BIOGRAPHICAL SKETCH

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NAME: Yung-Chi Cheng, Ph.D.

POSITION TITLE: Henry Bronson Professor of Pharmacology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Tunghai University, Taipei, Taiwan	B.S.	05/1966	Chemistry
Brown University, Providence, Rhode Island	Ph.D.	05/1972	Biochem Pharmacology
Yale University, New Haven, Connecticut	Postdoc	1972-1973	Pharmacology

A. Personal Statement

My interests are in the development of new drugs and in the improvement of the use of clinically proven drugs for the treatment of cancer, herpes virus, human immunodeficiency virus, and hepatitis B virus associated diseases. My research laboratory has focused on developing deoxyribonucleoside analogs, folate analogs and compounds that interfere with DNA and RNA metabolism. Over the past 20 years, I have also been interested in the potential uses of Chinese herbal medicines as adjuvant therapy for patients undergoing cancer chemotherapy. My laboratory has focused on a traditional Chinese medicine formula, PHY906, and we have explored its potential to increase antitumor activity and decrease side effects of chemotherapy and immune-checkpoint therapy. I believe that I have a demonstrated and productive research project in an area of high relevance for Chinese herbal medicine and immunotherapy

a. Wing Lam, Shwu-Huey Liu, Zaoli Jiang, Yung-Chi Cheng. Lessons from the development of the traditional Chinese medicine formula PHY906. Science 16 January 2015: Vol. 347 No. 6219 P. 337 S. 43
b. Wing Lam, Yongshen Ren, Fulan Guan, Zaoli Jiang, William Cheng, Chang-Hua Xu, Shwu-Huey Liu and Yung-Chi Cheng. Mechanism Based Quality Control (MBQC) of Herbal Products: A Case Study YIV-906 (PHY906) Front. Pharmacol., 19 November 2018 l https://doi.org/10.3389/fphar.2018.01324
c. Wing Lam, XiaoChen Yang, Zaoli Jiang, Xue Han, Fulan Guan, William Cheng, Shwu-Huey Liu, Lieping Chen and Yung-Chi Cheng. Abstract 2724: YIV906 (PHY906) enhanced the antitumor activity of immune checkpoint blockade therapy: Anti-PD1 against liver cancer DOI: 10.1158/1538-7445.AM2018-2724 Published July 2018

B. Positions and Honors

Positions and Employment

7/73 – 7/74	Research Associate (equivalent to Research Assistant Professor), Department of Pharmacology, Yale University, New Haven, CT
9/74 – 6/76	Senior Cancer Research Scientist, Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, NY
9/74 – 6/77	Assistant Professor, Department of Pharmacology, Roswell Park Division of the Graduate School, State University of New York, Buffalo
6/77 – 4/79	Associate Professor, Department of Pharmacology, Roswell Park Division of the Graduate School, State University of New York, Buffalo
9/77 – 4/79	Cancer Research Science V, Department of Experimental Therapeutics, Roswell Park

	Memorial Institute, Buffalo, NY
7/79 – 6/89	Professor, Departments of Pharmacology and Medicine, University of North Carolina School of Medicine, Chapel Hill, NC
7/79 – 6/89	Head, Drug Development Program, Lineberger Cancer Research Center, University of North Carolina School of Medicine, Chapel Hill, NC
2/87 – 12/87	Special Chair, Institute of Biomedical Science, Academia Sinica, Taipei, Taiwan, China
6/89 –Present	Professor, Departments of Pharmacology and Medicine and the Yale Comprehensive Cancer Center, Yale University, New Haven, CT
7/89 – Present	Henry Bronson Chair Professor, Yale University, New Haven, CT

Extramural Peer Review Committees

Chairman, Study Section of Experimental Therapeutics, Natl Cancer Inst NIH	1983-1984
Member, Board of Scientific Counselors, Division of Cancer Treatment NCI/NIH	1986-1990
Member, AIDS Research Advisory Committee, NIAID, NIH	1991-1994
Ad hoc Member, National Advisory Council for CAM/NIH, USA	2005
Chairman, Consortium for the "Globalization of Chinese Medicine" (CGCM)	2003-Pres

Honors

American Leukemia Society Scholar	6/76-6/81
Roads Memorial Award, American Association for Cancer Research	1981
Outstanding Investigator Award, National Cancer Institute	1987-1997
Member, Board of Directors, American Association for Cancer Research	1990-1992
Outstanding Alumni Award, Brown University, Providence, RI	1990
Member, Academia Sinica, Republic of China	1994
Member, Connecticut Academy of Science and Engineering	1998
ASPET Award (American Society for Pharmacol and Exp Therapy)	1999
Distinguished Alumni Award, Tunghai University, Taipei, Taiwan	1999
National Foundation for Cancer Research, Fellow	2000-2013
Presidential Award, Society of Chinese Bioscientists in America	2004
BMR Distinguished Visitor, Singapore	2005
Honorary Professor from more than ten different Universities	1998-Pres
1st Cheung on Tak Intl Award for Outstanding Contribution to Chinese Medicine	2011
Honorary Member, GP-TCM Association	2013
41st Annual Medical Award, Chinese Hospital, San Francisco CA	2014
1st Bin-Wen Lin Award, Institute of Clinical Medicine, National Cheng Kung University, Tainan, Taiwan	2016
Outstanding Contribution of Post-Marketing review of Chinese Medicine	2017
Society of Chinese Bioscientists in America, Lifetime Achievement Award	2024

