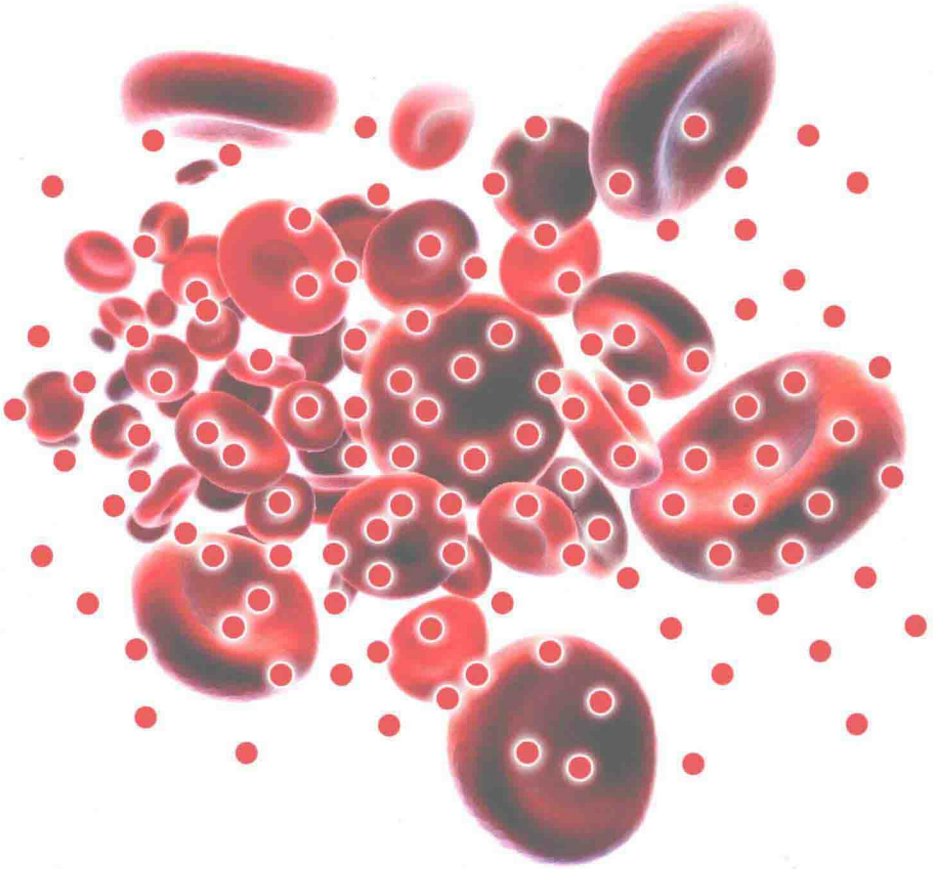
Regenerative Medicine. Artificial Cells and Nanomedicine – Vol. 3

SELECTED TOPICS IN NANOMEDICINE



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Thomas Ming Swi Chang

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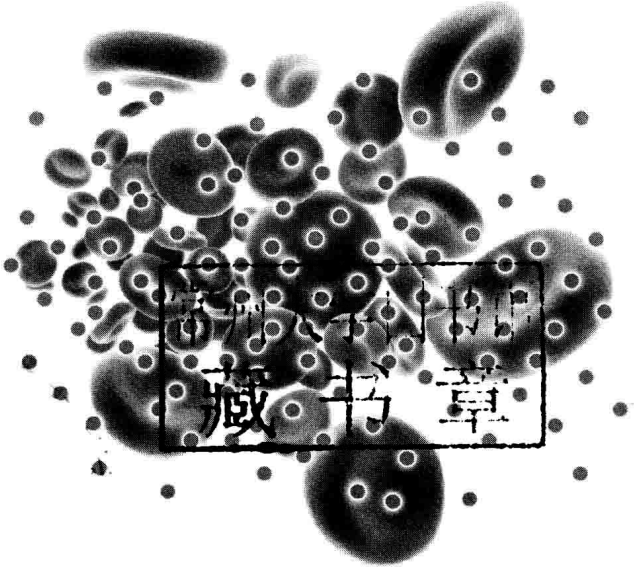

