial Cell Research Institute" with 4 artificial cells related research centres. This is the final stage of organisation as part of Shenzhen University's large new medical complex to be opened in mid 2020 with 1500 patient beds and research facilities. Shenzhen is the high technology zone in China.

2. "Academician TMS Chang Artificial Cell Research station" in Shantou University Medical School with research already ongoing.

**C. Artificial cell, Nanomedicine and Biotechnology, an international journal (Chang Editor in Chief (1986-2020), Emeritus editor (2020-) (Taylor & Francis Publisher)**

Recent explosive interest in these areas has also led to the annual submission increasing from the usual around 500 , to 1,389 in 2018 and > 2,400 before the end of 2019. Despite the usual acceptance of 36%, the publisher could not handle this and had to stop new submission until they have reorganized how to manage the large number of required external reviewers. Editor in chief is now also too time consuming thus resigned in 2020 but invited to stay on as emeritus editor.

**D. 2019 review (Chang)**

This has been viewed >3,000 times in less than 1 year. This review shows that progress in this area has now progressed well beyond his 1972 predictions. ARTIFICIAL CELL has evolved into nanomedicine, biotherapeutics, blood substitutes, drug delivery, enzyme/gene therapy, cancer therapy, cell/stem cell therapy, nanoparticles, liposomes, bioencapsulation, synthetic cells, cell encapsulation/scaffold, biosorbent/immunosorbent hemoperfusion/plasmapheresis, regenerative medicine, encapsulated microbe, nanobiotechnology, nanotechnology [https://www.tandfonline.com/doi/full/10.1080/21691401.2019.1577885](https://www.tandfonline.com/doi/full/10.1080/21691401.2019.1577885)
张明瑞院士介绍

- 世界人工细胞创始人，被誉为世界“人工细胞之父”，也是国际纳米医学创始人
- 诺贝尔奖风向提名（人工细胞和纳米医学领域的杰出成就，1985年和1998年
- 为了纪念麦基爾（McGill）大学190周年，大学提名700名校友入围为全世界投票选举麦基爾190 年历史最伟大的人。张明瑞院士以7,501票被选为“最伟大的麥基爾人”

1933 年出生於中國廣東省汕頭市. 在汕頭完成了小學和在香港
完成了中學後，就進入了加拿大著名的麥基爾大學進修醫科. 1957
年仍然是加拿大滿地可市的麥吉爾大學生理學的本科生，他就成功地發明了世界上第一人造細胞
被譽為“人造細胞之父”，“人造細胞是微米系和纳米系统的
原始,它的發明引致了『人造細胞』在納米醫學、納米生物技術、基因治療、酶療法、細胞/幹細胞治療、癌症
治療、再生醫學、血液代用品、和肝臟支持系統上的應用。它甚至產生了對農業，水產文化，發酵工業，食品
工業，生物技術，納米機器技術等諸多領域發展的影響.

- 1957年，『人造細胞』的研製成功
- 1957年，學士學位 (B.Sc., 麥吉爾大學)
- 1961年，醫學博士學位(MD,CM, 麥吉爾大學)
- 1965年，博士學位(Ph.D, 麥吉爾大學)

- 加拿大皇家醫學院院士 FRCPC (专业医学研究，包括设计和进行临床试验，导致FDA批准)
- 加拿大皇家學會院士 FRS(C)

- 获颁发加拿大勋章: 發明『人造細胞』
- 創辦主任 - 麥吉爾大學人造細胞及器官研究中心
- 终身教授 - 麥吉爾大學醫學院生理學部
- 终身教授 - 麥吉爾大學醫學院醫學部
- 终身教授 - 麥吉爾大學醫學院生物医学工程部.

- 国际人工细胞/血液代用品与生物技术协会创始人(现任名誉主席)
- 国际纳米医学学会创始人（现任名誉主席）
- 中国医学科学院名誉教授
- 北京协和医学院名誉教授
- 南开大学荣誉教授
- 汕头大学医学院张明瑞院士工作点

- 名譽總裁 - 國際人造細胞, 血液代用品,生物技術學會
- 名譽總裁 - 國際纳米醫學學會
- 《Nature》《Science》等国际高水平学术期刊上发表学术论文 560多篇
- SCI杂志《Artificial Cells, Nanomedicine and Biotechnology》主编 1980-2020 荣誉主编2020-
- Book series《Regenerative Medicine, Artificial Cells, Nanomediciney》创始人和主编2006-
部分的简历
http://www.medicine.mcgill.ca/artcell/1SeptDays.pdf

央电视台[华人世界]: 加拿大 华人科学家张明瑞: 克服困难 研究出人工细胞http://people.cctv.com/m/a/index.shtml?id=ARTI6IPLK2vvWJ2kzsQqIbWi180915


执行摘要

小型血液灌流装置
为了切实展示其潜力，他分析了超薄膜和少量显微人工细胞的大总表面积的作用。
他惊讶地发现其运输率是血液透析机的许多倍。在此基础上，他通过超薄膜包被的含吸附剂的人造细胞，并设计了一种小型血液灌流装置。经过他的体外研究和动物安全性及效率研究。
他亲自在McGill的RVH进行了临床试验，然后帮助一家蒙特利尔公司扩大规模并亲自进行了临床试验，从而获得了FDA批准和成功的血液净化设备。

健帆公司 最近他过去的一位受训者，已故的俞教授使用张的公开发表的方法在中国帮助了健帆公司 http://www.jafron.com 这公司有约200名研究人员和1800名员工。是中国第三大医疗器械公司。
他们的临床结果支持张在急性中毒，肾衰竭，肝衰竭等方面的临床结果。其产品已在中国和其他25个国家的患者中常规使用。这一成功激发了人们对人造细胞的广泛兴趣。

血液替代品
张院士的 第一代血液替代品 基础研究(聚血红蛋白研究)
己被公司开发以生产产品己用于在南非和俄罗斯来避免HIV感染的血液。
张院士刚刚完成了第3代血液替代品: 可溶纳米生物技术复合体（[聚血红蛋白-三种类型的红细胞酶]
增强了所有3种红细胞的功能）。他与中国一家公司合作，为临床开发。

2019评论（Chang）在一年中已查看了>3,500次。人工细胞已发展成为纳米药物，生物疗法，血液替代品，药物输送，酶/基因疗法，癌症疗法，细胞/干细胞疗法，纳米颗粒，脂质体，生物包囊，复制合成细胞，细胞包囊/支架，生物吸附剂/免疫吸附性血液灌流/血浆置换，再生医学，封装微生物，纳米生物技术，纳米技术
ARTIFICIAL CELL evolves into nanomedicine, biotherapeutics, blood substitutes, drug delivery, enzyme/gene therapy, cancer therapy, cell/stem cell therapy, nanoparticles, liposomes, bioencapsulation, replicating synthetic cells, cell encapsulation/scaffold, biosorbent/immunosorbent haemoperfusion/plasmapheresis, regenerative medicine, encapsulated microbe, nanobiotechnology, nanotechnology

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ABSTRACT
It is only in the last 20 years that many of the original ideas on artificial cells are being increasingly applied and extended by researchers around the world. Artificial cell has now evolved into nanomedicine, biotherapeutics, blood substitutes, drug delivery, enzyme/gene therapy, cancer therapy, cell/stem cell therapy, nanoparticles, liposomes, bioencapsulation, replicating synthetic cells, cell encapsulation/scaffold, biosorbent/immunosorbent haemoperfusion/plasmapheresis, regenerative medicine, encapsulated microbe, nanobiotechnology, nanotechnology and other areas. More futuristic research includes nanorobot, nanocomputer, multimodal locomotion delivery robot and others. This review starts with a general overview followed by specific examples in more details.

Idea of artificial cells

The very first humble “artificial cells” reported by Chang in 1957 [1] is not to reproduce biological cells, but to use available basic knowledge to prepare a very simple system for possible uses in medicine and other areas. It is only in the last 20 years that many of the original ideas on artificial cells are being increasingly applied and extended by researchers around the world. This is because many of the original ideas [2–7] were reported years before the modern era of nanotechnology, regenerative medicine, blood substitutes, biotechnology, gene therapy, stem cell therapy, cell therapy and other areas. Thus, following his 2005 review on “therapeutic applications of polymeric artificial cells” in Nature Review Drug Discovery [8], a timeline shows that the author has made 20 of the 23 major discoveries in related areas up to that time. However, since that time, other groups are making rapid and exciting progress and numerous discoveries.

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 the recognition of the importance and developments in biotechnology. Then there is the progress in molecular biology and genomics. All these have contributed to a quantum leap in the area of artificial cells. One can expect that there will be important future progress in other areas, for example, artificial intelligence and nanorobots, that will contribute to unlimited progress by increasing number of groups worldwide in the area of artificial cells.

This author predicted in his 1972 monograph on Artificial Cells [6] that “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”. This prediction is already out of date since the idea of artificial cells has progressed way beyond this 1972 prediction (Figures 1–3) [9–12]. There are unlimited possibilities in variations for the artificial cell membranes and contents (Figure 1). Artificial cells can now be of macro, micro, nano and molecular dimensions. Each of these has unlimited variations in configurations. Each configuration resulted in a new terminology that makes the field rather confusing to newcomers (Figure 2). One hopes that the many arbitrary subdivisions of "artificial cells" under the guise of different names can come together! When this takes place, the result of the pooling of talents, specialized know-how in this very interdisciplinary and international area will lead to progress beyond anyone’s imagination.
There are so many possibilities and this area is so interdisciplinary that this author decides to concentrate on innovative ideas, then to interest others with the specialized background to extend and develop these for clinical and practical uses. In addition, many groups around the world have started their own innovative approaches and efforts. Nevertheless, we have only touched the surface of the enormous potential of the extension, innovations and uses of artificial cells (Figures 1–3). Space only allows for a general overview follows by some examples of the different
ARTIFICIAL CELLS: APPLICATIONS (2019)
Microdevice and nanodevice
Drug delivery:
Blood Substitutes and oxygen therapeutics
Biotherapeutics, Immunotheutactics:
Enzyme and gene therapy:
Cell & Stem Cell Therapy:
Biotechnology & Nanobiotechnology
Nanomedicine
Regenerative medicine
Agriculture, Industry, Aquatic culture
Nanocomputers and nanorobatics
Nanosensors
Replicating synthetic cells etc
Other transformative possibilities

Figure 3. Examples of potential uses of the idea of Artificial Cells based on the above variations in configuration. Updates from Chang [9,10] with copyright permission.

configurations and their applications. More up to date details will be available elsewhere [12].

Basic methods
This review cannot cover all the important methods of the preparation of the numerous configurations of artificial cells. Instead, we shall first look at the historical basic approaches (Figure 4) to be followed later in more details using specific examples.

Micro and nano dimension
The basic principle is to use emulsion followed by the use of physical or chemical methods to form a membrane around each microdroplet [1–2]. The diameter is determined by the diameter of the emulsified micro or nano dimension droplets. Extensive novel emulsion methods developed around the world are now available for use. This principle has since been extended using modified physical or chemical methods for the preparation of microscopic or nano dimension artificial cells that are also called microcapsules, nanocapsules, liposomes, microparticles, nanoparticles, polymersomes, etc.

Macro dimension
The drop method for the preparation of large artificial cells [1] has now been extended and modified using modified physical or chemical methods for cell/stem cell/tissue encapsulation. This will be described in more details later.

Crosslinking of proteins
The original basic method [2,7] of the use of bifunctional agents to assemble and crosslink haemoglobin (Hb) into PolyHaemoglobin, has been extended into many other areas of nanobiotechnology and nanobiotherapeutics. This will be described in more details later.

Conjugation of protein
The original basic method of conjugating haemoglobin to polymer [2] has evolved into the conjugation of haemoglobin to soluble dextran or soluble (PEG) polyethylene glycol. Pegylation of proteins (PEG-protein) is now a popular approach in biotherapeutics.

Examples of routes of administration
Figure 5 contains examples of possible routes of administration for the function of artificial cells in the body. Generally speaking, regulatory agencies are less worried about the use of artificial cells that are not implanted or injected into the body. We, therefore, started with artificial cells that are not implanted but act in a device for the extracorporeal route. This has resulted in the early approval of the use of artificial cells in patients way back in 1980. This is in the form of a haemoperfusion device.

Total surface area and mass transfer
It is common knowledge that for the same volume of particles the smaller the particles, the larger would be the total surface area. It is also known that the theoretical diffusion across a membrane is proportional to the total surface area and inversely proportional to its membrane thickness. However, my 1966 analysis of the implication of combining all these factors for artificial cells of micro dimension is way beyond expectation [5]. Figure 6 shows an updated analysis [11] of the theoretical mass transfer of a fixed volume of 0.01 lm membrane thickness artificial cells with different diameters. This is compared to an artificial kidney (haemodialysis) machine with a mass transfer of 1. The mass transfer increases with decreasing diameter of artificial cells so that at the micro diameter range it can increase to 100 times that of an artificial kidney. At the nano diameter range, this can increase to an amazing 1000 times above that of an artificial kidney. Thus, artificial cells of different diameter containing different bioactive material can become efficient micro/nano dialyzer/bioreactor with unlimited possibilities (Figure 5).

Haemoperfusion
Based on this analysis, 70g of 90 micron diameter adsorbent artificial cells are retained inside a small container by screens at either end. The sorbent artificial cells remove toxins or drugs from the blood of patients perfusing through the column. The membrane of the artificial cells prevents the adsorbent from being released into the body and also prevents the adsorbent from damaging the blood cells (Figure 6). This results in a cup size miniaturized haemoperfusion device with a hundred times the efficiency of a
Figure 4. Upper left: Original (Chang 1957) emulsion method of preparing micro-dimension artificial cells. Since extended to physical or chemical methods for microscopic and nanodimension artificial cells. Lower left: Original (Chang 1957) drop method for the preparation of large artificial cells. This has been now been extended and modified for cell/stem cell encapsulation. Upper right: Basic method (Chang 1964 Science) of bifunctional agents to assemble and crosslink hemoglobin (Hb) into PolyHb that has evolved into the preparation of soluble polyhemoglobin and other biotherapeutics. Lower right: Basic method of conjugating hemoglobin to polymer (Chang 1964 Science) that has evolved into the use of other polymers like the Pegylation (PEG-protein) Updated from Chang [9,10] with copyright permission.

Figure 5. Contains examples of possible routes of administration for the function of artificial cells in the body. Generally speaking, regulatory agencies are less worry about the use of artificial cells that are not implanted or injected into the body. We therefore started with artificial cells that are not implanted but act in a device for the extracorporeal route. This has resulted in the early approval of the use of artificial cells in patients way back in 1980. This is in the form of a hemoperfusion device.
haemodialysis (artificial kidney), the size of a washing machine (Figure 5).

The author starts the study on the use of artificial cells containing adsorbents for haemoperfusion. This included personally carried out scaled up, animal testing and clinical trials with patients. He shows the safety and effectiveness for using this first in animals and then in patients. Figure 7 shows the result of one of the many patient trials the author has carried out [13]. This is a suicidal patient who ingests 3 times the lethal dose of a sleeping pill, methyprylon. Five hours of standard haemodialysis treatment cannot lower the drug level and the patient remains comatose, hypotensive with cardiac arrests. When the author starts haemoperfusion treatment the plasma methyprylon level decreases rapidly in 2 h and the patient is no longer comatose nor hypotensive and shortly recovers completely.

Following this first case, similar results are obtained in a number of other patients [13]. He has also shown its effectiveness as partial support in patients for kidney failure and liver failure to remove toxic molecules. These results have led to FDA approval for routine clinical uses. Haemoperfusion is now an accepted routine clinical use for the treatment of patients with suicidal or accidental overdose of some medications around the world. A 2017 book [11] by specialists around the world shows that the approach is being used extensively around the world, especially in countries where these can be manufactured with affordable costs.

What is more exciting is that extensive modifications and extension into many other uses including the use of specific bioadsorbents, immunosorbents. Furthermore, surface properties of artificial cell membranes 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 polysaccharides like heparin or polyethylene glycol (PEG) to increase biocompatibility [9–11,14–19] (Figure 7). This has led to systems for the specific removal of endotoxins, for the treatment of immunological diseases like Lupus and for the removal of unwanted cells. This is now such a large area with numerous publications that please refer to the book for more details [12].

Blood substitutes

Unlike the use of artificial cells in a haemoperfusion device that is outside the body, this is an example where large volumes artificial cells have to be infused intravenously into the body. Thus, even though this is a very important and urgent life-saving method, it needs more time before regulatory approval.

Why blood substitutes?

The following is from a recent editorial by the author [20]. Under normal circumstances, donor blood red blood cells (RBC) is the best replacement for blood. However:

- Natural epidemics (e.g. HIV, Ebola etc) or man-made epidemics (terrorism, war, etc) can result in contaminated
donor blood or disqualified disease contact donors.
Unlike RBC, blood substitutes can be sterilized.
- Heart attack and stroke are usually caused by obstruction of arterial blood vessels. Unlike RBC particles, blood substitute is a solution and in animal studies, it can more easily perfuse through obstructed vessels to reach the heart and brain.
- Severe blood loss from accidents, disasters or war may require urgent blood transfusion that cannot wait for transportation to the hospital for blood group testing. Unlike RBC, blood substitutes do not have blood groups and can be given on the spot (Figure 8).
- Red blood cells have to be stored in refrigeration for up to 42 days thus difficult to transport and store in disaster and frontline. Blood substitutes can be stored at room temperature for 1 year, compared to RBC of 1 day at room temperature.
- In very severe haemorrhagic shock there is usually a safety window of 60 min for blood replacement, beyond which there could be problems related to irreversible shock. Animal study shows that one type of blood substitutes with enhanced RBC enzymes can prolong the time.