C. Contribution to Science

1. Until early 1970, there was no selective and orally active antiviral drug available. Taking advantage that herpes virus family could induce viral specific thymidine kinase and their substrate behavior was different from human thymidine kinase, an "alternative substrate antiviral" approach was suggested. This led to the development of anti-herpes family drugs and to establish the foundation for today's development of antiviral drugs based on viral specified macromolecules.
   a. Cheng YC. Deoxythymidine kinase induced in the HELA TK- cells by herpes simplex virus type I and type II. Substrate specificity and kinetic behavior. Biochim Biophys Acta. 1976;452(2):370-81. PMCID: PMC188465.
   b. Cheng YC, Domin BA, Sharma RA, Bobek M. Antiviral action and cellular toxicity of four thymidine analogues: 5-ethyl-,5-vinyl-, 5-propyl-, and 5-allyl-2'- deoxyuridine. Antimicrob Agents Chemother. 1976; 10(1):119-22. PubMed PMID: 185944; PMCID: PMC185944.

c. Lee LS, Cheng Y. Human deoxythymidine kinase II: substrate specificity and kinetic behavior of the cytoplasmic and mitochondrial isozymes derived from blast cells of acute myelocytic leukemia. Biochemistry. 1976; 15(17):3686-90. PubMed PMID: 1066165; PMCID: PMC1066165.
d. Cheng YC. A rational approach to the development of antiviral chemotherapy: alternative substrates of herpes simplex virus Type 1 (HSV-1) and Type 2 (HSV-2) thymidine kinase (TK). Ann N Y Acad Sci. 1977;284:594-8. PMCID: PMC212988.

2. There was no anti-cytomegalovirus (CMV), a member of the herpes virus family, available before 1980. The first anti CMV chemical (Gangcyclovir, DHPG) was discovered in 1983 and approved as a drug. This drug was particularly helpful for patients with AIDS at an early stage of epidemic and when no effective anti HIV drug was available at the time.
a. Cheng YC, Huang ES, Lin JC, Mar EC, Pagano JS, Dutschman GE, Grill SP. Unique spectrum of activity of 9-[(1,3-dihydroxy-2-propoxy)methyl]-guanine against herpesviruses in vitro and its mode of action against herpes simplex virus type 1. Proc Natl Acad Sci U S A. 1983;80(9):2767-70. PMCID: PMC6302704.
b. Mar EC, Cheng YC, Huang ES. Effect of 9-(1,3-dihydroxy-2-propoxymethyl)guanine on human cytomegalovirus replication in vitro. Antimicrob Agents Chemother. 1983;24(4):518-21. PMCID: PMC6316844.
c. Mar EC, Patel PC, Cheng YC, Fox JJ, Watanabe KA, Huang ES. Effects of certain nucleoside analogues on human cytomegalovirus replication in vitro. J Gen Virol. 1984;65 (Pt 1):47-53 PMCID: PMC6319573.
d. Mar EC, Chiou JF, Cheng YC, Huang ES. Inhibition of cellular DNA polymerase alpha and human cytomegalovirus-induced DNA polymerase by the triphosphates of 9-(2-hydroxyethoxymethyl) guanine and 9-(1,3-dihydroxy-2-propoxymethyl)guanine. J Virol. 1985;53(3):776-80. PMCID: PMC2983088.

3. Following the introduction of the first generation of anti HIV drug, AZT, ddI and d4T in 1987, a delayed toxicity in patients was found following long-term treatment at clinical relevant dosages. The discovery of the mechanism of delayed toxicity due to their impact on mitochondrial DNA synthesis in 1989 has established the criteria for development of current antiviral drug which required long-term usage and it also facilitated the development of Lamivudine (L-SddC, 3TC) and Emtricitabine (L-FSddC, FTC) as anti HIV drugs due to their lack of mitochondrial toxicity demonstrated by the candidate's laboratory in 1991. Both drugs are still in use today.
a. Chen CH, Vazquez-Padua M, Cheng YC. Effect of anti-human immunodeficiency virus nucleoside analogs on mitochondrial DNA and its implication for delayed toxicity. Mol Pharmacol. 1991;39(5): 625-8. PMCID: PMC1851960.
b. Chen CH, Cheng YC. The role of cytoplasmic deoxycytidine kinase in the mitochondrial effects of the anti-human immunodeficiency virus compound, 2',3'-dideoxycytidine. J Biol Chem. 1992;267(5): 2856-9. PMCID: PMC1310674.
c. Medina DJ, Tsai CH, Hsiung GD, Cheng YC. Comparison of mitochondrial morphology, mitochondrial DNA content, and cell viability in cultured cells treated with three anti-human immunodeficiency virus dideoxynucleosides. Antimicrob Agents Chemother. 1994;38(8):1824-8. PMCID: PMC7986014.