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Contents

Chapter 1	Artificial Cells: The Beginning of Nanomedicine *Thomas Ming Swi Chang*	1
Chapter 2	The Clinical Development of Hemopure®: A Selective Commentary *A Gerson Greenburg*	45
Chapter 3	Glutaraldehyde Polymerized Porcine Hemoglobin: Preparation, Safety Evaluation and Pharmacodynamics Study *Chao Chen, Hongli Zhu and Kunping Yan*	63
Chapter 4	Evidence Regarding Some Pharmacologic Characteristics of Hemoglobin-Based Oxygen Carriers *Enrico Bucci*	91
Chapter 5	EAF PEG Hemoglobins: Novel Class of Nonhypertensive Resuscitation Fluids: Simplicity and Advantages of Extension Arm Chemistry for PEGylation *Seetharama A. Acharya, Amy G. Tsai and Marcos Intaglietta*	99
Chapter 6	Biocompatibility of a Highly Concentrated Fluid of Hemoglobin-Vesicles as a Transfusion Alternative *Hiromi Sakai*	133

Chapter 7	Molecular Basis of Haptoglobin and Hemoglobin Complex Formation and Protection against Oxidative Stress and Damage *Yiping Jia and Abdu I. Alayash*	149
Chapter 8	Polynitroxylated Hemoglobin as a Multifunctional Therapeutic for Critical Care and Transfusion Medicine *Li Ma and Carleton Jen Chang Hsia*	169
Chapter 9	Surface-Mediated Drug Delivery *Benjamin M. Wohl, Betina Fejerskov, Siow-Feng Chong and Alexander N. Zelikin*	195
Chapter 10	Use of Tunable Pores for Accurate Characterization of Micro- and Nanoparticle Systems in Nanomedicine *James Eldridge, Aaron H. Colby, Geoff R. Willmott, Sam Yu and Mark W. Grinstaff*	219
Chapter 11	Microfluidic Probes to Process Surfaces, Cells, and Tissues *Mohammad A. Qasaimeh, Sebastien G. Ricoult and David Juncker*	257
Chapter 12	Subcompartmentalized Systems Towards Therapeutic Cell Mimics *Leticia Hosta-Rigau and Brigitte Städler*	281
Chapter 13	Soft Magnetic Nanomaterials Towards Nanomedicine: Magnetism Principles, Preparation, Characterization and Potential Applications *G. W. Qin, S. Li, Y. P. Ren, F. Darain and K. Dimitrov*	301

Chapter 14 GoldMag Composite Particles and Their Applications in Nanomedicine 337
Mingli Peng, Xu Chao, Chao Chen and Yali Cui

Chapter 15 Nanoparticles for Imaging and Therapy: Functionalization, Endocytosis and Characterization 355
Yu Zhang, Yi Li, Gürer Budak, Mihrimah Ozkan and Cengiz S. Ozkan

Chapter 16 Noscapines: Novel Carrier Systems to Target Tumor Cells 381
Ramesh Chandra, J. Madan, Prashant Singh, Pradeep Kumar, V. Tomar, Sujata K. Dass and Ankush Chandra

Chapter 17 High-Throughput Methods for Miniaturization of Implantable Artificial Cells 411
Maryam Mobed-Miremadi

Chapter 18 Amphiphilic Core–Shell Nanoparticles Containing Hairy Polyethyleneimine Shells as Effective Nanocarriers for Gene and siRNA Delivery 429
Pei Li, Yuen Shan Siu, Kin Man Ho and Wei Li

Chapter 19 Nano-Chaperones: Nanoparticles Acting as Artificial Chaperones 449
S. Boridy and D. Maysinger

Chapter 20 Bio-Functional Polymer Vesicles for Applications in Nanomedicine 481
Hans-Peter M. de Hoog, Bo Liedberg and Madhavan Nallani

