UNC | ESHELMAN SCHOOL OF PHARMACY

NATURAL PRODUCTS RESEARCH LABORATORIES (NPRL)

UNC Eshelman School of Pharmacy, Dr. Kuo-Hsiung Lee, Director

Collaborations with over 65 laboratories Worldwide

NPRL Overview

Dr. Kuo-Hsiung Lee, the Director of NPRL, combines the fields of the most advanced natural products chemistry and synthetic medicinal chemistry as well as cutting-edge life science technologies to design and discover herbal medicine-based natural products and their analogs as clinical trials drug candidates. Since 1971, his efforts have led to the discovery of several thousand such compounds, providing leads for new generation drug design to develop future pharmaceutical agents in the same manner that numerous previously discovered bioactive natural products, including Taxol, ephedrine, and artemisinin, were developed as current pharmaceutical agents to treat cancers and other diseases. The lead compounds newly discovered by Dr. Lee's research group will provide a solid foundation of potential chemotherapeutic drug candidates in the 21st century.

NPRL PUBLICATIONS, PATENTS AND OTHER HIGHLIGHTS:

- More than 956 research articles in refereed journals, with 98 published in the *Journal of Medicinal Chemistry*
- More than 121 patents
- More than 457 invited lectures and presentations
- Served on the editorial advisory board for 29 journals, including *Journal of Medicinal Chemistry*, *Current Medicinal Chemistry,* and *Journal of Natural Products*

Dr. Kuo-Hsiung Lee, Kenan Distinguished Professor of Medicinal Chemistry & Director, Natural Products Research Laboratories (NPRL)

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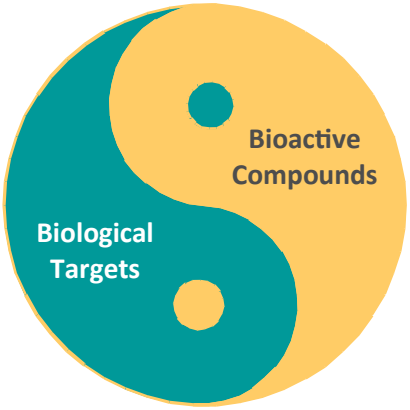
Visit us on the web at https://pharmacy.unc.edu/natural-products-research-laboratories/

Original Calligraphy by Dr. Kuo-Hsiung Lee



"Medicinal Chemistry is the art of combining Chemistry & Biology for Drug Discovery. Like Yin & Yang, Chemistry & Biology are Complimentary. The discovery of new bioactive compounds depends on valid biological targets."

-Dr. Kuo-Hsiung Lee

NPRL Research Philosophy/Methodology

Chinese Herbal Medicine (CHM) or Traditional Chinese Medicine (TCM) has been used for several thousand years to treat human illness, which makes CHM the best source to provide valuable & unique information for modern drug discovery & development. Development of CHM products as adjunct therapies to augment the efficacy & offset the toxicity of Western Medicine is an excellent approach for rapid advancement into US FDA-approved new drugs.

Developing CHM products as high quality dietary supplements for treating chronic diseases or health maintenance must particularly emphasize standardization through qualitative & quantitative quality controls (GAP, GMP & CMC) on single herbs & multiple herbs of the prescription formulas by using the most advanced scientific technology, especially toxicity profile testing.

A combination of advanced medicinal chemistry & natural products chemistry coupled with cutting-edge life science technology will play a very important role for converting CHM products, especially the pure single active principles, through modification & synthesis into clinical trial candidates very efficiently & effectively. Elucidation of the mechanism of action of active principles & active fractions, as well as effective & safe formulas, is needed to develop world-class new drugs.