What is the present status around the world?
After the first report of artificial red blood cells in 1964 [2], people felt that blood substitute is a simple matter that could be quickly developed when needed. Thus blood substitute research was put aside and only the other areas of artificial cells were extensively developed around the world for other widespread uses. When AIDS arrived in 1989, there were no blood substitutes and many patients were infected with H.I.V. contaminated donor blood. It is only then that intense R&D on blood substitutes was belatedly carried out around the world [20–35]. It was found out too late that blood substitute requires the same long-term research as in any other medical research for cancer and other diseases. Thus, the present status is as follows (Figure 7):

**Oxygen carriers (HBOCs)**
Red blood cells have 3 major functions (1): transport oxygen from the lung to the tissue (2), remove damaging oxygen radicals and (3) carry carbon dioxide CO₂ from the tissue to the lung to be removed. The urgency of H.I.V. in donor blood necessitates the development of the simplest system in the shortest time. The most extensive clinical trials were based on polyhaemoglobin (PolyHb) developed by Biopure (Hemapure: bovine PolyHb) [24] and Northfield (human PolyHb) [21a] using the basic principle of glutaraldehyde cross-linked haemoglobin first reported by Chang [7] (Figure 8). This has no blood groups and can be pasteurized to remove infective agents and can be stored at room temperature for more than 1 year. Large-scale clinical trials have been carried out including using human PolyHb in the ambulance without the need for typing or cross-matching [21a]. Greenburg, Jahr and others have carried out clinical trials using Hemapure: bovine PolyHb [23,24]. This has been
approved for routine clinical use in South Africa to avoid the use of H.I.V contaminated donor blood [24]. Other ongoing research includes the use of other sources of haemoglobin by Chen’s groups with porcine Hb [21b], Yang’s group with Placental Hb [22], and Bulow’s group and others with recombinant Hb [23].

**Oxygen carriers | removal of oxygen radicals**

Arterial obstruction can result in stroke and heart attack. Red blood cells, being 7 to 8 microns in diameter, have difficulty flowing through partially obstructed vessels to supply the needed oxygen. PolyHb, being a solution, can perfuse through to supply the needed oxygen. However, reperfusion with an oxygen carrier can release damaging oxygen radicals (Figure 8).

D’Agnillo and Chang have prepared a soluble complex of Polyhaemoglobin containing antioxidant enzymes to remove oxygen radicals (PolyHb-SOD-CAT) [25]. It has the dual function of an oxygen carrier that can also remove oxygen radicals (Figure 8). After 90 min of combined haemorrhagic shock and brain ischemia in rats, reinfusion of PolyHb-SOD-CAT did not cause brain edema (Figure 9) [26]. On the other hand, PolyHb or a solution contains free Hb, SOD and CAT causes significant increase in brain edema.

Ischemic small intestine releases damaging oxygen radicals when reperfused with PolyHb. However, PolyHb-SOD-CAT reperfusion does not increase oxygen radical release (Figure 8). This is important during intestinal surgery or organ storage for transplantation.

The work of Hsia’s group using conjugated haemoglobin containing synthetic antioxidants (PNPH) is another way to solve the problem [27]. Another example is that of Alayash’s group based on haptoglobin [28] Others included those of Simoni, Zal and other groups [20,23].

**All 3 RBC functions (carries oxygen | removes oxygen radicals | carries CO₂)**

Other conditions as in sustained severe haemorrhagic shock may require all three RBC functions. We have designed a novel soluble nanobiotecnological complex (PolyHb-SOD-CAT-CA) [29] (Figure 10). It not only has all 3 RBC functions, but it can have enhancement of all 3 RBC functions by increasing the concentrations of RBC enzymes in the complex [29]. These RBC enzymes can be extracted from RBC inexpensively [30]. This complex has no blood groups. The lyophilized preparation can be heat pasteurized at 68 F for 2h [31]. This can be important if there is a need to inactivate H.I.V. virus, Ebola virus, and other infective organisms. Unlike about 1 day for RBC at room temperature, this lyophilized preparation can be stored in room temperature for 320 days. Our result in a 90 min haemorrhagic shock animal model with 2/3 blood volume loss (Figure 10) [29] shows that it is superior to whole blood in the following ways: lowering of elevated intracellular pCO₂, recovery of ST elevation, troponin levels, lowering of elevated lactate, histology of the heart and

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**Figure 8.** Upper: comparing red blood cell substitutes to red blood cells. Lower Left: Artificial red blood cells of microscopic dimensions that can reversibly “crenate” in hypertonic solution. Lower Middle: Nano Artificial cells red blood of 80 nanometer mean diameters with Polyethylene-polylactide membrane. Lower right: 4 types of soluble nanobiotherapeutic complexes. Updated from Chang [9, 10] with copyright permission.
intestine. Long term study of bovine PolyHb-SOD-CAT-CA in rats shows safety and lack of immunological problems after 4 weekly 5% blood volume infusion followed by 30% volume exchange transfusion [32]. This includes the measurement of histamine and tryptase that show no anaphylactic reaction (Figure 10). Haemoglobin has very low antigenicity. Bovine PolyHb itself shows no immunological problems in patients [23,24]. For PolyHb-SOD-CAT-CA the small fraction of enzymes are nanoencapsulated inside the large excess of haemoglobin molecules [36] (Figure 10).

Nanodimension red blood cells

The original micro dimension artificial red blood cells are too large to survive in the circulation. Nanodimension artificial RBC is another way to solve this problem [33–35]. Lipid membrane vesicles itself do not circulate well and the addition of PEG to the membrane to form a PEG-lipid-polymer membrane vesicle has increased the circulation time. At present, this approach at the late Tsuchida’s group [35] is being continued by Sakai’s group [34]. In our laboratory, we have been using an 80 nm mean diameter biodegradable PEG-Polylactide polymeric membrane nano RBC that contains all the RBC enzymes (Figure 11) [33]. Both PEG-lipid and PEG-polylactide nano red blood cells can remain in the circulation longer than PolyHb or PolyHb-SOD-CAT-CA. However, they contain a substantial amount of nonfunctional lipid or a polymeric membrane. On the other hand, for soluble nanobiotherapeutic artificial RBC, PolyHb-SOD-CAT-CA, the “membrane” is functional in the form of oxygen-carrying haemoglobin (Figure 11). Thus, each has its own advantage.

Future directions

The editorial [20] concludes that international progress up to now shows that it is possible to tailor-make blood substitutes ranging from simple to complex. It is urgent to have these ready without again waiting until it is too late. We need to analyze the specific indications for 1,2,3 and 4 above. If a condition only needs oxygen, then there is no need to use a more complex one. On the other hand, it would be folly not to use a more complex one if indicated. We also need to intensify research on the many important ongoing research around the world. Examples include other novel approaches including novel crosslinkers; new sources of material from porcine, bovine, human cord RBC, recombinant, Arenicola marina; basic research on nitric oxide, oxidative stress, haptoglobin, the rate of oxygen supply; safety and efficacy analysis and many other areas.

Drug delivery systems

Biodegradable polymeric membrane artificial cells

Polylactide is biodegraded in the body to lactic acid and then water and carbon dioxide (Figure 12) and is an F.D.A.
approved material for medical implantation. Thus, in 1976 Chang reported the use of polylactide to prepare biodegradable membrane artificial cells containing enzymes, hormones, vaccines and other biologics [37] (Figure 12). Variations in the molecular weight of polylactides and thickness of the membrane and configurations can result in artificial cells that release insulin at a different rate (Figure 12). This approach has been extended and developed extensively worldwide as drug delivery systems in the form of nanoparticles, polymersomes or nanocapsules [37-41]. Bowerman et al. reported in 2016 that Docetaxel-loaded PLGA nanoparticles improve efficacy in taxane-resistant triple-negative breast cancer [40]. Ravanshad et al. in 2017 reported the use of nanoparticles in cancer detection by Raman scattering based techniques [41]. Abed et al. reported in 2018 the use of Lysozyme and DNAse I loaded poly (D, L lactide-co-caprolactone) nanocapsules as an oral delivery system [42]. However, onion-like multi-lamellar liposomes limits the loading of water-soluble drugs. Thus, in 1976 Deamer and Bangham [46] report the use of an “ether evaporation” method to form single bilayer lipid membrane vesicles. This “ether evaporation method” is an extension of the 1957 Chang method using ether for the preparation of artificial cells [1,2] (Figure 4). These lipid-membrane artificial cells have since been extensively studied and used as drug delivery systems around the world [47]. This is now a very successful approach for drug delivery. For the delivery of larger peptides, proteins and vaccines, the emphasis is using biodegradable polymeric system.

Targeting using surface ligands or magnetic properties and others

Back in the 1970, Chang’s group had investigated the incorporation of surface charges, polysaccharides and protein onto the surface of polymeric artificial cells (Figure 7) [2,6]. The most successful one is Davies of Enzon’s use of Polyethylene glycol (PEG). PEG has been incorporated to both types of nano artificial cells to result in longer circulation time. Further developments lead to the incorporation of antibodies onto the polymeric or lipid membrane of artificial cells (Figure 12), to allow for targeting to cells with the corresponding antigens. Brennick, C. A. et al. in 2017 report the use of neoepitopes as cancer immunotherapy targets [48]. Artificial cells containing biological materials and magnetic

Bilayer lipid membrane artificial cells: liposomes

In 1965 Bangham reports the use of microspheres of onion-like concentric multilamellar lipid bilayers as membrane models in basic research [43]. In 1968 Meuller and Rudin [44] reported that they use Chang’s method [2] to prepare single bilayer membrane vesicles. A McGill Ph.D. graduate, Gregoriadis, visits me before leaving for his postdoctoral fellowship in England. While there, he becomes the first person to start the use of liposomes as drug delivery systems [45].
materials have been prepared by Chang in 1966 [5] (Figure 12). This way, external magnetic fields can direct their movement; remove or separate them from a mixture; retain them at specific site of action; stir or agitate them as in bioreactors, and other possibilities. This principle is now being used very extensively in bioreactors; in removing specific materials from a mixture as in diagnostics kits; in drug delivery systems; for locating radioactive material or chemotherapeutic agents at the site of the tumor and other areas of application. A 2016 review by Karkan et al. on the use of magnetic nanoparticles for drug delivery is available [49].

A more futuristic approach is Hu et al’s 2018 report in Nature of Small-scale soft-bodied robot with multimodal locomotion with potential for drug delivery [50].

Enzyme and gene therapy

Figure 7 Enzymes inside artificial cells can act on external permeant substrates while avoiding protein sensitization, anaphylactic reaction, or antibody production with repeated injection [2–4,6,8,9] (Figure 13). Chang’s groups has been investigating the use of artificial cells for enzyme therapy since 1964 [2–10,25,26,29–33,51–55] (Figure 13).

Implanted urease artificial cells convert systemic urea into ammonia [6]. Implanted artificial cells containing catalase replaces the defective enzyme in mice with a congenital defect in catalase, acatalasemia [3]. Unlike the free catalase, there is no immunological problem with repeated injections [51]. Implanted artificial cells containing asparaginase delay the onset and growth of lymphosarcoma in mice [4]. This has been extended by other groups using PEG-asparaginase for the treatment of leukemia in patients [56]. PolyHb-tyrosinase suppresses the growth of the skin cancer, melanoma [54] Biodegradable PEG-PLA nano artificial cells containing PolyHb-tyrosinase are also effective [9,55]. These nanoparticles can also enter the melanoma cells to act internally [55] (Figure 5).

Some conditions like inborn errors of metabolism require administration throughout the life of the person. Instead of injections, orally administered artificial cells can act as they move down the intestine, then excreted without accumulation in the body (Figure 5). For example, Chang found that oral artificial cells containing urease and ammonia adsorbent can lower the systemic urea level [6]. This leads to NIH supported development by Kjellstrand’s group leading to clinical trials in patients [58]. Our study shows that artificial cells containing xanthine oxidase lower the toxic systemic hypoxanthine levels in an infant with Lesch–Nyhan Disease [52]. Bourget and Chang show that orally administered artificial cells containing phenylalanine ammonia lyase (PAL) lower the systemic phenylalanine levels in phenylketonuria (PKU) rats and improved the growth of the animals [53]. Following my usual policy, I seek an expert, Scriver in Phenylketonuria [59] and also a company to develop this for clinical use.
They, in turn, collaborate with another company and develop an injectable PEG-PAL that has just been approved for use in patients [57]. In order to avoid long term injection, they are now returning to look at doing this by oral administration [60]. In the same way, our study shows that oral artificial cells containing tyrosinase when given orally lowers the systemic tyrosine level [9]. Kaminsky et al. use argocytes containing enzyme nanoparticles to reduce toxic concentrations of arginine in the blood [61]. Abed et al. reported in 2018 the use of Lysozyme and DNase I loaded poly (D, L lactide-co-caprolactone) nanocapsules as an oral delivery system [42].

Artificial cells containing biological cells

Present status

The first artificial cells containing intact biological cells were first reported by Chang in 1964 [2] using the drop method. It was proposed that “protected from immunological process, encapsulated endocrine cells might survive and maintain an effective supply of hormone” (Figure 14) [6]. He helps Connaught Laboratory to enclose islet in artificial cells for use in diabetes [62]. This basic principle has been extensively developed around the world for cell therapy [8,9,62–75]. Examples include artificial cells containing endocrine tissues, for instance, islets for diabetes. Another extensively investigated area is artificial cells containing genetically engineered cells for a number of clinical conditions.

The result in animals has been promising. However, one implantation can only function for less than 1 year, and this is not practical for long-term illness like diabetes. Repeated injections would have retention problems. There are at present 4 ways to solve this problem (Figure 15):

1. Improved biomaterials with better long-term biocompatibility and improvement in the method of preparation as shown in Figure 14.
2. Oral administration of artificial cells containing microorganisms; Garofalo & Chang in 1991 show the effectiveness of artificial cells containing microorganisms for the in vitro removal of serum cholesterol [67]. In 1996, Prakash and Chang [68] show that artificial cells containing genetically engineered E. coli DH5 cells given orally to kidney failure rats effectively lower the elevated blood urea level. Even though Reardon in his 2018 Nature paper [69] supports the use of genetically modified bacteria in the fight against diseases, regulatory agencies are still hesitant about the use of genetically engineered microbes. In anticipation of this Chang’s group in 2003 [70] use artificial cells containing modified lactobacilli, since lactobacilli are being safely used in Yogurt. This also avoids the use of genetically engineered microbe and allows the safer use for oral administration in a human. Prakash’s group has since carried out extensive research into the use of this approach for clinical use in patients [71].
3. Use in regenerative medicine that only needs months of function, for example, the use of artificial cells containing bone marrow stem cells in liver regeneration. Liu and Chang [72,73] study this in rats using artificial cells

Figure 12. Left: Biodegradable membrane artificial cells containing enzymes, hormones, vaccines and other biologicals (Chang, 1976). Variations result in the release of insulin at different rates. Extended now to many different configurations and dimensions. Right: Artificial cells containing magnetic material. Updated from Chang [9,10] with copyright permission.
**Figure 13.** Left: Enzymes inside artificial cells, unlike those in free solution, do not have immunological problems. These can be in the form of membrane encapsulation, protein encapsulation or PEG covering of the enzyme molecule. Right: This approach has been studied for a number of medical applications. Updated from Chang [9,10] with copyright permission.

**Figure 14.** Upper left: Cells inside artificial cells protected from outside. Lower: Cells can be bioencapsulated inside artificial cell or entrapped in scaffold of fibers or nanofibers. Upper right: Bioencapsulation of islets, cells, genetically-engineered cells, microorganisms and stem cells. Updated from Chang [9,10] with copyright permission.
containing bone marrow stem cells. When implanted into 90% hepatectomized rats, this increases the recovery of the rats to 100% vs 11% in the control group and 33% in the free bone marrow stem cells (Figure 15).

4. The use of biodegradable scaffolds started by Langer, Sefton and other groups, this is now a very popular and exciting approach. Grant’s 2018 review [75] shows that this is now a very promising and active area. Biodegradable scaffolds are prepared in the shape of specific tissue or organs. The cells are seeded into the scaffold and allow to grow in the scaffold until they reach the required shape and dimension and take over the biodegraded scaffold support.

Towards a completely artificial “BIOLOGICAL CELL”

Red blood cells are the simplest of all human cells. As described above, complete artificial red blood cells have already been successfully prepared. Researchers are now interested in doing this for the more complicated types of cells as discussed by Gopfrich et al. in 2018 [76].