Chapter 21	Carbon Nanotubes in Cancer and Stem Cell Therapeutics *Wei Shao, Arghya Paul and Satya Prakash*	505
Chapter 22	Chitosan-Based Nanocarriers for Efficient and Targeted siRNA Delivery *Surendra Nimesh and Ramesh Chandra*	531
Chapter 23	Application of Polyethylenimine-Based Nanoparticles for RNA Therapeutics *Surendra Nimesh and Ramesh Chandra*	551
Chapter 24	Nanosilver System Technology for Applications in Nanomedicine *Helmut Schmid*	571
Index		587

Chapter 1

Artificial Cells: The Beginning of Nanomedicine

Thomas Ming Swi Chang

A. Introduction

1. *Nanomedicine*

Nanomedicine is the use of nanotechnology and nanobiotechnology in medicine. There are different ways to define these features, but the most common ones include:

i. Nano diameter
ii. Nanodimension thickness membrane
iii. Nanobiotechnological complexes
iv. Others

Artificial cells have all the features for nanotechnology and nanobiotechnology. What are artificial cells and how do they initiate a number of areas in nanomedicine?

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2. *The "What," "When," "How," and "Why" of Artificial Cells*

What and when: The first artificial cells were prepared in 1957 while the author was an undergraduate at McGill University (Chang, 1957) (Fig. 1). His further research shows the potential of artificial cells in basic research and applications (Chang, 1964, 1965, 1966, 1971a, 1971b, 1972; Chang *et al.*, 1966; Chang and Poznansky, 1968) (Fig. 1). This initial research forms the basic principle that has been greatly extended into different areas, including nanomedicine.

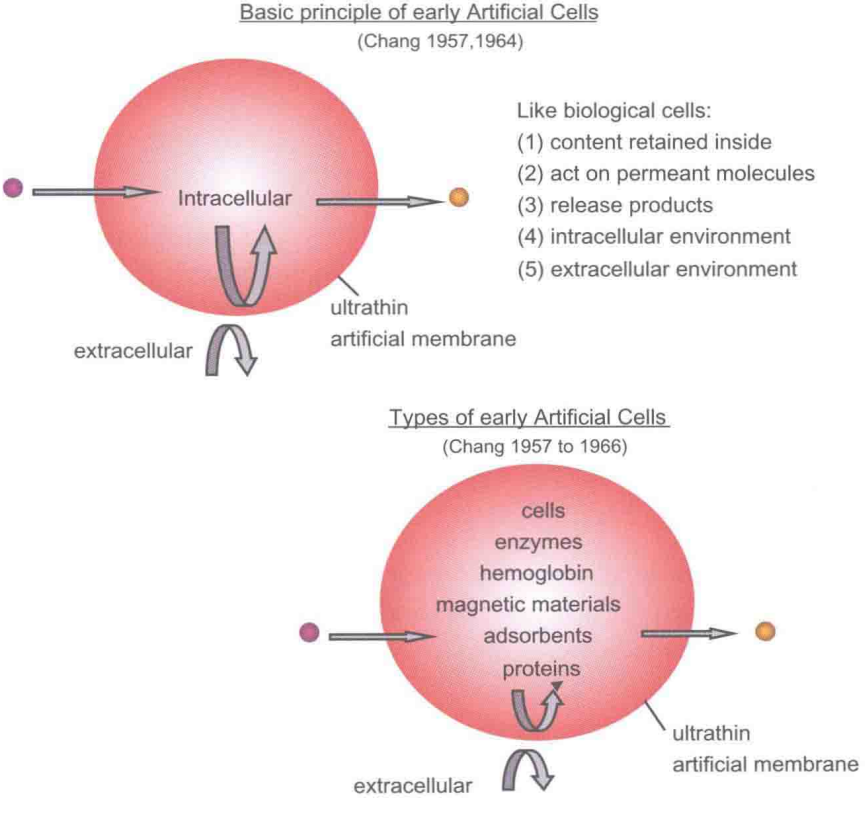

Fig. 1. Upper: Basic principles of early artificial cells. Lower: Different types of early artificial cells based on these basic principles. (*With copyright permission from Chang 2007 Monograph on Artificial Cells.*)