4. Before 1990, there was no chemical without serious side effects for the treatment of HBV hepatitis. It is not believed that a nontoxic anti HBV drug will be possible. The demonstration of Lamivudine (L-SddC) and Emtricitabine (L-FSddC) in their racemic mixture as active and potent compound against HBV with poor cytotoxicity in 1991 leads to the discovery of Lamivudine and emtricitabine, both are in L-nucleoside configuration as anti HBV drugs and are currently in use by millions of people. It also opened this field of investigation.
a. Doong SL, Tsai CH, Schinazi RF, Liotta DC, Cheng YC. Inhibition of the replication of hepatitis B virus in vitro by 2',3'-dideoxy-3'-thiacytidine and related analogues. Proc Natl Acad Sci U S A. 1991;88(19):8495-9. PMCID: PMC1656445.
b. Chang CN, Doong SL, Zhou JH, Beach JW, Jeong LS, Chu CK, Tsai CH, Cheng YC, Liotta D, Schinazi R. Deoxycytidine deaminase-resistant stereoisomer is the active form of (+/-)-2',3'-dideoxy-3'-thiacytidine in the inhibition of hepatitis B virus replication. J Biol Chem. 1992;267(20):13938-42. PMCID: PMC1321132.

c. Chang CN, Skalski V, Zhou JH, Cheng YC. Biochemical pharmacology of (+)- and (-)-2',3'-dideoxy-3'-thiacytidine as anti-hepatitis B virus agents. J Biol Chem. 1992;267(31):22414-20. PMCID: PMC1331054.
d. Chu CK, Ma T, Shanmuganathan K, Wang C, Xiang Y, Pai SB, Yao GQ, Sommadossi JP, Cheng YC. Use of 2'-fluoro-5-methyl-beta-L-arabinofuranosyluracil as a novel antiviral agent for hepatitis B virus and Epstein-Barr virus. Antimicrob Agents Chemother. 1995;39(4):979-81. PMCID: PMC7786007.

5. Traditional Chinese medicine is evolved based on human experience. The novelty of Chinese medicine is its holistic and system-wide approach and multiple chemicals which may work on the same sites synergistically or antagonistically or work on different sites in the same or different organs. Currently, it is not accepted world-wide due to the uncertain of the consistency of different batches of preparation of Chinese medicine, the acceptable clinical evidence to support its claims and the lack of information of the site of actions and active compounds involved. Furthermore, the potential interaction with current drugs used by patients is not clear. To study the essence of Chinese medicine, we will have to take a different approach from those taken using reduction approach commonly in the world. In order to advance this human experience based on medicine which could offer a different approach from the current mainstream drug discovery approach to meet the unmet clinical needs, in 1999, the candidate's laboratory started to explore a traditional Chinese medicine formula "Huang Qin Tang", which was first described 1800 years ago and is consists of four herbs. This formula was claimed to be useful for the treatment of diarrhea, anoxia, vomiting, fever and pain. It is still in use today by Chinese medicine practitioners. Those claims are common side effects associated with cancer patients undergoing chemotherapy. It was proposed this formula will be useful to relieve those side effects in combination with chemotherapy if this formula does not compromise anticancer activity of chemotherapy. I listed only four publications related to our exploration of Chinese medicine as follows:

a. Lam W, Bussom S, Guan F, Jiang Z, Zhang W, Gullen EA, Liu SH, Cheng YC. The four-herb Chinese medicine PHY906 reduces chemotherapy-induced gastrointestinal toxicity. Sci Transl Med. 2010;2(45):45ra59. PubMed Central PMCD: 20720216
b. Lam W, Hu R, Liu SH, Cheng P, Cheng YC. YIV-906 enhances nuclear factor of activated T-cells (NFAT) activity of T cells and promotes immune checkpoint blockade antibody action and CAR T-cell activity. Front Pharmacol. 2023 Jan 4;13:1095186. doi: 10.3389/fphar.2022.1095186. PMID: 36686648; PMCID: PMC9846171.
c. Yang, X., Lam, W., Jiang, Z. *et al.* YIV-906 potentiated anti-PD1 action against hepatocellular carcinoma by enhancing adaptive and innate immunity in the tumor microenvironment. *Sci Rep* **11**, 13482 (2021). https://doi.org/10.1038/s41598-021-91623-3
d. Lam, W., Jiang, Z., Guan, F. *et al.* PHY906(KD018), an adjuvant based on a 1800-year-old Chinese medicine, enhanced the anti-tumor activity of Sorafenib by changing the tumor microenvironment. *Sci Rep* **5**, 9384 (2015). https://doi.org/10.1038/srep09384
e. Lam Wing , Ren Yongshen , Guan Fulan , Jiang Zaoli , Cheng William , Xu Chang-Hua , Liu Shwu-Huey , Cheng Yung-Chi. Mechanism Based Quality Control (MBQC) of Herbal Products: A Case Study YIV-906 (PHY906). Frontiers in Pharmacology. 9. 2018. DOI=10.3389/fphar.2018.01324.

Complete List of Published Work in MyBibliography:
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