Multienzyme systems with cofactor recycling

Most enzymes in the body function as multienzyme systems with cofactor recycling. Gu and Chang [77] have prepared artificial cells containing multienzyme system with cofactor recycling and show that they can be used to convert metabolic waste like urea and ammonia into essential amino acids (Figure 16). The cofactor, NADH, can be retained inside the artificial cells in the form of NADH-dextran or by the use of lipid-polymer membrane. We have also included all the multienzyme system of red blood cells inside nanodimension artificial red blood cells [33] (Figure 12).

Artificial cells with intracellular compartments

Biological cells contain organelles that allow for more effective compartmental function. We have prepared artificial cells with intracellular compartments [6,78] (Figure 16). This can allow for more efficient stepwise enzymatic or other biological functions. This principle has been extended for possible use in therapy by Hosta-Rigau and Stadler [79].

Artificial cells containing microsomes, cytosol, ribosome and polymerase

Yuan and Chang isolate microsomes and cytosol from rat liver and encapsulated into polymeric membrane artificial cells [80]. 20NADPH-cytochrome C reductase and lactate dehydrogenate are used as the marker enzymes for respectively microsomes and cytosol and show retention of activities.

Figure 15. Artificial cells containing cells can only function for up to 1 year after implantation. This has been resolved by (1) biomaterial and method improvement (2) use in regenerative medicine that only need 3-4 months of function for example stem cells in liver regeneration. (3) Oral administration and (4) the use of biodegradable scaffold. Updated from Chang [9,10] with copyright permission.
Monnard and Deamer [81] prepare models for primitive cellular life by encapsulating T7 RNA polymerases and templates into lipid membrane artificial cells, lipid vesicles. They can synthesize an RNA transcript from the DNA template. This is a slow process because the lipid membrane has low permeability to the needed 4 nucleoside triphosphates. Oberholzer et al. encapsulate a complex polymerase system into liposomes and show that the PCR reaction could be carried out [82]. The problem is again the low permeability of the lipid membrane to the needed substrates. They have also encapsulated ribosomes into liposomes and obtain some translation product. More permeable polymeric or lipid-polymer membranes may solve these permeability problems. In another study, Griffiths and Tawfik use compartmentalization to load the transcription/translation system in a water-in-oil emulsion. This way each gene can occupy a separate water emulsion to carry out its function. Artificial cells containing “subcellular compartments” can be another possible way of doing this [6,83] (Figure 16).

**Synthetic genome for replicating synthetic cells**

After extensive research, in 2016 Venter’s group report in Science their successful preparation of a synthetic minimal bacterial genome [84]. Instead of a synthetic membrane, by microinjection, they have ingeniously made use of the complete membrane of the microbe. By doing this, they are able to prepare synthetic replicating cells using their synthetic genome.

**Nonmedical uses of artificial cells**

There are many developments and uses of the principle of artificial cells for agriculture, bioreactors, cosmetics, food production and aquatic culture [85].

Another area is the use of artificial cells in nanorobatics and nanocomputers that in 2004 becomes the European Commission sponsored Programmable Artificial Cell Evolution (PACE) and in 2008 becomes the European Centre for Living Technology [86].

**Future of artificial cells**

The following prediction in Chang’s 1972 monograph on “Artificial Cells” is already out of date: “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”. Artificial cells have now already progressed way beyond this 1972 prediction. Even then, we have only just touched the surface of the enormous potential of artificial cells. One hopes that the many arbitrary subdivisions of “artificial cells”

**Figure 16.** Upper: Artificial cells containing multi-enzyme systems with cofactor recycling can convert waste, urea and ammonia, into useful essential amino acids. Upper right: Artificial cells that contain liver cytosol and organelles like microsomes. Lower right: Reverse hemolysis to load red blood cells with drugs. Microinjection to introduce synthetic DNA into microbes. Updated from Chang [9,10] with copyright permission.
under the guise of different names can come together! When this takes place, the result of the pooling of talents, specialized know-how in this very interdisciplinary and international area will lead to progress beyond anyone’s imagination [87].

Disclosure statement

No potential conflict of interest was reported by the authors.

References


FDA, U.S.F.D.A. FDA approves a new treatment for PKU, a rare and serious genetic disease; 2018.


ARTIFICIAL CELLS, NANOMEDICINE, AND BIOTECHNOLOGY


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-fetchd, 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)
DEGREES:
1957 B.Sc. (Honours Physiology) McGill University ("invented" artificial cells while an undergraduate student on honours research project).
1961 M.D., C.M. Faculty of Medicine, McGill University.
1965 Ph.D. (on artificial cells including blood substitutes), Departments of Chemistry & Physiology, McGill University.
1972 F.R.C.P.(C), Medical Sciences, Royal College of Physicians and Surgeons of Canada (based on examination of research and clinical trials on artificial cells).

APPOINTMENTS

(1) RESEARCH APPOINTMENTS AT Mc Gill
1962-1965 Medical Research Council of Canada Research Fellow, Department of Chemistry then Department of Physiology.
1965-1968 Medical Research Council of Canada Scholar (career development award),
1975-1978 Director, Artificial Organs Research Unit, Department of Physiology, McGill University.
1978-1979 Director, Artificial Organs Research Unit, Faculty of Medicine, McGill University.
1979-ongoing: Director, Artificial Cells and Organs Research Centre, McGill University.

(2) ACADEMIC APPOINTMENTS AT Mc GILL
Physiology
1965-1966 Lecturer of Physiology, McGill University.
1966-1969 Assistant Professor of Physiology, McGill University.
1969-1972 Associate Professor of Physiology, McGill University.
1972-2007 Professor of Physiology (tenured since 1975), McGill University.
2007-ongoing In order to be more flexible in my research and international collaborative research and international scientific activities, I requested McGill to appoint me as Emeritus Professor of Physiology, McGill University.

Medicine
1972-1975 Assistant Professor of Medicine and Clinical Medicine, McGill University and Royal Victoria Hospital (clinical trials).
1975-2007 Professor of Medicine (tenured), McGill University and Royal Victoria Hospital (clinical trials).
2007--ongoing In order to be more flexible in my research and international collaborative research and international scientific activities, I requested McGill to appoint me as Emeritus Professor of Medicine, McGill University.

Biomedical Engineering (Department formed in 1990)
1990-2007 Professor of Biomedical Engineering (tenured).
2007-ongoing In order to be more flexible in my research and international collaborative research and international scientific activities, I requested McGill to appoint me as Emeritus Professor of Biomedical Engineering.

Chemical Engineering and Chemistry
1983-2002 Associate of Chemical Engineering, McGill University (Until Biomedical Engineering Department’s Ph.D. program was approved. Before this, half of his Ph.D. students graduated from the Department of Chemical Engineering).
1985-2000 Associate of Chemistry, McGill University (Until Biomedical Engineering Department’s Ph.D. program was approved).
(3) HONORARY ACADEMIC APPOINTMENTS OUTSIDE McGill University
1983- ongoing Honorary Professor, Nankai University, Tianjin, China
2007- ongoing Honorary Professor, Peking Union Medical College, Beijing, China
2011-ongoing Honorary Professor and key consultant on blood substitutes, Blood Transfusion Institute of the Chinese Academy of Medical Sciences,
2013- ongoing Honorary Professor, Shantou University Medical College
2019-ongoing. Director, "Academician TMS Chang Research station" (Chang with 3 STU full professors) Shantou University Medical School.
2020-ongoing Director, "TMS Chang Artificial Cell Translational Research Institute" (containing 4 artificial cells related research centres) at Shenzhen University’s new Medical Complex. Shenzhen is China’s well-known high technology zone (Final stage of organization)

VOLUNTRY SERVICE AT COMMUNITY MONTREAL CHINESE HOSPITAL:
1966-1967 Director of Medical Board and Director of Laboratory, until Medicare started
1968-1981 Consultant
1982-1987 Honorary Consultant
1987- ongoing Honorary Staff
2016-ongoing Honorary President, Province of Quebec Branch of the Overseas Chew Choa (Shantou) Association.

EXAMPLES OF HONOURS AND AWARDS:
◆ Medical Research Council of Canada (MRC) Research Fellow Award 1962-65
◆ MRC Research Scholar Award (career development award) 1965-68
◆ Career Investigator Award, Medical Research Council of Canada 1968-1999
◆ First Incentive Lecturer. The Annual Incentive Lectures were instituted in Sweden in 1969. The first Incentive Lecturer was "invited to inaugurate these annual lectures". The lecture on "The Clinical Potential of Enzyme Technology" was given at: Karolinska Institute, Stockholm, University of Lund, University of Gothenberg Hospital (1969).
◆ Clemson Award for "Basic Research in the Development of the Microcapsule Artificial Kidney", World Congress of International Society for Biomaterials, Vienna, Austria. (1980)
◆ Honorary President IV International Symposium of Hemoperfusion and Artificial Organs, Ankara, Turkey (1982).
◆ Honorary President, VI International Symposium on Hemoperfusion, Mexico (1985).
◆ Honorary Professor, Nankai University, Tianjin, PRC. 1983-present
◆ Annual Award of the Education Foundation Federation of Chinese Canadian Professionals, Toronto. (for invention of "Artificial Cells including blood substitutes"), 1986
◆ “Ambassador by Appointment" and, AGORA Trophy, Societe du Palais des Congres de Montreal, 1986
◆ Honorary President, 8th International Symposium on Hemoperfusion, Sorbents and Immobilized Bioreactants, Germany, 1988.
◆ Silver Medal Award for outstanding scientific contribution from Academic Senate of University of Bologna for the 9th Centenary of University of Bologna, 1988
◆ Honorary President 9th International Symposium on Hemoperfusion, Sorbents and Immobilized Bioreactants, Tokyo, Japan. , 1989
◆ Honorary president 10th International Symposium on Hemoperfusion, Sorbents and Immobilized Bioreactants, Rome, Italy, 1990
◆ Congress President, VIII World Congress, International Society Artificial Organs, 1991
◆ Honorary President, International Society for Artificial Cells, Blood Substitutes and Immobilization Biotechnology (since 1991). (formed by originally group on Hemoperfusion, Sorbent and Immobilized Bioreactants)
◆ Officer of the Order of Canada, for the invention of artificial cells 1992.
◆ First Julius Silver Lectureship, Julius Silver Institute of Biomedical Engineering and Israel Society for Biomedical Engineering, 1992.
◆ 125th Anniversary of Canadian Confederation Medal Award from Governor General of Canada, 1993
◆ Honorary Congress President, XI World Congress, International Society for Artificial Cells, Blood Substitutes and Immobilization Biotechnology, (Congress president: Professor R.Langer of MIT who organized the congress) Boston, 1994
◆ President, International Society for Artificial Organs, 1994-96
◆ Honorary member, International Society for Microencapsulation, since 1995
◆ Queen Elizabeth 25th Jubilee Medal, Governor General of Canada, 2002
◆ Honorary Congress President XII World Congress, International Society for Artificial Cells, Blood Substitutes and Immobilization Biotechnology (Congress President, is the president of the Chinese Academy of Medical Sciences that organizes the congress) co-congress president is the President of the Chinese Red Cross Society, Beijing, 1997
◆ 1999 ISBP Annual Award, International Society for Blood Purification (Sir Roy Calne was winner of 1998 Award, other previous winners are Robert Rosenberg from NIH, Charles Dinarello then at Tufts and Colton from MIT)
◆ “VIRAGE” AWARD FOR CENTRE OF EXCELLENCE IN BIOTECHNOLOGY, Quebec Ministry of Higher Education, Science and Technology (1985- permanent since 1990 with salaries for 4 professors for the centre now integrated into the faculty salary budget).
◆ Honorary President, IX International Symposium on Blood Substitutes, Tokyo, Japan 2003
◆ Fellow of the Royal Society of Canada, FRS(C) 2004
◆ Honorary President, X International Symposium on Blood Substitutes, Rhone Island, Providence, U.S.A. 2005
◆ Nominated for Nobel Prize in Medicine & Physiology, and also for Nobel Prize in Chemistry
◆ Honorary President, 2007 XI International Symposium on Blood Substitutes, Beijing, (President of Symposium, Professor Liu Qian, Vice Minister of Health of China, president of Beijing Union Medical College Hospital and Vice President, Chinese Academy of Medical Sciences)
◆ Special Award “For his 50 years Outstanding Contribution on artificial cells and Blood Substitutes” from Professor Liu Qian, Vice Minister of Health of China and President of the 2007 XI International Symposium on Blood Substitutes, Beijing, China
◆ Honorary President, 2009 XII International Symposium on Blood Substitutes, Parma, Italy
◆ Founding President, International Academy of Nanomedicine 2009-2010
◆ First “Outstanding Research Award of the International Academy of Nanomedicine”, at the First World Congress of the International Academy of Nanomedicine.
◆ 2011 Voted as the Greatest McGillian in McGill University’s 190 years history. (Out of 700 nominee and 20 finalists that included Rutherford, Penfield, Osler, James McGill, Cohen and others) [http://www.medicine.mcgill.ca/artcell/voting%20result.pdf]
◆ Honorary President, International Academy of Nanomedicine, since 2012 then continue when it was reorganized into the International Society for Nanomedical Sciences.
◆ Honorary President, International Society for Nanomedical Sciences, since 2013
◆ Honorary President. 2013 XIV ISBS International Symposium on Blood Substitutes, Institute of Blood Transfusion, Chinese Academy of Medical School, President will be vice president of the Chinese Academy of Medical Sciences.
◆ Queen Elizabeth Diamond Jubilee Medal 2013
◆ Honorary President. 2015 XIV ISBS International Symposium on Blood Substitutes, Lund, Sweden. President Professor Leif Bulow
◆ Chinese Canadian Legend 2015
◆ Honorary President, 2017 XV ISBS International Symposium on Blood Substitutes, Montreal
◆ Honorary President, 2017 V ISNS World Conference on Nanomedicine, Montreal
◆ Honorary President, 2018 V ISNS World Conference on Nanomedicine, Delhi, India
EXPERIENCE IN RESEARCH, DEVELOPMENT & CLINICAL TRIALS:

◆ **Invention of artificial cells**: including microencapsulation of biologically active materials and blood substitute while a final year B.Sc. student at McGill University in 1956 – published this as a 1957 research report to McGill available at the McIntyre Medical Library. Parttime independent research on artificial cells during premedical and medical school. Starting winter of 1956 and continued to 1961 then full time starting in 1992 to present.
  
  

◆ **First paper in this area in Science, 1964** After medical school and internship, continued with this research in the Chemistry Department and Department of Physiology and obtained a Ph.D. in 1995. This resulted in the first demonstration of the detailed methodology, in vitro feasibility and in vivo feasibility of artificial cell. Published the first paper in the area of artificial cells including blood substitutes (Chang, Science, 1964).

◆ **Areas of major discoveries**: It is only in the last 15 years that many of his original ideas on artificial cells are being increasingly applied and extended by researchers around the world. This is because many of his original ideas were reported years before the modern era of nanotechnology, regenerative medicine, blood substitutes, biotechnology, gene therapy, stem cell therapy, cell therapy and other areas. The editor of Nature Review Drug Discovery worked out a time line for Chang’s 2005 review on “therapeutic applications of polymeric artificial cells”
  

◆ **Nanomedicine and Nanobiotechnology**: Researchers in the academic world of nanomedicine considered his work as the forerunner of nanomedicine and nanobiotechnology and elected him to be the founding president of the International Academy of Nanomedicine (2009) including their first “Outstand Research” Award at their 2009 World Congress. In 2013, this has evolved into the International Society for Nanomedical Sciences that has elected him to honorary president. He is editor of a 2013 book on “Selected topics in Nanomedicine” with the opening chapter of “Artificial Cells: the beginning of Nanomedicine”


◆ **Hemoperfusion: invention, animal testing, clinical trials and successful transfer of technology** In 1966, he invented the use of artificial cells containing adsorbents for hemoperfusion – perfusion of patient’s blood through a column of artificial cells. He personally carried out scaled up, animal testing and clinical trial in patients. He showed the safety and effectiveness for treating patients with poisoning, kidney failure and liver failure. Right from the beginning, he formed an international symposium series rotating around the world including Montreal, UK, China, Germany, Russia, Israel, Japan, Turkey and Mexico, to freely help and stimulate others to develop this. As a result hemoperfusion devices are produced in China, Russia, Italy, UK, U.S., Sweden, Japan and other countries around the world. This led to extensions and productions by centers and companies around the world. Despite offers from many major companies outside Canada, he chose to do this in Montreal with a small Canadian start up company. Since he held no stock or interest in this company he was able to test the products in animal and clinical trial in patients. His results led to F.D.A.’s approval for routine use. He assigned the inventor’s income for this to support this research center. This product is more successful than those produced by larger industries (Smith Nephew, Gambro, etc) – as a result, it was bought over by the National Medical Care, New Jersey, U.S.A. (now a subsidiary of Grace Co.). In a recent visit to China, they have used this to save thousands of accidental poisoned patients. Furthermore researchers in China and Japan have extended this into hemoperfusion systems in routine clinical uses for the selective removal of endotoxin and also in immunological diseases like lupus erythematosi etc.