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How does it develop: Thus, major progress in other areas has led to stepwise progress in artificial cells. First, there is the coming of age of polymer chemistry and biomaterials. Then there is the increasing interest in biotechnology, molecular biology, genomics and nanobiotechnology. Examples of the ongoing development and extension of the basic features of artificial cells include microcapsules, bioencapsulation, nanocapsules, nanoparticles, polymersomes, nanosensors, macroenapsulation, red blood cell mimics, polyhemoglobin, conjugated hemoglobin, nanotubules, lipid vesicles, liposomes, polymer-tethered lipids, synthetic cells and others (Chang, 2005, 2007, 2013) (Fig. 2).

Uses for artificial cells: The principle of artificial cells is already in routine patient use as a miniature device for the treatment of severe acute poisoning; approved for routine use in patients for blood transfusion in South Africa to avoid HIV-contaminated blood and in Russia to boost blood supply; in a number of drug delivery systems. It is also being extensively developed around the world for many other

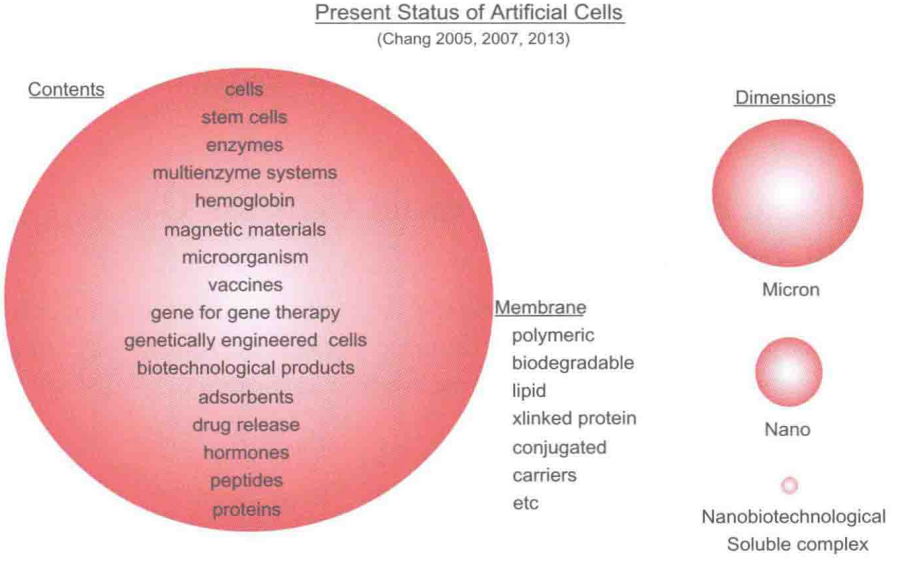

Fig. 2. Present status of artificial cells with wide variations in contents, membrane material and dimensions. (*With copyright permission from Chang 2007 Monograph on Artificial Cells.*)

Fig. 3. Some areas of use for artificial cells.

areas of application. These include treatment for diabetes, liver failure, kidney failure, genetic diseases, endocrine diseases, cancer, biosensors, etc. Non-medical uses include agriculture, industry, food science, aquatic culture, nanocomputers, nanorobatics and others (Fig. 3).

One area that has been extensively developed is the use of some of the basic features of artificial cells in nanomedicine. This chapter contains a brief summary. Detailed papers on selected areas of nanomedicine will follow in this book.

B. Basic Features of Artificial Cells for Use in Nanomedicine

These include nanodimension diameter, extensive variations in contents, large number of possible soluble nanobiotechnological complexes, nanodimension thickness membrane and others.

1. *Nanodimension Diameter*

The original method of emulsion followed by evaporation (Fig. 4) (Chang, 1957, 1964) has been extended to the use of emulsion followed by interfacial polymerization (Chang, 1964; Chang *et al.*, 1966). This basic principle has been extended even further to many variations

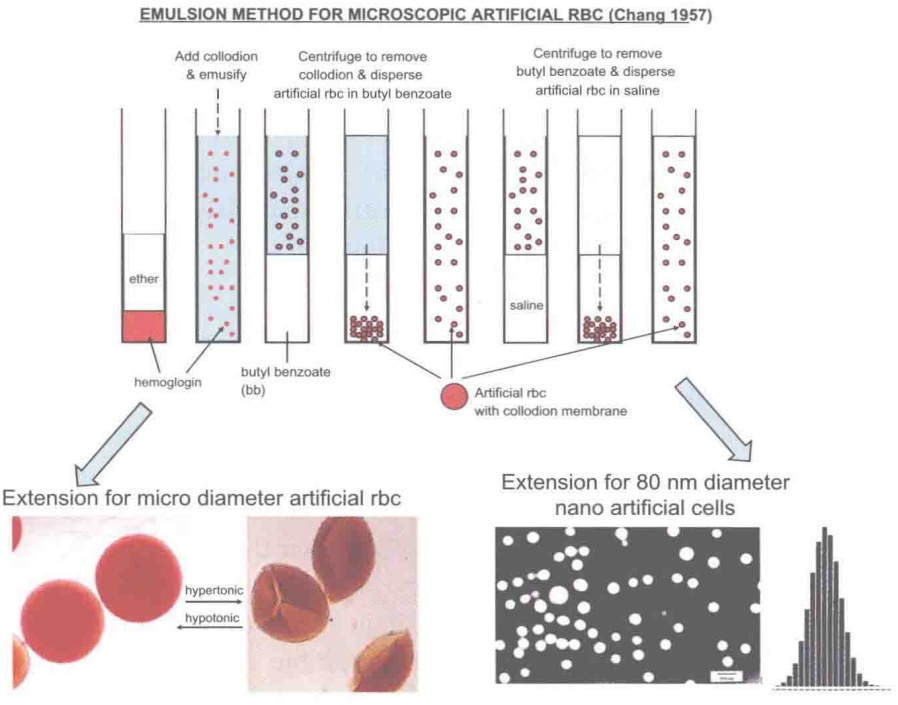

Fig. 4. (Upper): Original (1957) emulsion phase separation method of preparing artificial cells. This principle has since been extended to methods for the preparation of microscopic or nanodimension artificial cells that are also called microcapsules, nanocapsules, lipid membrane vesicles, microparticles, nanoparticles, polymersomes, etc. (Lower left): Micro dimension artificial rbc with ultrathin nylon-protein membrane. (Lower right): E/M of nanodimension (80 nanometer) artificial red blood cells containing hemoglobin and enzymes. (*With copyright permission from Chang 2007 Monograph on Artificial Cells.*)

to prepare nanodimension diameters material for use in nanomedicine. For example, decreasing the emulsion diameter to nanodimension range by different means would result in nanodimension systems (Fig. 4).

2. *Variations in Contents*

Artificial cells can contain the same biological material as biological cells, including hemoglobin and all red blood cell enzymes,

microsomes, cytosol, polymerases, ribosomes and transcription/translation system. What is even more useful in nanomedicine is that the content could be from almost anything. Some examples include adsorbents, magnetic materials, drugs, enzymes, multienzyme systems, multi-compartment systems, hemoglobin, vaccines, genes, hormones, peptides, magnetic material and many other materials, which can be included separately or in combination (Fig. 2).

3. *Soluble Nanobiotechnological Complexes*

The first nanobiotechnology approach reported is the crosslinking of hemoglobin into ultrathin polyhemoglobin (PolyHb) membrane with nanodimension thickness (Chang, 1964, 1972a) (Fig. 3). This is used to form the membrane of artificial red blood cells (Chang, 1964, 1972a). If the emulsion is made very small, then the whole submicron artificial cells can be crosslinked into PolyHb of nanodimension. Glutaraldehyde can crosslink hemoglobin into soluble PolyHb each consisting of an assembly of 4–5 hemoglobin molecules (Chang, 1971b) (Fig. 5). Sebacyl chloride crosslinks hemoglobin and diamine to form polyamide conjugated hemoglobin (Chang, 1964, 1972a) (Fig. 5). An extension of this is the crosslinking of single protein molecule to soluble polymers (Wong *et al.*, 1968; Park *et al.*, 1981) (Fig. 5).