  [www.medicine.mcgill.ca/artcell/HPBk_Ch1.pdf](http://www.medicine.mcgill.ca/artcell/HPBk_Ch1.pdf)

◆ **Blood Substitutes**: In the mid 1980’s, worries regarding HIV in donor blood have resulted in extensive development and extensions around the world on blood substitutes. The most successful ones are based on nanotechnology based polymerized hemoglobin, an idea shown by Chang in his 1964 Science paper
and also in a later 1971 paper on glutaraldehyde crosslinking. His nanobiotechnology based glutaraldehyde polymerized hemoglobin principle has been developed and produced by two companies in the U.S. One of these has been approved for routine human use in the world in South Africa and Russia. Polyhemoglobin only carries oxygen, thus his team has developed a second generation nanobiotechnology based polyhemoglobin-superoxide dismutase-catalase (D’Agnillo & Chang, Nature Biotechnology, 1998, Powanda & Chang 2002, Chang, 2008, Gu and Chang, 2009, Chang 2009) This carries oxygen and also remove oxygen radicals. Even more recently, his team has developed a polyhemoglobin-superoxide dismutase-catalase-carbonic anhydrase with enhanced rbc enzymes. This has all 3 functions of red blood cells: carries oxygen and carbon dioxide and remove oxygen radicals on an enhanced level. Result can be found in a 2017 summary www.artcell.mcgill.ca/summary.pdf with details as follows: Details shows that this is superior to whole blood in severe hemorrhagic shock beyond the 60mins safety window. http://informahealthcare.com/doi/pdf/10.3109/21691401.2014.964554 Other studies include Long term safety and immunology in rats www.artcell.mcgill.ca/safety_immune.pdf temperature stability www.artcell.mcgill.ca/temp_srtability.pdf and methods of extracting the needed enzymes www.artcell.mcgill.ca/extract_enzymes.pdf

For many years, Chang has been coordinating the international effort in the area of blood substitutes as honorary president and editor in chief of the international network: International Society for Artificial Cells, Blood Substitutes & Immobilization Biotechnology and as chairman, cochairmen and since 2003 honorary president of the biannual International Symposium Series on Blood Substitutes (ISBS). The XIII ISBS was held in Mass General Hospital, Harvard Medical School, with Professor Warren Zapol as president. http://www.medicine.mcgill.ca/artcell/536.pdf The XIV ISBS was held in the Blood Transfusion Institute of the Chinese Academy of Medical Sciences with the vice-president of the Academy as the symposium president. Professor Lief Bulow from Lund University in Sweden organized the 2015 XV ISBS in Sweden. In 2017 Professor Chang organized the 2017 XVI ISBS in Montreal in conjunction with the 60th Anniversary of the invention of artificial cells www.artcell.mcgill.ca There was a narrow election margin for China for the 2019 ISBS. For collegial reason and to help advance this file in Japan, China has agreed to co-organized this jointly with Japan in Nara Japan.

◆ **Enzyme therapy:** His team shows that microencapsulated enzymes can be implanted into animals to treat hereditary enzyme defects, acatalesemia (Chang and Poznansky Nature 1968) and for lymphosarcoma using asparaginase (Chang, Nature 1972). The problem was the need for injection. This has now been solved by his basic research that there is a very extensive recycling of amino acids between the body and the intestine (Chang et al 1989). This way, he showed that microencapsulated enzyme given by mouth could remove unwanted amino acids (e.g. Phenylketonuria – PKU). He has encouraged Professor Charles Scrivier to help in developing this for clinical use with an U.S. company that has modified this approach for clinical testing. Chang’s group is also studying the use of tyrosinase artificial cells and nanobiotechnology based PolyHb-tyrosinase for lowering systemic tyrosine to inhibit the growth of melanoma in (BLYu & Chang, Melanoma Research J, 2004, Furstier & Chang, 2011, Yun & Chang, 2013, 2015 and ongoing)

◆ **Encapsulation of living cells including stem cells:** He was the first to prepare artificial cells containing living cells to protect the cells from the immunological rejection system of the body (Chang 1964 Science, 1965, Chang et al 1966, Chang 1972). Despite offer from an U.S. company, he chose to help a Canadian company (Conaught Laboratory, Toronto) where Sun then devoted his whole research career on cell encapsulation. With international interest in biotechnology, Chang’s basic research is now being extensively investigated by many groups around the world for encapsulating islets(for diabetes) liver cells (for liver failure), genetically engineered cells (for many conditions) and other cells (Nature Medicine Cell encapsulation: promise and progress” G. Orive et al Nature Medicine 2003 9:104-107, Chang: Nature Review: Drug Discovery 2005). Chang’s recent research includes artificial cells containing bone marrow stem cells. When implanted into 90% hepatectomized rats, this increases the recovery of the rats to 100% vs 11 to 33% in the control and in free bone marrow stem cells (Liu and Chang, 2007, 2009, 2011)

◆ **Oral administration of artificial cells containing microorganisms** Research by Chang with his then graduate student (Prakash & Chang, Nature Medicine 1996; Chang Nature Medicine 1997), showed that encapsulated E.coli DH5 cells can be given orally to kidney failure rats to lower their blood urea level and
◆ other uremic waste product. This avoids the need to inject genetically engineered materials in gene therapy. His group has shown the possibility to use artificial cells containing modified lactobacilli that are used in Yogurt (Chow, Liu, Prakash and Chang 2003). Professor Eli Friedman, a well known, nephrologist in New York, is working with a U.S. company in clinical trial to use this for chronic renal failure patients with promising results. Dr. Prakash, now a full professor of this centre, is developing this approach in his start up company in ongoing clinical trials for other clinical conditions.

**Other areas including drug delivery, biotechnology, chemical engineering, aquatic culture**

Other areas including drug delivery, biotechnology, chemical engineering, aquatic culture, agriculture, nanorobotics, food industry, cosmetic industry and other areas. His work on microencapsulation of biological material has been extended by many research groups and pharmaceutical companies to produce drug delivery systems for drugs, peptides and other biotechnological products. His use of a biodegradation polymer, polylactic acid, for microencapsulation (Chang, Bioengineering, 1972) is now being extended and developed extensively as a drug delivery system as nanoparticles, polymersomes or nanocapsules. His basic study on artificial cells containing magnetic materials (1966) is being extensively in nanomedicine. Another extension of his work is the use of Bangham’s lipid membrane to form lipid membrane artificial cells – liposome. This also has wide spread applications as other delivery system. Artificial cell is also being developed in other areas of biotechnology, chemical engineering, aquatic culture, nanorobotics and other areas.

Further information: [www.medicine.mcgill.ca/artcell](http://www.medicine.mcgill.ca/artcell)

**OTHER INTERESTS: besides medicine and science**

Continuing updating on most recent approaches in management, project control, organization, negotiation, interpersonal relationship, techniques in clear writing and speaking.

Continuing updating on new approaches in microcomputer especially word processing, database, website management, organization, project control, negotiation, graphics, clear writing, and other areas. Also in mobile communications.

Classical music, tennis, badminton, table tennis, weight training, physical conditioning, martial arts, books on history and cultural developments and others.

**EXAMPLES OF INTERNATIONAL ACTIVITIES**

Please see next page
Artificial Cells & Organs Research Centre: an international centre [www.artcell.mcgill.ca]
Director TMS Chang

Full time members
Prof. TMS Chang
Prof. S. Prakash

Associate members
Dr. Paul Barre
(Medicine)
Prof. E. Georges
(Biotechnology)
Dr. C. Hoesli
(Chem Engineer)
Dr. M. Kinsell
(Bioengineering)
Prof. D. Nicolau
(Bioengineering)
Prof. D. Shum-Tim
(Surgery)

International Network of Artificial Cells, Blood Substitutes & Biotechnology
(An international network)
[www.artcell.mcgill.ca/ISABI.pdf]
TMS Chang, Coordinator & Honorary President
Executive committee members: 21 from around the world

International conferences
McGill, Italy, Israel, Turkey, China
(Chinese Academy of Medical Sciences), Mexico, USSR Academy of Sciences, McGill, Germany, Japan, Italy, McGill, U.S.A., U.S.A (MIT), China (Chinese Academy of Medical Sciences), Italy,
Most recent ones:
2011 XIII ISBS MGH Harvard
President: Prof. W. Zapol
Honorary President: Chang
2013 XIV ISBS BTI Chinese Academy Medical Sciences
President: VP CAMS
Honorary President:
Prof. TMS Chang McGill
2015 XV ISBS Lund, Sweden
President: Prof. Lief Buhlow
Hon. President: Prof. TMS Chang
2017 XVI ISBS McGill Univ
Montreal, Canada
Hon. Presid: Prof. TMS Chang
2019 XVII ISBS Nara, Japan
Presidents: C. Yang, H. Sakai
Hon. President: TMS Chang
2021 XVIII ISBS Berlin Germany
President: H. Baumler
Hon. President: TMS Chang

International Journal
Artificial Cells, Nanomedicine & Biotechnology (Taylor & Francis)
[http://informahealthcare.com/oiv/abb]
TMS Chang
Editor in chief: 1980-2020
Emeritus editor 2020-

Associate Editors:
S. Bruno (Italy)
G. Budak (Turkey)
G. Chen (China)
E. Georges (Canada)
C. Guo (China)
S. Prakash (Canada)
H. Sakai (Japan)
B. Yu (U.S.A)
Hongli Zhu (China)

Editorial Board
40 members from:
Canada, China, U.K.
Japan, USA, Israel,
Turkey, France, Iran, Italy
Swiss, Austria,
Germany, Slovak,
Czech Russia

Other international networks

International Society for Nanomedical Sciences
Hon President: Prof. TMS Chang
President: Dr. G. Budak

Honorary professorships
China: TMS Chang
Peking Union Med College
Nankai University
Blood Transfusion Institute of Chinese Academy Medical Sciences
Shantou University Medical College
TMS Chang Academic work station
India: S. Prakash
Bundelkhand University (Hon Prof)

[www.medicine.mcgill.ca/artcell]
Website by TMS Chang on “Artificial Cells, Blood Substitutes & Nanomedicine” Public service website with free access to reviews, videos and Chang’s monographs

Book series on Regenerative Medicine Artificial Cells & Nanomedicine:
[www.worldbooks.com/biosci6195.html]
Editor in chief: TMS Chang
KEY OFFICIAL POSITIONS

◆ Honorary President, International Society of Nanomedical Sciences (2012-ongoing)
◆ Senior Member, Society of Biomedical Engineering, since 1989.
◆ Honorary presidents, Chairman and co-chairman of International Symposia on Hemoperfusion, Sorbent and Immobilized Bioreactants. I (Montreal), II(Italy), III(Israel), IV(Turkey), V(PR China), VI (Mexico), VII (USSR), VIII(Germany), IX (Japan), X (Italy),
◆ Honorary Congress President, XII Congress, International Society for Artificial Cells, Blood Substitutes and Immobilization Biotechnology, Congress president: President of the Chinese Academy of Medical Sciences & Peking Union Medical College; Congress co-president: is President of the Chinese Red Cross Society, Beijing, 1997.
◆ Chairmen of III(87,Montreal), IV(91,Montréal), VI (96,Montreal) and Co-Chairman of V(93,San Diego, USA), VII(97,Toyo, ), VIII (99, San Diego) International Symposia on Blood Substitutes.
◆ Honorary President, 2003 IX International Symposium on Blood Substitutes, Tokyo, Japan 2003
◆ Honorary President 2005 X International Symposium on Blood Substitutes, Brown University, Providence, U.S.A.
◆ Honorary President, 2007 XI International Symposium on Blood Substitutes, Beijing, China 2007 organized by the Chinese Academy of Medical Sciences and Union Medical College. The symposium chairman was Professor Liu Qin vice-president of the Chinese Academy of Medical Sciences and President of the Union medical College Hospital – now vice premier of Health of China.
◆ Honorary President, 2009 XII International Symposium on Blood Substitutes, Parma, Italy. Symposium president was Professor Mazarrilli of University of Parma, Parma, Italy.
◆ Honorary President, 2011 XIII International Symposium on Blood Substitutes, Harvard Medical School, Boston, U.S.A. The symposium chairman was Professor Zapol, Professor and Chief of Anesthesia and Critical Care Medicine, Mass General Hospital, Harvard Medical School. _http://www.medicine.mcgill.ca/artcell/536.pdf_
◆ Honorary President, 2012 III Congress of the International Academy of Nanomedicine, Ankara, Turkey
◆ Honorary President. 2013 XIV International Symposium on Blood Substitutes, Institute of Blood Transfusion, Chinese Academy of Medical School, President was the Director of the Institute.
◆ Honorary President. 2015 XV International Symposium on Blood Substitutes, President will be Professor Leif Bulow, University of Lund, Lund, Sweden
◆ Honorary President 2015 IV ISNS World Nanomedicine Congress, Turkey.
◆ Honorary President 2017 V ISNS World Nanomedicine Congress, Montreal
◆ Honorary President. 2017 XV International Symposium on Blood Substitutes, Montreal
◆ Honorary President 2018 V ISNS World Nanomedicine Congress, Delhi, India
◆ Honorary President. 2019 XV International Symposium on Blood Substitutes, Nara, Japan
◆ Honorary President. 2022 XVI International Symposium on Blood Substitutes, Berlin, Germany
EDITORIAL BOARDS:

**Editor-in-Chief** (1986 - 2020), **Emeritus Editor** (2020- ) Artificial Cells, Nanomedicine and Biotechnology, An International Journal, Informa Publisher now Taylor & Francis, UK.

(1986 invited to take over and modernize and reorganize the oldest journal in the field originally “Biomaterials, Medical Devices and Artificial Organs”, an International Journal. In order to keep updated with the rapid progress in this area it has evolves into Artificial Cells, Blood Substitutes and Biotechnology, An International Journal and then its present name starting in 2013. Submissions increased from 300-400 to 1300 in 2018 and > 2400 for 2019. Despite high rejection rate, annual issues increased from 4 issues in 2015 to 6 issues in 2016 and 8 issues in 2017 and 8 issues with 3 supplementary issues in 2018. As a result, starting in 2019 it has become an Open Access journal in order to accommodate the increasing number of papers. 2019 Reuter Impact Factor: 4.462. With an increase in submissions >2,400 in 2019, It became more than a full-time position. With his many other research related responsibilities, he resigned but was asked to continue as emeritus editor in May 2020.

**Editor-in-chief** of a book series on “Regenerative Medicine, Artificial Cells and Nanomedicine”, World Scientific Publisher/Imperial College Press (official publisher of Nobel Prize Award Lectures since1921).


(2) Second in this series is the 2011 book on Novel Therapies in Terminal Renal Failure edited by Professor Eli Friedman’s group.

(3) Third in this series is the 2013 book on Selected Topics in Nanomedicine edited by Chang.


(5) Nanobiotherapeutic based Blood Substitutes (Editors; Chang, Saki and Jahr (in press for 2020 )

(6) 6th in this series will be the 2nd edition of the monograph by Chang 2017 on “ARTIFICIAL CELLS: biotechnology, nanomedicine, regenerative medicine, blood substitutes, bioencapsulation, and cell/stem cell therapy” 650 pages


◆ **Editorial Board**, New Biotechnology

◆ **Editorial board**, International Journal on Theoretical and Applied Nanotechnology (IJTAN) of The International Academy of Science, Engineering and Technology (2012- )

◆ **Honorary Editor**, Journal of Hepato-renal and artificial detoxication(2003- )

◆ **Associate editor**, Nanomedicine Journal (2014- )

◆ **Editorial Board**, Journal Biotherapy (2014- )

◆ **Editorial Board**,J Biotechnology Bioengineering (2014- )

◆ **Associated editor**, Nanomedicine Research J (2014- )

**Previous editorial boards**


◆ Associate Editor, Biotechnology Annual Rev, Elsevier Science, Netherlands.(1995-2011)


BIBLIOGRAPHIC
REFERENCES:

7. American Men and Women of Science (ongoing)
10. American Biographical Institute "Five Hundred Leaders of Influence" (1995)

GRADUATE STUDENTS SUPERVISED by CHANG (as the sole supervisor):

Before 1985 (one example given):

Ph.D. (Physiology): Mark Poznanski was Professor Chang's first Ph.D. graduate in Physiology. He has recently been honoured with the Order of Ontario and Order of Canada. He has been for a number of years the president of University of Western Ontario's "Robart Institute for Medical Research" and has built up the institute to "600+ people with an average of $600,000+ per investigator" (www.robarts.ca). He is a founding member and past chair of the Council for Health Research in Canada, a research advocacy group in Ottawa, and also chairs the Scientific Advisory Board of the Canadian Medical Discoveries Fund, and Director of the Ontario Genomics Institute, he also founded London Biotechnology Incubator Inc., in addition to being on many biotechnology-industry related boards. He is now president of his own consulting firm.

After 1985 (complete list):

GRADUATE STUDENTS SUPERVISED by CHANG (as the sole supervisor):

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After 1985 (complete list):


1986 M.Eng. (Chem.Eng.): Maurice Cattaneo (continued for Ph.D. with Chang)

1986 Ph.D. (Expt. Med.): Zhi Qing Shi, M.D. Vice President REMD Biotherapeutics Inc, CA, USA. Was Medical Director, Genzyme Co, US, and Research
scientist at Amgen Biotechnology Co. in U.S.A. after Assistant Professor in Physiology, University of Toronto
1987 Ph.D. (Physiology): **Louis Bourget** (then dentistry at McGill, now a dental surgeon)
1987 Ph.D. (Physiology): **Vivek Dixit** (retired Professor and Director, Laboratory of Artificial Liver Support, Department of Medicine, University of California at LA)

1987 M.Sc. (Physiology): **Andrew Budning** (completed McGill University M.D., physician)
1987 M.Eng. (Chem.Eng.): **Flavio Garofalo** (continued for Ph.D. with Chang)
1987 M.Eng. (Chem.Eng.): **David Morley** (completed Law at McGill University and Oxford)
1989 Ph.D. (Physiology): **Soudabeh Aghazaman Kashani**, M.D. (now in clinical medicine)
1990 Ph.D. (Chem.Eng.): **Maurice Cattaneo**, Consultant (Previously Director, Technology Development, Cambridge Scientific Inc. Cambridge, MA. Adjunct Professor, Northeastern University, Boston. (Previously Research Scientist, NRC, Biotechnology Research Institute, Montreal)
1990 Ph.D. (Ad Hoc) **Kang Fu Gu** retired Senior scientist of a Biotechnology Company in China (Was senior Scientist, U.S. Biotechnology before this he was Senior Research Scientist of IBEX Technology, a Montreal biotechnology company)
1991 Ph.D. (Physiology): **Jing Ning**, M.D. (She was Research Scientist at Hemosol Inc., Etobicoke, Ontario, a blood substitute company. Retired from Health Canada Regulatory division)
1991 M.Eng. (Chem.Eng.): **Vaia Coromili** (continued to Ph.D. with Chang)
1991 M.Eng. (Chem.Eng.): **Maryam Mobed** (continued to Ph.D. with Chang)
1991 M.Eng. (Chem.Eng.): **Daniel Duguay** (continued to Ph.D. in Ottawa)
1992 Ph.D. (Chem.Eng.): **Khaled Alsugair** (started as assistant Professor in Saudi Arabia)
1993 Ph.D. (Chem.Eng.): **Ian Lloyd George** Manager, Research & Development, Polychem Product Ltd., Montreal (awarded NSERC Research Fellowship at Bureau of Medical Device, Ottawa)
1994 Ph.D. (Physiology): **Silvia Bruni**, M.D. (returned to Italy in clinical practice)
1996 M.Eng (Chem.Eng.): **Sarah Safos** (continued her Ph.D. with Dr. Scriver on use of artificial cells in PKU mice)
1996 Ph.D. (Biomed.Eng.): **Satya Prakash** now a Full Professor of Biomedical Engineering, McGill (Came to me as International scholar in Biotechnology from India)
1996 M.Sc. (Biomed.Eng.): **Elizabeth Quebec**
1997 Ph.D. (Chem.Eng.): **Maryam Mobed**, was Endowed Chair in Bioengineering, Davidson College of Engineering, U.S. (previously Research scientist, Bioscience Products Division, Agilent Technologies, a California Biotech company.)
1997 Ph.D. (Physiology): **Felice D’Agnillo** Graduated on dean’s honours list (was N.I.H. International Forgarty Fellow, Bethesda, USA) , Now Senior Staff Scientist at FDA-NIH
2000 Ph.D. (Chem Eng): **Vaia Coromili** - no communication after graduation
2002 M.Sc (Physiology): **Douglas Powanda** (FCAR Scholarship) Continued to compete his Master of Management at Concordia University
2004 Ph.D. (Biomed.Eng) **Binglan Yu** graduated on Dean’s honours list with Geddes Award for best graduate student in Biomedical Engineering. Research fellow with Professor Zapol, previously Chief of Anesthesiology, Mass General Hospital, Harvard Medical School, then instructor, and now assistant professor.
2004 M.Sc. (Biomed Eng) **Noami Wong** (NSERC studentship). Then was a staff engineer, Merck Frosst Co. Montreal. Now home as house wife
2005-2007 M.Sc (Biomed Eng) **Caroline Fustier** (scholarship student from Paris, France) Now a research scientist in a French Company.
2006-2007 M.Sc. (McGill Program on Biotechnology) **Jessie Rong**. Continued to Medical School at University of Montreal
2007-2008 M.Sc. (McGill Program on Biotechnology) **Wei He** after graduation continued work in a research lab.
2008-2009 M.Sc (McGill Program on Biotechnology) **Qianqian DU**, completed her M.Sc and continued as research assistant in this laboratory for 1 year
2010-2014 Ph.D. (Biomedical Engineering) **Yuzhul BIAN**. Came with M.Sc. from Tsinghua University, Beijing. Graduated in June 2014. Now staff in a consulting company in Beijing, China.
2011- Feb 2015 Ph.D. (Experimental Medicine) **Yun WANG** came with M.Sc. from Peking Union Medical College of the Chinese Academy of Medical Sciences. With a China Scholarship Council Scholarship. Now research staff at the 3rd Hospital of Peking University Medical School.

2011-2012 Ph.D. Trainee (Physiology) **Wei** came with China Scholarship Council Scholarship. Was Assistant Professor then associate professor, Xian University, PRC

2014 M.Sc. (McGill Program on Biotechnology) **Chen Guo**, continued to PhD here.

2015 M.Sc (McGill Program on Biotechnology) **Shou Ma**

2015 M.Sc (McGill Program on Biotechnology) **Christopher Lee**

2015-2018 Ph.D. (Experimental Medicine) **Chen Guo**. Completed PhD in 2018 now research staff in a Chinese company

2017 M.Sc (McGill Program on Biotechnology) **Amir Shahein**

2018 M.Sc (McGill Program on Biotechnology) **Petko Komsalov**

2019. M.Sc. (McGill Program on Biotechnology) **J. Zhang**

2020 M.Sc. (McGill Program on Biotechnology) **Hoq**

**Postdoctoral Fellows and Visiting Scholars**
Large number coming from around the world and returning to take up senior positions as full professors, director of units etc.

**OTHER TEACHING AT McGill:**

Physiology 518a: Course coordinator: 25 hours (1972 - Ongoing)

Physiology 518a 8 hours of lectures and 6 hours seminar(1972-Ongoing)

Biomedical Engineering 399-501A 2.5 hours of lectures (ongoing)

Biomedical Engineering (Prof Prakash’s new course) 2 hours of lectures (ongoing)

Med 1 Physiology 5 hours of lectures (before 1972 to 2008)

Biotechnology 202-505B 3 hours of lectures

518a “**Artificial Cells and Biotechnology**” For many years, Professor Chang has organized this course and gives about half the lectures for this course. This is a difficult and highly demanding interdisciplinary advance course. This is included in the suggested courses for Physiology, Biomedical Engineering, Biotechnology Diploma, Biotechnology minor and others students came from Experimental Medicine; and anatomy and molecular biology and occasionally from the faculty of engineering.

**PUBLICATIONS AND INVITED LECTURESHIPS:**

**Summary:** More than 560 papers and chapters (abstracts not included) and 29 books and symposium volumes. Invited to more than 400 international invited lectureships including opening plenary lectures, special lectureships, keynote lectures, plenary lectures. He has also assigned 30 patents and patent applications to McGill University,
PUBLICATIONS: (abstracts not included)

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47. CHANG TMS (1975) Rationale for the use of the ACAC microcapsule artificial kidney
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nonthrombogenic surface by radiation grafting of heparin: Preparation and in-vitro
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53. CHANG TMS (1975) Experience with the treatment of acute liver failure patients
by haemoperfusion over biocompatible microencapsulated (coated) charcoal. in "Artificial
Support Systems for Acute Hepatic Failure" (R WILLIAMS, ed.) Whitefriars Press, Ltd.,
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"Im mobilized Enzymes, Antigens, Antibodies, and Peptides" (HH WEETALL, ed.)
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on platelet retention in extracorporeal surfaces. Int J Biomaterial, Medical Devices &
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applications and perspectives. "Microencapsulation" (J NIXON, ed.) Marcel Dekker,
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within semipermeable aqueous microcapsules containing a multi-enzyme system.
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methods, products & clinical trials" Karger, Basel, pp 73-81.
441. CHANG TMS & S PRAKASH (1999) Chapter on "Removal of urea in uremia and ammonia in liver failure with emphasis on the use of artificial cells containing genetically engineered cells" for book on "Handbook of Cell Encapsulation" (eds WM Kuhitreiber,RP Lanza & WL Chick), Birkhauser & Springer-Verlag. 379-416
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472. YU BL, CHANG TMS (2004) Effects of Long-Term Oral Administration of Microencapsulated Tyrosinase on Maintaining Decreased Systemic Tyrosine Levels in


482. CHANG TMS (2005). The role of artificial cells in cell and organ transplantation in regenerative medicine Panminerva Medica, journal on clinical and experimental medicine 47: 1-9


489. YU BL, ZC LIU & TMS CHANG (2006). Polyhemoglobin with different percentage of tetrameric hemoglobin and effects on vasoactivity and electrocardiogram. Artificial Cells, Blood Substitutes & Biotechnology, international journal 34: 159-175


491. LIU ZC & TMS CHANG. (2006) Polymeric artificial cells for coencapsulation of hepatocytes
516. CHANG, TMS (2008) Safety of red blood cell substitutes compared to donor red
blood cells. Artificial Cells, Blood Substitutes & Biotechnology 36:1-2
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530. CHANG TMS (2011) Editorial on “What is in a name?”. Artificial Cells, Blood Substitutes & Biotechnology 39: 118


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541. Yuzhu Bian, Gao Wei and Thomas M.S. Chang (2013) Lowering of elevated tissue PCO2 in a hemorrhagic shock rat model after reinfusion of a novel nanobiotechnological polyhemoglobin-superoxide dismutase-catalase-carbonic anhydrase that is an oxygen and carbon dioxide carrier with enhanced antioxidant properties. Artificial Cells, Nanomedicine and Biotechnology, an international journal 41: 60-68 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3618434
550. Wenhua Jiang1, Yuzhu Bian, Zhenghui Wang, and Thomas Ming Swi Chang (2016 June online)
560. Wang Y and Chang TMS (2020) Analysis of the effects of the different components of Polylactide nanocapsules containing polyhemoglobin-tyrosinase on in vivo suppression of B16F10 murine melanoma. (to be submitted)

561. Does conventional early life academic excellence predict later life scientific Discovery? An assessment of the lives of Great Medical Innovators
David J. A. Jenkins1-5, Viranda H. Jayalath2,3,6, Vivian L. Choo1,3,7, Effie Viguiliouk1,3, Cyril W. C. Kendall1,3,8, Korbua Sirichaikul3,9, Arash Mirrahimi3,10, Charles N Bernstein11,12, Thomas MS Chang13, Phil Gold14, R. Brian Haynes15, Morley D Hollenberg16, Andres M. Lozano17, Barry J. Posner18, Allan R. Ronald19, Mladen Vranic20, Yu Tian Wang21, Laura Chiavaroli1,3, Russell J. de Souza1,15,22, Stephanie Nishi1,3, Sathish C. Pichika1,3,23, Chantal Gillett3,24, Tom Tsirakis3, John L. Sievenpiper1,3-5

562. TMS Chang History and Potential of nanobiotechnology based blood substitutes, artificial cells and nanobiotherapeutics Chapter in Multiauthor book edited by Chang, Jahr, &
Sakai "Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres" Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

563. TMS Chang Biotechnology based-Oxygen Carriers Chapter in Multi-author book edited by Chang, Jahr, & Sakai "Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres" Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

564. TMS Chang. A NANOBIOTECHNOLOGIC THERAPEUTIC THAT TRANSPORT OXYGEN AND REMOVE OXYGEN RADICALS Chapter in Multi-author book edited by Chang, Jahr, & Sakai "Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres" Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

565. Powanda D & Chang TMS. Cross-linked polyhemoglobin-superoxide dismutase-catalase supplies oxygen without causing blood brain barrier disruption or brain edema in a rat model of hemorrhagic shock with transient global brain ischemia. Chapter in Multi-author book edited by Chang, Jahr, & Sakai "Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres" Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

566. Chen Gang & TMS Chang Dual effects include antioxidant and pro-oxidation of ascorbic acid on the redox properties of bovine hemoglobin Chapter in Multi-author book edited by Chang, Jahr, & Sakai "Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres" Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

567. Chang TMS Soluble nanobiotherapeutics with enhancements of all 3 major red blood cell functions Chapter in Multi-author book edited by Chang, Jahr, & Sakai "Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres" Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

568. Bian, YZ and TMS Chang. A novel nanobiotherapeutic Poly-[hemoglobin-superoxide dismutase-catalase-carbonic anhydrase] with no cardiac toxicity for the resuscitation of a 90 minutes sustained severe hemorrhagic shock rat model with 2/3 blood volume lost Chapter in Multi-author book edited by Chang, Jahr, & Sakai "Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres" Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

569. Chen Guo and Thomas Ming Swi Chang Long term safety and immunological effects of a nanobiotherapeutic, bovine poly-[hemoglobin-catalase-superoxide dismutase-carbonic anhydrase], after four weekly 5% blood volume top-loading followed by a challenge of 30% exchange transfusion Chapter in Multi-author book edited by Chang, Jahr, & Sakai "Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres" Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

570. C. Guo, M.Gynn and TMS Chang Extraction of Superoxide Dismutase, Catalase and Carbonic Anhydrase from stroma-free red blood cell hemolysate for the preparation of the nanobiotechnological complex of PolyHemoglobin-Superoxide Dismutase-Catalase-Carbonic Anhydrase Chapter in Multi-author book edited by Chang, Jahr, & Sakai "Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres" Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

571. YZ Bian, C Guo & TMS Chang Temperature stability of Poly-[hemoglobin-superoxide dismutase-catalase-carbonic anhydrase] in the form of a solution or in the lyophilized form
during storage at -80 °C, 4 °C, 25 °C and 37 °C or pasteurization at 70 °C. Chapter in Multiauthor book edited by Chang, Jahr, & Sakai “Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres” Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

572. Chang TMS Nanoencapsulated nano-artificial red blood cells. Chapter in Multiauthor book edited by Chang, Jahr, & Sakai “Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres” Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

573. Chang TMS, Powanda D & Yu WP Analysis of polyethyleneglycol-polylactide nano-dimension artificial red blood cells in maintaining systemic hemoglobin. levels and prevention of methemoglobin formation. Chapter in Multiauthor book edited by Chang, Jahr, & Sakai “Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres” Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

574. Liu ZC & TMS Chang Effects of PEG-PLA-nano artificial cells containing hemoglobin on kidney function and renal histology in rats Chapter in Multiauthor book edited by Chang, Jahr, & Sakai “Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres” Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

575. LIU ZC & TMS Chang Long term effects on the histology and function of livers and spleens in rats after 33% toploading of PEG-PLA-nano artificial red blood cells. Chapter in Multiauthor book edited by Chang, Jahr, & Sakai “Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres” Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

576. Wei G, Bian YZ & Chang TMS. Polylactide-Polyethylene membrane nanoencapsulated Polyhemoglobin-superoxide dismutase-catalase-carbonic anhydrase. nano artificial red blood cells that act as O₂ and CO₂ carrier with enhanced antioxidant activity: Chapter in Multiauthor book edited by Chang, Jahr, & Sakai “Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres” Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

577. TMS Chang, Jiang WH, D’Agnillo F, Razack S. NANOBIOOTHERAPEUTICS AS PRESERVATION FLUIDS FOR ORGANS AND CELLS Chapter in Multiauthor book edited by Chang, Jahr, & Sakai “Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres” Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)

578. Wong, N & TMS Chang Polyhemoglobin-fibrinogen: a novel blood substitutes with platelet-like activity for extreme hemodilution Chapter in Multiauthor book edited by Chang, Jahr, & Sakai “Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College Pres” Regenerative Medicine, Artificial Cells & Nanomedicine volume 5:(for 2020)


580. Wang,Yun, Thomas Ming Swi Chang(submitted) A nanobiotherapeutic approach for melanoma based on polylactide artificial cell nanoencapsulated polyhemoglobin-tyrosinase: in vitro 3D culture and in vivo suppression of B16F10 murine melanoma in C57BL6 mice.
BOOKS AND SPECIAL ISSUES:

   - Scientific American, Vol 227, November 1972
   - Mayo Clinic Proceedings, Vol 47, November 1972
   - Chemical Engineering Journal, May 14, 1973
   - Biological Abstracts, 55(6), March 15, 1973
   - Biomedical Engineering Journal, April 1973
   - Quarterly Journal of Experimental Physiology
   - Nephron, Vol 10, No 23, 1973
   - Annuals, Royal College of Surgeons of England, July 1974
   - New Zealand J Med Lab Tech, 26, November 1972