4. *Nanodimension Thickness Membrane with Possible Variations in Properties*

The artificial cell membranes, especially ultrathin nylon membrane (Chang, 1964), can be ultrathin and yet strong (Fig. 6).

The membrane of an artificial cell separates its contents from the outside, but at the same time the membrane can be prepared to selectively allow different types of molecules to cross. For example, the membrane material includes polymer, biodegradable polymer, lipid, crosslinked protein, lipid-polymer complex, lipid-protein complex and membrane with transport carriers. This way, one can prepare artificial cell membranes that selectively allow the movement of molecules according to molecular size, lipid solubility, affinity to carrier mechanisms, etc. (Fig. 7).

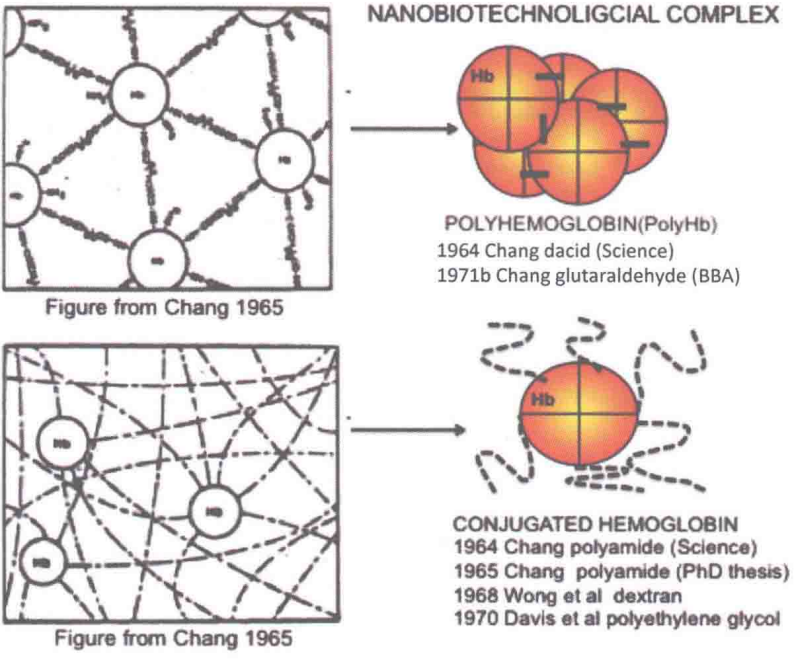

Fig. 5. (Upper left): Basic method of using bifunctional agents to assemble and crosslink hemoglobin (Hb) into PolyHb. (Upper right): Soluble complex of polyhemoglobin. (Lower left): Basic method of conjugating hemoglobin to polymer. (Lower right): Conjugation of hemoglobin to soluble dextran or polyethylene glycol. (*With copyright permission from Chang 2007 Monograph on Artificial Cells.*)

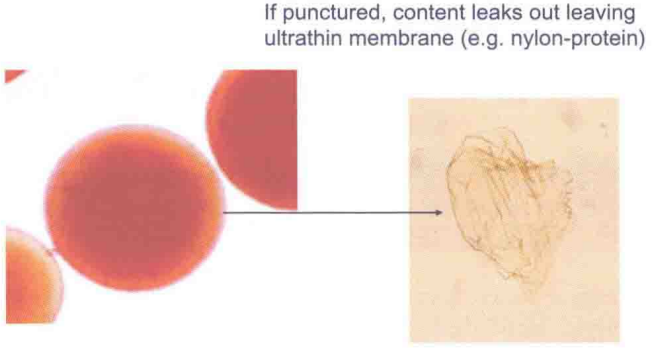

Fig. 6. Artificial red blood cells with ultrathin nanothickness nylon-protein membrane. Although strong, the membrane can be punctured using a fine needle to release the content, leaving behind the flexible ultrathin membrane. (*With copyright permission from Chang 2007 Monograph on Artificial Cells.*)