   **Book Translated into:**
   2) Russian (1979) by Prof. V NICOLAEV, USSR.

20. CHANG TMS (ed) (1992). Blood substitutes and oxygen carriers. Marcel Dekker Publisher, USA, 784 pages. Book Reviews: " excellent very useful and easy to read " recommended arr important addition to medical and basic-science libraries." Canadian Medical Association Journal. "The authors of the papers represent a list of "who's who" in the field." Hematologic Pathology
27. CHANG TMS (May 2007) Monograph on “ARTIFICIAL CELLS: biotechnology, nanotechnology, blood substitutes, regenerative medicine, biencapsulation, cell/stem cell therapy” World Scientific Publisher/Imperial College Press 435 pages. (Since April 2010 has obtained copyright to place this book for noncommercial free online viewing or download on: 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.”
28. CHANG, TMS (2013) editor, Book on “Selected Topics in Nanomedicine” World Scientific Publisher/Imperial College Press pp590.
http://www.medicine.mcgill.ca/artcell/HPBk_Ch1.pdf
31. Chang, Jahr, & Sakai (for 2020) A multiauthor book on “Nanobiotherapeutic basis for blood substitutes and oxygen therapeutics World Scientific Publisher/Imperial College (for 2020)
INVITED LECTURES:
1963 Invited speaker, Red Cell Club, NIH, Bethesda, Maryland, USA.
1963 Invited lecturer, Dept. of Physiology, University of Pennsylvania, Philadelphia, USA.
1964 Invited lecturer, Gordon Research Conference on Medicinal Chemistry, New Hampshire, USA.
1964 Invited lecturer, Merck, Sharpe and Dohe, New Jersey, USA.
1964 Invited lecturer, Eli Lilly, Indianapolis, Indiana, USA.
1965 Invited lecturer, University of Montreal, Montreal, Quebec, Canada.
1965 Invited lecturer, New York Blood Center, New York, USA.
1965 Invited lecturer, Battelle Memorial Institute, Columbus, Ohio, USA.
1966 Invited lecturer, NCR, Dayton, Ohio, USA.
1967 Invited lecturer, Dept. of Artificial Organs, Cleveland Clinic, Cleveland, Ohio, USA.
1968 Invited lecturer, Microencapsulation Symposium, New Jersey, USA.
1968 Guest speaker, Association of Professional Engineers, Ottawa, Ontario, Canada.
1968 Guest speaker, Stamford Section, American Chemical Society, Stamford, Connecticut.
1968 Invited lecturer, New York Blood Center, New York, USA.
1969 First Incentive Lecturer, The Annual Incentive Lectures were instituted in Sweden in 1969 to invite once a year a foreign scientist to give an Incentive Lecture in Stockholm and other Swedish universities. The first Incentive Lecturer was "invited to inaugurate these annual lectures". The lecture on "The Clinical Potential of Enzyme Technology" was given at:
   1) Karolinska Institute, Stockholm, Sweden.
   2) Chemical Centre, University of Lund, Lund, Sweden.
   3) University of Gothenberg Hospital, Gothenberg, Sweden.
1969 Invited lecturer, Dept. of Physiology, University of Toronto, Toronto, Ontario, Canada.
1969 Invited lecturer, Dept. of Pathology, Rhode Island Hospital, Rhode Island, USA.
1969 MRC Visiting Professor, Dept. of Biophysics, University of Western Ontario, London, Ontario, Canada.
1969 Invited lecturer, Dept. of Artificial Organs, University of Utah, Salt Lake City, Utah.
1969 Invited lecturer, Alza Co., Pala Alto, California, USA.
1970 Invited lecturer, Cardiovascular Research Institute, San Francisco, California, USA.
1970 Invited lecturer, Renal Unit, Sydney Hospital, Sydney, Australia.
1970 Invited lecturer, Dept. of Physiology, University of Sydney, Sydney, Australia.
1970 Invited lecturer, Renal Unit, Prince Henry Hospital, Sydney, Australia.
1970 Invited lecturer, Biomedical Symposium, Australian Academy of Science and Society of Engineers, Sydney, Australia.
1970 Invited lecturer, Microencapsulation Symposium, New Jersey, USA.
1971 Invited lecturer, Dept. of Chemical Engineering, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
1971 Invited lecturer, Gordon Research Conference on Biomaterials, New Hampshire, USA.
1971 Enzyme Engineering Conference, New Hampshire, USA.
   1) Invited lecturer.
   2) Invited panel discussant on "Future of Enzyme Engineering".
1971 Invited lecturer, Life Science Seminar, Battelle Memorial Institute, Columbus, Ohio.
1972 Invited lecturer, National Foundation Symposium on Enzyme Replacement, Sarasota, Florida, USA.
1972 Invited lecturer, Chemical Engineering Dept., Princeton University, New Jersey, USA.
1972 Invited lecturer, Biomedical Engineering Symposium, MRC Bioengineering Unit, University of Strathclyde, Glasgow, Scotland.
1972 Invited lecturer, Renal Unit, Edinburgh Royal Infirmary, Edinburgh Medical School, Scotland.
1972 Invited guest speaker, Canadian Kidney Foundation Annual Meeting.
1972 Invited lecturer, NIH, General Medical Sciences, Bethesda, Maryland, USA.
1972 Invited lecturer, Microencapsulation Symposium, New Jersey, USA.
1973 Invited lecturer, First International Microencapsulation Symposium, Athens, Georgia.
1973 Chairman, session on "Biomedical Applications" and invited lecturer, International Conference on Insolubilized Enzymes, Milan, Italy.
1973 Co-chairman, session on "Future Applications of Enzyme Engineering", Enzyme Engineering Conference.
1973 Invited lecturer, International Nephrological course, Parma, Italy.
1973 Invited lecturer, Canadian High Polymer Forum of Membranes, St. John, Quebec.
1973 Annual guest speaker, Japanese Society for Artificial Organs, Sandai, Japan.
1973 Guest speaker, Japanese Society for Promotion of Renal Transplantation, Tokyo, Japan.
1973 Invited lecturer, Tokyo Science University, Tokyo, Japan.
1973 Guest discussant, Panel on "Microcapsule Hemoperfusion for Chronic and Renal Failure", Tokyo College of Medicine and Dentistry, Tokyo, Japan.
1974 Visiting professor, Medical Engineering Session, Faculty of Medicine, University of Minnesota, Minneapolis, Minnesota, USA.
1974 Invited lecturer, Dept. of Anatomy, University of Minnesota, Minneapolis, Minnesota.
1974 Invited lecturer, American Chemical Society Symposium on "Polymer Graft in Biochemistry", California.
1974 Invited lecturer, Microencapsulation Workshop, New Jersey, USA.
1974 Invited discussant, Biomedical Research in Narcotic Abuse Problems, organized by the Non Medical Use of Drugs Directorate, Health & Welfare Canada.
1975 Conference on "Sorbents in Uremia and Hepatic Failure", Sponsored by the International Society of Nephrology, NIH Chronic Uremia Program and the Clinical Dialysis and
Invited introductory lecturer on "Microencapsulation and Coating for Adsorbent".
Invited lecturer on "Microencapsulated Adsorbent for Acute Intoxication, Liver Failure and Uremia".
Chairman of the session on "Hemoperfusion".
Panel discussant of second day sessions.
1975 Invited speaker, Symposium of the International Pharmacological Congress, Helsinki, Finland.
1975 Invited speaker, New York Nephrology Society, New York, USA.
1975 Invited speaker, Downstate University of New York, School of Medicine, New York, USA.
1975 Invited lecturer, "Microencapsulation Workshop", New Jersey, USA.
1975 Invited lecturer, NIH group on "Liver Failure Support", Clinical Center, NIH, Bethesda, Maryland, USA.
1975 Invited lecturer, Nephrology Dept., Children's Hospital, National Medical Center, Washington, D.C., USA.
1975 Invited speaker, symposium on "Immobilized Enzyme Applications", Chemical Institute of Canada, Toronto, Ontario, Canada.
1975 Invited lecturer, Gordon Conference on "Transport Phenomena in Synthetic and Biological Membranes", New Hampshire, USA.
1975 Invited speaker, symposium on "Immobilized Enzyme Applications", Chemical Institute of Canada, Toronto, Ontario, Canada.
1975 Invited lecturer, Gordon Conference on "Transport Phenomena in Synthetic and Biological Membranes", New Hampshire, USA.
1975 Poona International Workshop and Symposium on Enzyme Engineering, Poona, India. Main speaker on "Microencapsulated Enzymes". Main speaker on "Medical Applications of Immobilized Enzymes". Panel discussant on "Technique and Novel Approaches". Chairman of session on "Applications of Immobilized enzymes".
1975 Invited speaker, University of Poona, Poona, India.
1975 Invited participant, Second International Federation of Institutes of Advanced Studies Workshop, Poona, India.
1975 Chairman, session on "Biomedical Applications of Microencapsulation" and Invited speaker, 3rd International Symposium on Microencapsulation, Tokyo, Japan.
1975 Chairman, "Panel on Adsorbent Hemoperfusion for Uremia, Acute Intoxication and Liver Failure", Annual Meeting, American Society for Artificial Internal Organs, San Francisco, California, USA.
1975 Consultant and participant, "Drug Delivery Systems Workshop", NIH, Bethesda, Maryland, USA.
1975 Invited lecturer, Gordon Research Conference on "Immobilized Enzymes", New Hampshire, USA.
1975 Invited speaker, "Lecture Series on Possibilities of Synthetic Biology", Dept. of Life Sciences (James F. Danielli) Worcester Polytechnic Institute, Worcester, Massachusetts, USA.
1975 Co-chairman, Session 3 on "Artificial Organs", llth International Conference on Medical and Biological Engineering, Ottawa, Ontario, Canada.
1975 International Enzyme Engineering Conference, Germany. Chairman, session on "New Medical Applications in Immobilized Enzymes". Invited speaker, "New Approaches of Biodegradable Polymer Membranes, Microcapsules and Microencapsulation of Multistep Enzyme Systems."
1975 Organizer and program chairman, McGill Artificial Organs Research Unit International Symposium on "Some Novel Approaches in Artificial Kidney, Artificial Liver and Detoxification", McGill University, Montreal, Quebec, Canada.
1975 NIH International Conference on "Fulminant Hepatic Failure", Bethesda, Maryland. Chairman, session on "Hemoperfusion Through Sorbents". Invited speaker on "Albumin Cellulose Nitrate Coated Charcoal Hemoperfusion in FHF". Invited speaker on "Microencapsulation of Multienzyme Systems and Recycling of Cofactors".
1975 Guest speaker, "Biomedical Applications of Artificial Cells", Montreal Physiological Society, Montreal, Quebec, Canada.
1975 Chairman, panel workshop on "Some Problems Related to Adsorbent Therapy", Annual Meeting, American Society for Artificial Internal Organs, Montreal, Quebec, Canada.
1975 Invited speaker, "Biomedical Applications of Enzymes" Symposium on Enzymes, American Chemical Society, Amherst, Massachusetts, USA.
1977 First International Society of Artificial Organs Meeting, Tokyo, Japan. Chairman, session on "Sorbents in Artificial Kidney". Invited panelist, "Hepatic Assist Devices".
1977 Invited speaker, "Artificial Cells", Dow Cordis Artificial Kidney Division, Concord, California, USA.
1977 Invited speaker on "Hemoperfusion", Canadian Conference on Clinical Engineering, Notre Dame Hospital, Montreal, Quebec, Canada.

1977 Visiting Professor by invitation of the Chinese Academy of Sciences, lectured at:
   i. Biophysics Institute, Chinese Academy of Sciences, Peking (12 hrs lectures, plus seminars and demonstrations).
   ii. Capital Hospital (previously Union Medical School), Peking.
   iii. National Symposium, Lang Fang (12 hours of lectures, plus seminars & demonstrations).
   iv. Suchiachung Medical School, Suchiachung.
   v. Hongchow Medical School, Hongchow.
   vi. Shanghai Medical Association, Shanghai.
   vii. Canton Medical and Scientific group, Canton.
1978 International Symposium on "Hemoperfusion, Dialysate and Diafiltrate Purification", Tutzing, Munich, Germany. Chairman, session on "Hemoperfusion". Invited introductory lecturer on "Hemoperfusion". Invited lecturer on "Hemoperfusion in Fulminant Hepatic Failure". Invited lecturer on "Conversion of Urea and Ammonia into Amino Acid".
1978 Invited speaker in symposium on "Nondialytic Management of Uremia", sponsored by NIH, Downstate Medical Center and New York Society of Nephrology, New York, USA.
1978 Invited speaker on "Biodegradable Drug Carriers", Gordon Research Conference, Plymouth, New Hampshire, USA.
1978 Invited speaker on "Immobilized Enzymes in Therapy", Conference on "Enzyme Economy", Chicago, Illinois, USA.
1978 Keynote speaker, Annual meeting of the Biomaterials Society, University of Toronto, Toronto, Ontario, Canada.
1978 Chairman, session on "Hemodialysis", International Congress of the International Society of Nephrology, Montreal, Quebec, Canada.

1979 Invited speaker on "Progress in Polymer Encapsulation of Enzymes, Biospecific Adsorbents and Drugs", American Japanese Chemical Societies joint symposium, Honolulu, Hawaii, USA.
1979 Reporteur, Enzyme Therapy in Congenital Diseases Symposium, Hilton Head, North Carolina, USA.
1979 Symposium co-chairman and invited speaker, International Workshop on "Hemoperfusion", Haifa, Israel.
1979 Invited speaker, Faculty of Medicine, University of Edmonton, Alberta, Canada.
Invited speaker on "Artificial Cells".
Chairman of session on "Artificial Cells".

1980
International Symposium on "Artificial Liver Support", Hannover, Germany.
Invited speaker on "Effects of Artificial Liver Support for Galactosamine Fulminant Hepatic Failure Rats".
Co-chairman, session on "Hemoperfusion".
Invited speaker on "Encapsulated Enzymes and Adsorbent" in replacement therapy.
International Symposium on "Therapy in Congenital Diseases", Swiss Academy of Medical Sciences, Interlaken, Switzerland.

1980
Annual Meeting, American Society for Artificial Internal Organs, New Orleans, Louisiana, USA.
Invited plenary speaker on "Artificial Blood Cells" in plenary symposium.
Chairman, panel conference on "Adsorbent Hemoperfusion in Blood Purification".
Co-chairman, sessions on "Artificial Liver".
Recipients "Clemson Award" for "Basic Research in the Development of the Microcapsule Artificial Kidney", World Congress of International Society for Biomaterials, Vienna, Austria.
Guest speaker, Mexico Society of Nephrology, Mexico on: Artificial Cells.
Hemoperfusion in Chronic Renal Failure. Hemoperfusion in Acute Intoxication and Liver Failure.

1981
International Symposium on "Hemoperfusion", Bologna, Italy.
Invited speaker on "Hemoperfusion in 1981".
Session chairman on "Hemoperfusion General".
Guest editor of symposium proceedings.
International Symposium on Detoxification Approaches in Chronic Schizophrenia, Berlin, East Germany.
Invited speaker on "Endorphin and Middle Molecule Removal in Schizophrenia".
Co-chairman on "Detoxification Session".
"Distinguished Honoured Guest", Preview Ceremony, International Center for Artificial Organs and Transplantation, Cleveland, Ohio, USA.
Annual Meeting, American Society for Artificial Internal Organs, Anaheim, California.
Co-chairman, session on "Plasma Manipulation and Enzyme".
Program Committee.
Invited plenary lecturer on "Blood Compatible Adsorbent Hemoperfusion in Extracorporeal Blood Treatment", 4th International Symposium on Affinity Chromatography and Related Techniques, Katholieke Universiteit, Nijmegen, The Netherlands. (Unable to attend just before meeting, paper presented as publication in book)
Invited speaker on "Present Status of Microencapsulated Adsorbent", Symposium on "Adsorbent in Uremia", Congress of the International Society of Nephrology, Athens, Greece. (Paper read in absence by Dr. E. Espinosa)
Invited speaker on "Hemoperfusion" in opening plenary symposium on "Controversies and Issues in Artificial Organs".
Chairman, session on "Hemoperfusion".
Keyman of Hemoperfusion, program committee of International Society.
(Paper read in absence by Dr. M. Poznansky)
International Symposium of Chemical Engineering, Montreal, Quebec, Canada.
Invited speaker plenary lecturer on "The Present Status of Research in Artificial Cells".
Chairman, session on "Artificial Organs and Implants".
Invited speaker, "Microcapsules" in "Colloquium on Microcapsules and Microcarriers"
1981 Invited speaker, Biotechnology Seminars, McGill University, Montreal.

1982 Chairman of Gordon Research Conference on "Drug Carriers in Biology and Medicine", New Hampshire, USA (also session chairman and invited speaker on Artificial Cells).
1982 IVth International Symposium of Hemoperfusion and Artificial Organs, Ankara, Turkey. Honorary President of symposium. Invited speaker on "Past, Present and Future Perspectives of Hemoperfusion".
1982 Invited speaker, Canadian Science Writing Association Meeting, Montreal.

1983 President, organizer and invited speaker, Fifth International Symposium on "Microencapsulation, including Artificial Cells", Montreal, Canada.
1983 Chairman and invited speaker, Symposium on Hemoperfusion, Congress of the European Society for Artificial Organs.
1983 Invited speaker on "Artificial Cells", symposium on "Plastics and Artificial Organs", American Chemical Society, Seattle, Washington, USA.
1983 Invited speaker on "Clinical Trial on Hemoperfusion" in Workshop on Hemoperfusion organized by Hopital Necker, Paris, France.
1983 Invited speaker, Pediatric Research Symposium and Workshop. Faculty of Medicine, University of Alberta, Edmonton, Alberta.
1983 Invited speaker on the Composite Artificial Kidney Reviews of indications and applications, Societe Quebecoise de Nephrologie Annual Scientific Meeting, Val David, Quebec.
1983 Invited speaker on "Composite Artificial Kidney in Uremic Patients" Symposium on Hemoperfusion, Amsterdam, Holland. (Paper read in absence by Dr. P. Barre)
1983 Invited speaker on Membrane Biotechnology in Artificial Cells in "Membrane


1983 Invited speaker, Nankai University, Tianjin, People's Republic of China.

1983 Invited speaker, Chongqing Medical College and Chongqing Biomedical Engineering Society, Chongqing, People's Republic of China.

1983 Invited speaker, Shanghai First Medical College, Shanghai, People's Republic of China.

1983 Invited speaker, Institute of Biochemistry, Shanghai, People's Republic of China.

1984 Invited speaker and session chairman, Gordon Research Conference on "Drug Carriers in Biology and Medicine".

1984 Invited speaker, Biocatalysis Group, University of Iowa, Iowa, Ill.

1984 Guest Faculty, Postgraduate Medicine course on "Life Support Systems in Intensive Care", University of Michigan Medical School, Ann Arbor, Michigan.

1984 Invited lecturer, NATO Advanced Study Institute on Biopolymer, Turkey.


1984 Invited speaker in Seminar on "Hemoperfusion in Hemodialysis Patients", NJ, USA.

1985 Chairman of session on Immobilized Cells, 8th Biannual International Enzyme Engineering Conference, Denmark.

1985 5th Congress of International Society of Artificial Organs, Chicago, USA.

Chairman, Program Committee on "Artificial pancreas/artificial liver".

Chairman, Workshop on "Artificial Cells".

1985 Invited Speaker, Science Council of Canada/Canadian Plastics Institute Meeting on

1985 Invited Lecturer, "Artificial Cells", DuPont Co., Wilmington, DE, USA.


1985 VIth International Symposium on Hemoperfusion, Mexico

Honorary president

Invited speaker.

1985 Invited speaker for special breakfast meeting on "Hemoperfusion in chronic renal failure and aluminum removal", 25th Anniversary of Chronic Dialysis" to honour Professor B. Scribner, Seattle, USA.

1985 Invited participant, Science Council Workshop on Medical Devices, Toronto.

1985 Opening Plenary Lecturer, State art on "Artificial Blood", Annual Meeting of American Society of Artificial Internal Organs, Atlanta, USA.


1986 Honorary President of Symposium, Cochairman, Program Committee, and invited speaker, 7th International Symposium on Hemoperfusion, Kiev, USSR, sponsored by the USSR Academy of Sciences, September.

1986 Invited speaker, Czechoslovakia Society of Nephrology and Czechoslovakia Academy of Sciences, Prague.

1986 Special invited lecturer and session chairman, Annual Meeting of the Controlled Release Society, Virginia, USA.

1986 Chairman of two sessions, invited speaker and Program Committee on Artificial Kidney "International Symposium on Biomedical Engineering, Artificial Organs, and Transplantation" to honour Professor W. Kolff, Utah, USA.


1986 Invited speaker, Workshop on Drug and Enzyme Delivery Systems, Annual Meeting of
1986 Invited speaker on "Artificial Cells" Workshop on Biotechnology, Canadian Society of Biological Sciences, Guelph, Ontario.

1987 Chairman of Symposium and Opening Plenary speaker, III International Symposium on Blood Substitutes, Montreal.
1987 Invited Speaker on "Immobilization of enzymes, liver cell cultures and hemoglobin" in Session on Medical Applications, 9th International Conference on Enzyme Engineering, Santa Barbara, California.
1987 Invited plenary lecturer and chairman of session, 7th International Symposium on Microencapsulation, Zegreb, Yugoslavia.
1987 Invited speaker, NATO Workshop on Immobilized Enzymes, Italy.
1987 Invited panelist, Symposium on "Role of Hemoperfusion in acute liver failure", Georgetown University, Washington.
1987 Invited Guest speaker, American Society on Material (Edmonton, Alberta).
1987 Invited speaker, Grand Round, Faculty of Medicine, University of Alberta, Edmonton.

1988 Opening Ceremony State Art Lecturer on "Artificial Cells" 1988 Congress of the European Society for Artificial Organs, Prague, Czechoslovakia.
1988 Honorary President and Opening Ceremony Festive Lecturer on "Artificial Cells" 8th International Symposium on Hemoperfusion, Adsorbents and Immobilized Bioreactants, Rostock, Germany.
1988 Special invited speaker on "Artificial Blood". Symposium, Mexico City, Mexico.
1988 Invited lecturer on "Blood Substitutes". Mexican Academy of Surgery, Mexico City.
1988 Invited lecturer on "Blood Substitutes". Medical Centre, Mexico City, Mexico.
1988 Chairman of session and introductory lecture Gordon Research Conference on "Drug Carriers" New Hampshire, USA.
1988 Special invited speaker on "Clinical Applications of hemoperfusion in intoxication and hepatic coma". Symposium, Mexico City, Mexico. 1988 Invited Lecture on Artificial Cells, Shiga University, Japan.
1988 Invited Speaker International Congress on "New Trends in Nephrology, Dialysis and Transplantation". 9th Centenary, University of Bologna, Bologna, Italy.
1988 Session chairman, Artificial liver/pancreas, Annual Meeting of the American Society Artificial Internal Organs, Reno, USA.
1988 Invited keynote lecture, Hybrid Artificial Organs Symposium, Bordeaux, France.

1989 Honorary president and invited speaker, 9th International Symposium on Hemoperfusion, adsorbents and immobilized bioreactants, Tokyo, Japan.
1989 Invited lecturer, Plenary session on "Enzyme Engineering in Medical Field". 10th International Conference on Enzyme Engineering, Kashikojima, Japan.

1989 Invited speaker and chairman of session, International Symposium on Red Blood Cell
Substitutes sponsored by the Japanese Red Cross Society.

1989
Invited lecturer. "Immunological aspects of modified hemoglobin as blood substitute"
Biomedical Engineering Society, Symposium on "Blood Substitutes". Federation of American Biological Sciences, New Orleans, U.S.A.

1989
Invited lecturer, "Modified hemoglobin: in vivo studies" American Trauma Society Annual Meeting, Florida, USA.

1989
Invited lecturer, Red Blood Cell Substitutes, Waseda University, Tokyo Japan.

1989

1989
Chairman and speaker, Workshop on Blood Substitutes, European Society of Artificial Organs, Brussels, Belgium.

1989
Invited speaker on Blood Substitutes, Montreal Red Cross Society, Montreal.

1989
Invited speaker, Biotechnological and Medical applications of Artificial Cells in International Conference on Biotechnology, Slamanca, Spain

1990
Honorary president and invited plenary speaker, X International symposium on Hemoperfusion, absorbent and immobilized bioreactants, Rome, Italy

1990
Invited plenary speaker on Biotechnological approach based on artificial cells, Congress of the European Society for Artificial Organs, Bologna, Italy

1990
Invited plenary speaker, VI International Symposium on Microencapsulation, Glasgow

1990
Invited speaker on Artificial Cells. "International Conference on Membrane," Chicago, IL

1991
Invited speaker, symposium, American Chemical Society, Annual Meeting, Washington, DC, USA

1991
Invited speaker in panel on Hybrid Artificial Organs, Annual Meeting, American Society of Artificial Internal Organs, Chicago USA.

1991
Invited speaker and session chairman on "Blood Substitutes"; Annual Meeting, American Society of Artificial Internal Organs, Chicago, USA.

1991

1991
Congress President VIII World Congress, International Society of Artificial Organs, Montreal, Canada. Opening ceremony speaker on "35 years of artificial cells"

1991
Symposium Chairman and plenary speaker, on "Modified hemoglobin as blood substitutes", IV International Symposium on Blood Substitutes, Montreal, Canada.

1991

1992
Chairman of panel on "Blood substitutes", and speaker on "Modified hemoglobin and clinical safety", American Society for Artificial Internal Organs, Annual Meeting, Memphis, USA.

1992
Invited plenary speaker on Blood Substitutes., XIX Congress of the European Society for Artificial Organs, Rhode Island, Greece.

1992
1st Julius Silver Lectureship, Julius Silver Symposium organized by the Julius Silver Institute of Biomedical Engineering, Technion Institute, Israel and the Israel Society of Biomedical Engineering. International

1992
Invited speaker, 8th International Symposium on Microencapsulation, Dublin, Ireland,

1993
Co-chairman and invited plenary speaker, V International Symposium on Blood Substitutes, San Diego, California, USA.

1993
Chairman and opening speaker, IB Conference on Blood Substitutes, Philadelphia, USA.

1993
Open plenary lecturer, Inaugurative congress of the founding of the Japanese Society for Blood Substitutes. Tokyo

1994
Honorary Congress President and Opening Plenary Speaker, XI Congress of the International Society for Artificial Cells, Blood Substitutes and Immobilization Biotechnology, with Professor R. Langer of MIT as organizer and congress president, Boston, USA.
1994 Invited speaker, on Blood Substitutes International Conference on Bioengineering, Krems, Austria.
1995 Invited speaker on "Artificial Cells Technologies" Meeting on Cell Transplantation. Technologies Applicable to Cell Therapy, Miami, U.S.A.
1995 Invited speaker Symposium on Tissue Engineering using Biomedical Polymers. Kyoto
1995 Invited Main Lecturer. (at last minute substituted by my recent Ph.D. graduate because too many invited lectures this year.) International Symposium on Polymer, Institute of Macromolecular Chemistry, Czech Academy of Science, Prague, Czech.
1995 Invited Special Lecturer on "Present Status of Modified Hemoglobin as Blood Substitutes" II Congress Japanese Society for Blood Substitute, Tokyo, Japan. This was followed by Invited Lecturer on "Specially designed modified hemoglobins" Waseda University, Tokyo and also Shonan Research Centre, Tokyo.
1995 Presidential address & Key note speaker on "Artificial Cells Biotechnology for Artificial Organs in the 21st Century". X World Congress of the International Society for Artificial Organs, Taipei, Taiwan.
1995 Invited Plenary lecture on "Microcapsule artificial cells containing enzyme, hepatocytes or genetically engineered microorganisms: implications in therapy and biotechnology" in the International Symposium on Microencapsulation, Drug Dynamics Institute, College of Pharmacy, U of T at Austin, Texas, U.S.A.
1996 Co-chairman and invited speaker on "Deveopment of bioartificial liver" in Symposium on "Plasmapheresis and/or transplant for fulminant hepatic failure" International Conference for Apheresis, Kyoto, Japan.
1997 Honorary congress president and plenary lecturer. XII Congress of the International Society for Artificial Cells, Blood Substitutes and Immobilization Biotechnology. Organized by the Chinese Academy of Medical Sciences, Beijing, PRC. September.
1997 Keynote speaker, "Blood substitutes - present status and future relevance in national blood supply policies" Canadian Society for Transfusion Medicine, Ottawa.
1998 Invited Plenary Lecturer on "Artificial Cells including Blood Substitutes" 8th Asian-Pacific Congress of Clinical Biochemistry, Kuala Lumpur, Malaysia
1998 Invited "State of the art lecture" on hemoglobin-based blood substitutes. XXVth Congress of the Int. Soc of Blood Transfusion. Oslo, Norway,
Conference on Resuscitation Fluids, Institute of Medicine, National Academy of Science, Washington, D.C.

1999 Chairman and opening speaker. Panel on Artificial Blood. Annual Meeting of the American Society for Artificial Internal Organs
1999 Invited lecturer and chairman of panel on “Bioencapsulation” Innovation and Trends in Biotechnology, Laval, Quebec, Canada,
1999 Invited lecturer on “Artificial Cells including blood substitutes”, Therapeutic Products Program, Continuing Education, Health Canada, Ottawa, Canada
1999 Invited speaker in symposium on “The bowel as an artificial kidney” Congress of the International Society for Artificial Organs, Edingburgh, UK.
1999 ISBP Award Plenary Lecture, Congress of the International Society for Blood Purification, Prague. (Sir Roy Calne was the winner of the 1998 ISBP Award Lecturer other previous winners have included Robert Rosenberg at the NIH, and Charles Dinarello then at Tufts)

2000 Invited Lecturer on Artificial Cells, Abbott Laboratory, Chicago
2000 Invited Lecturer on Blood Substitutes, International Conference on Transfusion Medicine 2001, Cambridge University, United Kingdom
2000 Invited Lecturer on Blood Substitutes, European Society for Trauma Surgery, Pisa, Italy
2000 Invited Plenary Speaker, Bionics for Human in 3rd Millenium, L'Aquila, Italy
2000 Chairman, Session on Award Lectures, Congress of the International Society for Blood Purification, Rome, Italy
2000 Session Chairman on Clinical Trials and Invited Lecturer on Present Status(1)Blood Substitutes (2) Oral therapy for uremia, III Bioartificial Organ Conference, Switzerland
2000 Invited Lecturer, Poly2000, American Chemical Society, Hawaii

2001 Chairman & Invited Speaker in panel on “Artificial Organs”. 6th Symposium of World Artificial Organs, Immunology & Transplantation Society, Ottawa, Canada
2001 Invited Speaker in panel on “Treatment of Type 1 Diabetes”, 6th Symposium of World Artificial Organs, Immunology & Transplantation Society, Ottawa, Canada
2001 Panelist in public panel on “Ask the Experts”. 6th Symposium of World Artificial Organs, Immunology & Transplantation Society, Ottawa, Canada
2001 13th Congress of the International Society for Artificial Organs, Osaka, Japan. International Scientific committee, chairman of Panel session on “Genetic Engineering and Biotechnology in Artificial Organs”, and invited panel lecturer on “Artificial Cells for genetically engineered cells and modern biology in artificial organs”
2001 Invited speaker on Artificial Cells as visiting professor, Chinese Hong Kong University Medical School.
2001 Invited speaker on Artificial Cells. Capital Medical School Affiliated ChouYaung Hospital, Beijing.

2002 Invited lecturer on “Artificial Cells in Tissue Engineering with emphasis on oral therapy using artificial cells containing genetically engineered cells”. Tissue Engineering
2002 Invited plenary speaker on “Future generations of Blood Substitutes” and member of Organizing committee of Conference on Blood Substitute organized by Karolinka Institute, Stockholm, Sweden.
2002 Keynote speaker on “Artificial Cells in Biotechnology and Medicine”, World Congress. Seoul, South Korea.
2003 Invited Special Plenary speaker on Artificial Oxygen Carriers, International Symposia for Life Science and Medicine, Keio University, Tokyo, Japan (March)
2003 Honorary president and invited plenary speaker, 9th International Symposium on Blood Substitutes, Tokyo, Japan (March)
2003 Invited Speaker, Symposium, Research Fund Bayer/Canadian Blood Service/Hema Quebec
2003 Invited speaker on Artificial Cells in Medicine and Biotechnology. CIHR Workshop Regenerative Medicine and Artificial Organs, Toronto, Canada. (March)
2003 Visiting Professor, Invited Lecture on Blood Substitutes, Grand Round, Department of Anesthesia and Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, U.S.A. (December).
2003 Invited plenary speaker. TEDA-Waston International Biotechnology Conference, Tianjin, PRC
2003 Invited speaker. Life Sciences Faculty, Nankai University, Tianjin, PRC
2003 Invited speaker. Chinese Academy of Medical Sciences/ Beijing Union Medical College. Beijing, PRC
2003 Invited speaker. Pharmaceutical Sciences and Biotechnology Faculty, Tianjin University, Tainjin, PRC
2004 Keynote speaker, Graduate Program Conference, Department of Pharmaceutical Sciences, University of Toronto, Canada.
2004 Invited speaker, VIP guest, scientific committee, the 3rd TEDA-WATSON International Forum on Biotechnology and Biomedicine, Tianjin, China
2004 Invited plenary speaker and Investiture as Visiting Professor Shen Zhen University, National Symposium on Hemoperfusion. ShenZhen, China
2004 Keynote speaker, 5th International European Molecular Biology Laboratory Ph.D. Students’ Symposium. European Molecular Biology Laboratory (EMBL), Heidelberg, Germany
2005 Keynote Speaker on “Artificial Cells in Regenerative Medicine” II World Congress Regenerative Medicine, Lipzig, Germany
2005 Invited speaker on “Blood Substitutes: molecular biotechnology to nanobiotechnology” International Conference on New Technologies in Medicine, Krems, Austria
2005 Invited speaker on “Artificial Cells of macro, micro, nano and molecular dimensions” Department of Biomedical Engineering Seminar Series, McGill University.

2006 Invited Speaker, Biomedical Engineering Department Seminar Series, McGill University.

2006 Opening Plenary lecturer for the 3 days Business Conference section of the 9th International Conference on “Gene and Drug Therapy in Molecular Medicine” Crete, Greece. “Therapeutic Application of Polymeric Artificial Cells”

2006 Invited opening session lecture on “Therapeutic applications of polymeric artificial blood cells” International visions on blood substitutes. Hemoglobin-based oxygen carriers, from chemistry to clinic” University of Parma, Parma, Italy.