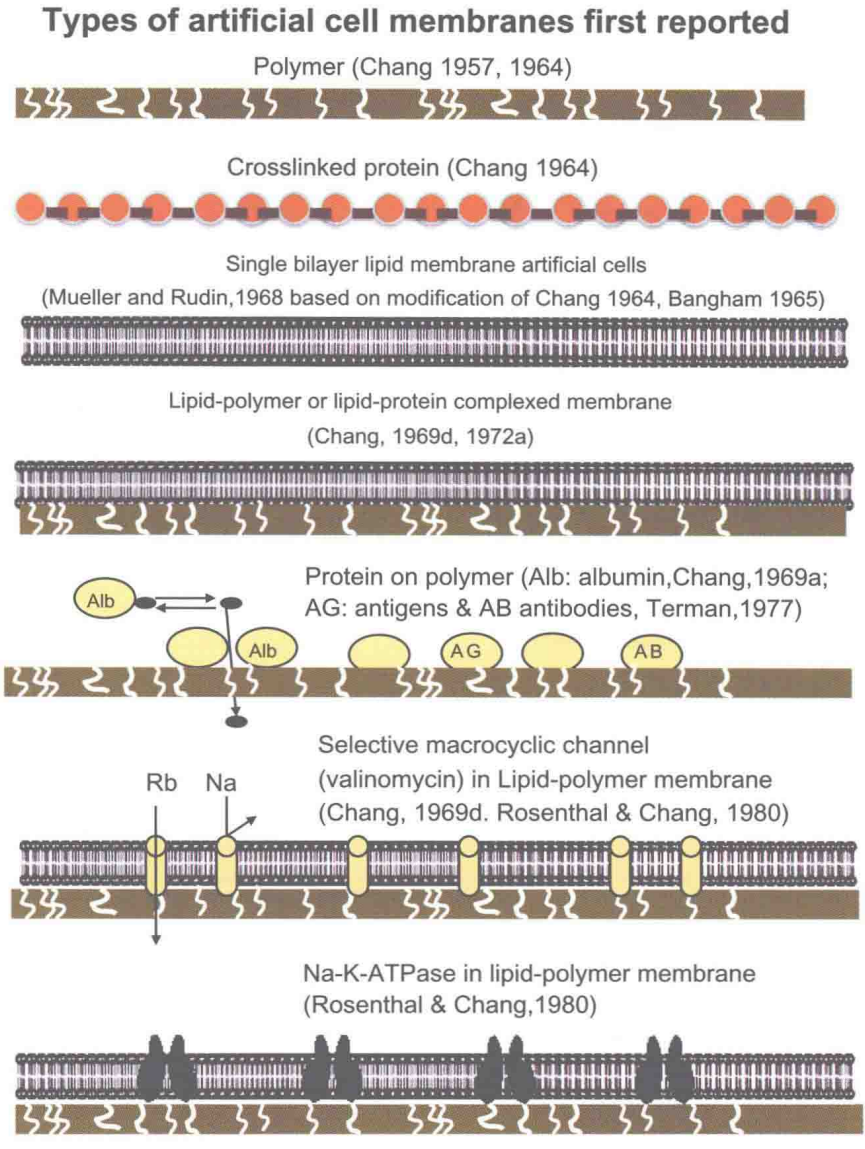

Fig. 7. Schematic representation of examples of ultrathin artificial cell membranes: polymer membrane, crosslinked protein membrane, lipid membrane, lipid-polymer membrane, membrane with albumin or other proteins, lipid-polymer membrane with cyclic channel carrier, lipid-polymer membrane with Na-K-ATPase transport carriers. (*With copyright permission from Chang 2007 Monograph on Artificial Cells.*)

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