2006 Invited speaker: Technology in Liver Regeneration Conference on Stem Cells in Regenerative Medicine, Ankara, Turkey.(cancel because of airline security problem)

2006 Invited speaker on nano artificial red blood cell to the Nanoscience Group, University of Duisburg-Essen in Western Germany (Postponed because of airline security problem)

2007 Invited Opening keynote lecturer, 2007 Oct XI International Symposium on Blood Substitutes, Organized by Chinese Academy of Medical Sciences and Beijing Union Medical College, Beijing, China

2007 Chairman and panelist, Satellite symposium of XI ISBS on Toxicology of Blood Substitutes, Xian, China.

2007 Invited Opening keynote lecturer, XI International Symposium on Blood Substitutes, Organized by Chinese Academy of Medical Sciences and Beijing Union Medical College, Beijing, China

2007 Co-Chairman and panelist, Satellite symposium of XI ISBS on Toxicology of Blood Substitutes, Xian, China.

2007 Invited Speaker, Faculty of Medicine, Shantou University, Shantou, China

2007 Visiting Professor and invited speaker, Northwest University in Xian, China

2008 Invited lecturer, International Conference on Drug Design and Discovery, Dubai, UAE Dubais invited speaker

2008 International Drug Discovery Science & Technology Conference (IDDST) Opening keynote session in session on Regenerative Medicine, Beijing, China.

2008 Plenary speaker and chair of session, International Academy of Nanomedicine Symposium, Washington DC (Potomac MD) USA

2008 Guest Professor award ceremony and invited lecture. Shantou University, Shantou, China

2008 Plenary Keynote speaker, World Congress on Cancer, Shanghai, China (did not go because of unexpected illness)

2008 Invited Keynote speaker, Joint meeting of the 15th Japanese Society for Blood Substitutes and 6th Current Issues in Blood Substitutes, Keio University, Tokyo, Japan (did not go because of unexpected illness)

2009 Honorary President, opening speaker, invited speaker and panelist, XII International Symposium on Blood Substitutes, Parma, Italy.

2009 Opening plenary lecturer, First World Congress of the International Academy of Nanomedicine, Hainan, China


2010 Opening Keynote plenary lecturer, 2nd World Congress of the International Academy of Nanomedicine, Antalya, Turkey

2010 Opening Keynote plenary lecturer. International Congress on Nanotechnology, Ottawa

2010 Opening Keynote plenary lecture BIOMED2010, Istanbul

2010 Opening Keynote plenary lecturer BIT 3rd Congress on Regenerative Medicine and Stem Cells, Shanghai, China.

2010 Opening Keynote plenary lecturer BIT 1st Congress on Nanomedicine, Beijing, China

2010 Invited Lecture, Tsinghua University, Beijing, China

2010 Invited Lecture, Peking University Health Sciences, Beijing, China

2010 Invited Lecture, Polytech University, Hong Hong, China
2010 Invited Lecture, Transfusion Institute, Beijing, China

2011 Acceptance speech for being voted the “Greatest McGillian” in McGill University’s 190 years history. Result of a worldwide poll to vote on 700 nominee and 20 finalists to celebrate the 190th anniversary of McGill University.

2011 Kjeldgaard Lecturer, Department of Molecular Biology, Aarhus University, Denmark

2011 Honorary president and opening lecture, XIII International Symposium of Blood Substitutes, Mass General Hospital, Harvard Medical School, Boston, Symposium president is Professor W Zapol, previously chief of Critical Care and Anesthesiology at at Mass General Hospital of Harvard Medical School.


2011 Opening Keynote Speaker, Conference on Micro and Nano Systems, Chongqin, China

2011 Invited Speaker, Blood Transfusion Institute of the Chinese Academy of Medical Sciences and Peking Union Medical College.

2011 Invited Speaker, Ordos Blood Substitute Congress, Ordos, Inner Mongolia, China

2012 Opening Keynote lecturer on Frontier in Transfusion Medicine based on nanobiotechnological blood substitutes, BIT International Congress on Hematology, Beijing, China.

2012 Invited lecturer, Microcirculation Institute of the Chinese Academy of Medical Sciences, Beijing, China

2012 Invited lecturer, Beijing Transfusion Institute, Beijing, China

2012 Opening Keynote Lecturer and honorary president, III International Academy of Nanomedicine Congress, Ankara, Turkey.

2012 Invited Speaker, XX Conference on Bioencapsulation, Ontario, Canada

2013 Opening Plenary lecturer and Honorary Symposium President of the XIV International Symposium on Blood Substitutes and Oxygen Therapeutics. at the Blood Transfusion Institute of the Chinese Academy of Medical Sciences, China. Symposium president is the president of the Chinese Academy of Medical Sciences and the other honorary symposium president is the vice minister of health of China.

2013 “Fronteir in Medicine” lecture series, Shantou University Medical School. Title of lecture “Blood substitutes in transfusion medicine: present clinical status and future perspectives”

2013 “Distinguished speaker lecture series” title of lecture “Artificial Cells” Calgary University Biomedical Engineering group

2014 Opening Plenary Lecturer 3rd Congress of the International Society for Nanomedical Science (postpored because of unsettle condition in region)

2015 Honorary President and invited speaker on Nanobiotherapeutics with enhanced rbc functions, 4th Congress of the International Society for Nanomedical Sciences, Turkey

2015 Honorary President and invited speaker on Red blood cell replacement or Nanobiotherapeutics with enhanced rbc functions?, XIV International Symposium on Blood Substitutes, Lund, Sweden

2015 Invited lecturer on Blood substitutes and nanobiotherapeutic Blood Transfusion Institute of the Chinese Academy of Medical Sciences

2015 Invited lecturer on Blood substitutes: Present status and future perspectives Tianjin International Biotherapeutic Research Institute, Tianjin, China.

2016 Invited “Eminent researchers” round table for Canada’s Science Review, Toronto, Canada

2016 Chinese Canadian Legend Award and address, Toronto, Canada

2017 Opening plenary speaker:

60th Anniversary of the Invention of Artificial Cells in conjunction with of XVI International Symposium on Blood Substitutes and V ISNS Nanomedicine Conference, Evolution of Artificial Cells to Nanobiotherapeutic, blood substitutes, Bioencapsulation, Hemoperfusion, Nanomedicine, etc. www.medicine.mcgill.ca/artcell/60AC.m4v
2017 Keynote lecture
60th Anniversary of the Invention of Artificial Cells in conjunction with of XVI International Symposium on Blood Substitutes and ISNS Nanomedicine Conference,
*Individual Roles of (1) Oxygen carriers, (2) Oxygen carries with antioxidant and (3) Oxygen carries with antioxidant and CO2 transport.*

2018. Opening Plenary Speaker on 3rd general blood substitute. Chinese Society Symposium on Blood Substitute, Chengdu, China
2018. Lecture on design of clinical trial, Chinese Society Symposium on Blood Substitute, Chengdu, China
2018. Closing remarks, Chinese Society Symposium on Blood Substitute, Chengdu, China
2018 Invited speaker, International workshop on Bioencapsulation and Industry, Montreal
2018 Invited speaker, Biomedical Symposium, University of Quebec at Montreal
2019. Invited plenary speaker and Honorary President, 2018 ISNS World Conference on Nanomedicine, Delhi, India
2019. Plenary Lecturer 13th Asian Science Camp (ASC 2019) Shantou, China
2019. Honorary President and opening presidential lecture, XVII International Symposium on Blood Substitutes, Nara, Japan
2019 Plenary Lecture Pacific-Asia Society of Blood Purification Nephrology Subdivision, Shenzhen, China.
2019 A number of smaller invited talks during a visit to China for the planning of the "Chang Artificial Cell Research Centre"
2019 Invited Speaker, Shantou University First Affiliated Hospital, Shantou, China., (invited speaker).

2020 COVID 19 pandemic did not participate in meetings

**PATENTS and PATENT APPLICATIONS:**

3. T.M.S. Chang (1971) "Nonthrombogenic microcapsules" Canadian Patent, 876,100
4. T.M.S. Chang (1973) "Blood compatible microcapsules containing detoxicants" U.S. Patent, 3, 725, 113
5. T.M.S. Chang (1976) "Blood compatible microcapsules containing detoxicants" Canadian Patent, 982, 941


17 Satya Prakash & T.M.S. Chang (April, 28, 1999). Microencapsulated genetically engineered E. Coli DH5 cells for the removal of undesired electrolytes and/or metabolites. U.S.A. Provisional Application. Serial Number 60/131,468


COMMITTEES AND BOARDS:

1. Diocesan Boys' School, Hong Kong:  
   Head Prefect of Boarding School.  
   Captain, Featherstone House (sports).  
   Pianist, General Assembly and Chapel services.

2. McGill University Undergraduate:  
   Social Convenor and Student Council, Douglas Hall of Residence, McGill.  
   McGill Intercollegiate Wrestling Team (Letter award).  
   Sunday School Teacher, Christ Church Cathedral, Montreal.

3. Free voluntary community service in Montreal Chinese Hospital:  
   First of the annually rotating chairmen, Medical Board, newly built Montreal Chinese Hospital (free voluntary service) (1966-1967).  
   Attending staff and chief of laboratory (free voluntary service) (1966 until
Biotechnology Research Group, Faculty of Graduate Studies and
Standing Committee on Biotechnology, McGill University

Founding Advisory Board, Biannual International Enzyme Engineering Conference, Japan

Departmental Policy Committee, Dept. of Physiology, McGill Univ.

Admissions Committee, Faculty of Medicine, McGill University


Postgraduate Awards Committee, Faculty of Medicine, McGill University (1972-79).


Project Site Visit and Special Study Section, National Institutes of Health (USA) (1974).

Project Site Visit and Special Study Section, National Institutes of Health (USA) (1975).

Advisory Board, Biannual International Enzyme Engineering Conference (1975)


Statutory Committee for Professors in Medicine, McGill University (1975).

Statutory Committee for Professors in Biochemistry, McGill University (1977).


Program Committee, American Society for Artificial Internal Organs (1978-81).

Project Site Visit and Special Study Section, National Institutes of Health (USA) (1978).

Search Committee for Physiology Chairman, McGill University (1978).


McGill University Ad Hoc Committee on visiting scholars, fellows and students from China (1979).


Organizer and initiator, Canadian Society for Artificial Organs, Artificial Organs, Artificial Cells and Medical Devices (1979).

Member of International Program Committee, Symposium on Control Aspects of Artificial Organs. International Federation of Automatic Control and International Society for Artificial Organs, Warsaw, Poland (1979-1980).


Admissions Committee, Faculty of Medicine, McGill University (1979-1982).


Founding President, Canadian Society for Artificial Organs, Artificial Cells and Medical Devices (1980-1982).


Biotechnology Research Group, Faculty of Graduate Studies and Research, McGill University (1981-1984).
42. Honorary President, 4th International Symposium on "Hemoperfusion", Turkey and member of International Organizing Committee (1982).
43. Member, McGill University Regional Advisory Group of International Development Research Centre of Canada (IDRC) on People's Republic of China (1982-present).
45. Symposium President and Chairman of Organizing Committee, Fifth International Symposium on "Microencapsulation, Including Artificial Cells", Montreal, Canada (1983).
57. 5th Congress of the International Society of Artificial Organs, Chicago, U.S.A. (1985) Chairman, Program Committee on "Artificial pancreas/artificial liver". Chairman, workshop on "Artificial Cells"; Specialty Chairman on "Plasmapheresis Blood Manipulation Field".
58. Chairman, Search Committee for Cardiovascular Physiologist, Dept. of Physiology, McGill University (1986).
62. Committee on Appointment, Tenure and reappointment, Physiology, McGill (1983-85)
63. International Program Committee for the Joint World Congress of International Society of Artificial Organs and European Society of Artificial Organs, Munich, Germany, 1987.
65. Program committee on Artificial Cells and Hemoperfusion. 1988 Congress of the European Society of Artificial Organs, Prague, Czechoslovakia.
69. Member of Chairman's Advisory Committee, Department of Physiology, McGill University (1988-present)
70. Honorary President, 8th International Symposium on Hemoperfusion, Sorbent and Immobilized Bioreactants, Germany, 1988.
73. Program Committee, 1989 Congress of the International Society of Artificial Organs, Sapporo, Japan.
76. Congress President, 8th World Congress of the International Society of Artificial Organs, in conjunction with the 4th International Symposium of Blood Substitutes, Montreal, 1991.
78. Member, McGill Biotechnology Committee (1984 to present).
79. Member, Subcommittee on Research Centers, Faculty of Graduate Studies (1991).
85. Honorary congress president, XI Congress of the International Society for Artificial Cells, Blood Substitutes and Immobilization Biotechnology. (Congress president Professor R.Langer of MIT which organized this), Boston, 1994.
88. Program Chairman, International Organizing Committee, Xth World Congress of the International Society for Artificial Organs, Taipei, Taiwan (1995).
90. Organizing Committee, Congress of the International Society for Artificial Organs, Rhode Island, U.S.A.
91. Cochairman, VI International Symposium on Blood Substitutes Tokyo, Japan 1997
92. Honorary congress president, XII Congress of the International Society for Artificial Cells, Blood Substitutes and Immobilization Biotechnology. Organized by the Chinese Academy of Medical Science with president of academy as congress president) Beijing, PRC, 1997
93. Cochairman and member of organizing committee, VIII International Symposium on Blood Substitutes, San Diego, 2000
94. Honorary Chairman, International Society for Artificial Cells, Blood Substitutes & Immobilization Biotechnology XIV Conference on “Artificial Cells & Cells in Novel Medical Application” Istanbul, Turkey
95. Member of MRC and CIHR “Pharmaceutical Sciences” Grants Review Committee. (1999-2001)
97. Member, International Scientific Committee of the 13th Congress of the International Society for Artificial Organs, Osaka, Japan, 2001
98. Member, Organizing committee of Conference in Blood Substitute organized by Karolinka Institute, Stockholm, Sweden. 2002 June
101. Honorary President and Member of International Advisory Committee, IX International Symposium on Blood Substitutes, Tokyo, Japan 2003 March
102. Scientific committee and VIP guest, III International Symposium on Biotechnology and Biomedicine, Tianjin, PRC. 2004
103. Honorary President and Member of International Advisory Committee, X International Symposium on Blood Substitutes, Providence, Rhode Island 2005 June
104. Member, Scientific Board, 2nd World Congress on Regenerative Medicine, Germany 2004
105. 2004 Olympic Summer Games, Athen. Expert consultant (blood substitutes) for the ad hoc Court of Arbitration for Sport (CAS) on doping related matters (e.g. blood substitutes).
106. 2006 XX Olympic Winter Games, Turin. Expert consultant for the ad hoc Court of Arbitration for Sport (CAS) on doping related matters (e.g. blood substitutes).
107. 2006 March XVIII Commonwealth Games, Melbourne. Expert consultant for the ad hoc Court of Arbitration for Sport (CAS) doping related matters (e.g. blood substitutes).
108. Honorary President and Member of International Advisory Committee, XI International Symposium on Blood Substitutes, Beijing, China 2007
109. International Scientific Board, Congress of ESAO 2007 Austria
110. Founding member, International Academy of Nanomedicine 2008-
111. NATO co-director of workshop on Advance Institute of Science 2008
112. Honorary President and Member of International Advisory Committee, XII International Symposium on Blood Substitutes, Parma, Italy. 2009
113. President and member of the board, International Academy of Nanomedicine, 2009-2010
114. International Scientific Advisory Committee First World Congress of the International Academy of Nanomedicine, Hainan, China
115. International Scientific Advisory Committee 2nd World Congress of the International Academy of Nanomedicine, Antalya, Turkey
117. International Scientific Advisory Committee 2010 BIT 3rd Congress on Regenerative Medicine and Stem Cells, Shanghai, China.
118. International Scientific Advisory Committee BIT 1st Congress on Nanomedicine, Beijing, China, 2010
120. International Scientific Advisory Committee 2012 3rd World Congress of the International Academy of Nanomedicine, Ankara, Turkey
121. Honorary President, International Scientific Advisory Committee 2013 XIV International Symposium on Blood Substitutes, Institute of Blood Transfusion, Chinese Academy of Medical Sciences, China
124. 2017, Honorary President, Quebec Branch of the Chiu Chow Association (Hometown of Shantou)
125. Chinese government’s Overseas Chinese Expert Advisory Committee on Trade, Science and Technology 2017-2021
126. Honorary President, VI ISNS World Nanomedicine Conference, Delhi, India.
127. Honorary President and International Scientific Advisory Committee 2019 XVII International Symposium on Blood Substitutes, Nara, Japan
128. Key consultant, Chinese Research Alliance on Innovation and Industrial development of Blood Engineered Products 2018-

129. 2019 Honorary President, 30th Anniversary of the Quebec Branch of the Chiu Chow Association (Hometown of Shantou)

130. 2022 Honorary President and International Scientific Advisory Committee 2019 XVII International Symposium on Blood Substitutes, Berlin, Germany

T.M.S. Chang