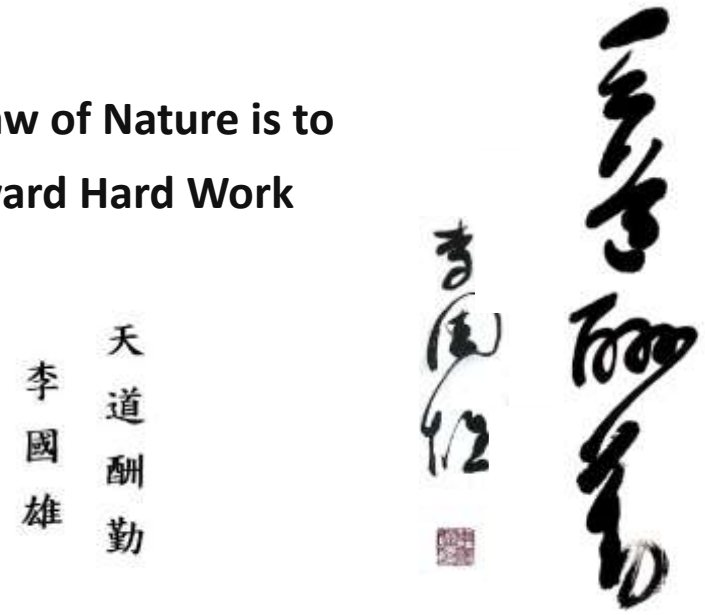
Future of TCM/CHM Research

Establishment of an international collaborative platform mechanism, including academic exchange programs targeting research & development technology, clinical trials, and botanical drug approval guidelines, will help to ensure the advancement of world-class botanical drug discovery & development. Building up a very strong research team with top-notch synthetic medicinal chemists, natural products chemists & life science biomedical scientists with ample funding support is absolutely needed for the efficient & effective discovery & development of world-class botanical drugs targeted at unmet medical needs. Selective investigation on those several thousand active compounds already discovered from my NPRL research program should lead to a quick discovery & development of world-class new drugs.

Current NPRL Research Programs

- Medicinal Chemistry
- Bioactive Natural Products
- New Anti-COVID-19 Drug Discovery/Development
- New Anticancer & Anti-HIV Drug Discovery/ Development
- Traditional Chinese Medicine

The Law of Nature is to Reward Hard Work



Original Calligraphy by Dr. Kuo-Hsiung Lee

NPRL Research Accomplishments

The following example products discovered by NPRL are currently in clinical use, clinical trial or preclinical study.

1. **PG-2** was discovered and developed by Pharmagenesis and PhytoHealth Corporation of Taiwan based on the initial advice of Dr. Lee. It is composed of polysaccharide immunostimulatory principles from *Astragalus membranaceus* (Huang Qi). **PG-2** was approved for clinical use in treating cancer-related fatigue by the Taiwan Department of Health in 4/2011, especially for cancer patients who developed severe fatigue after receiving chemotherapy. The US FDA also approved **PG-2** for treatment of idiopathic thrombocytopenic purpura in May, 2012.
2. **Bevirimat** (**DSB**, **PA-457**, **MPC-4326**), derived from natural triterpenes found in *Syzigium claviflorum* (Pang Hua Chih Nan), was licensed to Panacos Pharmaceuticals, Inc. It succeeded in Phase IIa anti-AIDS clinical trials and notably targets a different stage of the HIV virus compared with the current anti-AIDS drugs. *Bevirimat* is the first member of a completely new class of HIV drug candidates called "maturation inhibitors." Research is very actively ongoing in the NPRL aimed at producing an improved candidate compound, without a partial drug-resistant problem encountered by *bevirimat* during its Phase IIb clinical trials. Big Pharma (GSK & BMS) continues to develop *bevirimat* analogs in clinical trials.
3. **JC-9** (or **ASC-9**), based on the natural product curcumin from *Curcuma longa* rhizome (Jiang Huang) was discovered and developed in the NPRL and licensed to AndroScience Corporation. **JC-9** succeeded in a Phase II clinical trial against acne and is a clinical trial candidate for prostate and other cancers.
4. **GL-331**, a synthetic analog of podophyllotoxin found in *Podophyllum emodi* (Gui Jiu), was discovered and developed in the NPRL with co-inventorship with Dr. Yung-Chi Cheng of Yale University. The product was licensed to Genelab Technologies Inc. of CA and reached Phase II clinical trial as an anticancer drug.
5. **Neo-tanshinlactone**, a natural product found in *Salvia miltiorrhiza* (Tanshen), was newly discovered and synthesized by Dr. Lee's group. Neo-tanshinlactone is more active and selective than tamoxifen, a currently used anti-breast cancer drug. Further syntheses and development of new analogs of neo-tanshinlactone as clinical trials candidates for treating breast cancer are ongoing.
6. **PBTs**, novel phenanthrene-based tylophorine analogs discovered and synthesized by Dr. Lee's group based on the natural alkaloid tylophorine isolated from *Tylophora* species, were found for the first time to inhibit lung cancer progression through the Slug signaling pathway resulting from a collaboration with Dr. Pan-Chyr Yang of National Taiwan University. This finding may offer a novel path of drug development to treat lung cancer.
7. Preclinical studies on many other novel promising antiviral natural product-based leads are in progress. These include khellactone structural analogs (**DCK**) of the natural coumarin suksdorfin, which appears to inhibit HIV reverse transcriptase by a different mechanism from that of currently available non-nucleoside RT inhibitors. Experiments are ongoing to identify the specific molecular target. Certain structurally related pyranochromone analogs (**DCP**) have also shown excellent activity against both non-drug-resistant and drug-resistant HIV strains.
8. Development of novel anti-HIV diterpenes, including **stelleralide A** and **gnidimacrin**-related daphnane diterpenes and derivatives to eliminate the latent HIV-1 are currently actively ongoing. Gnidmacrin is the most potent HIV latency reversing agent and the only single agent that can consistently reduce the frequency of latent HIV-1 infected cells at pico molar level.

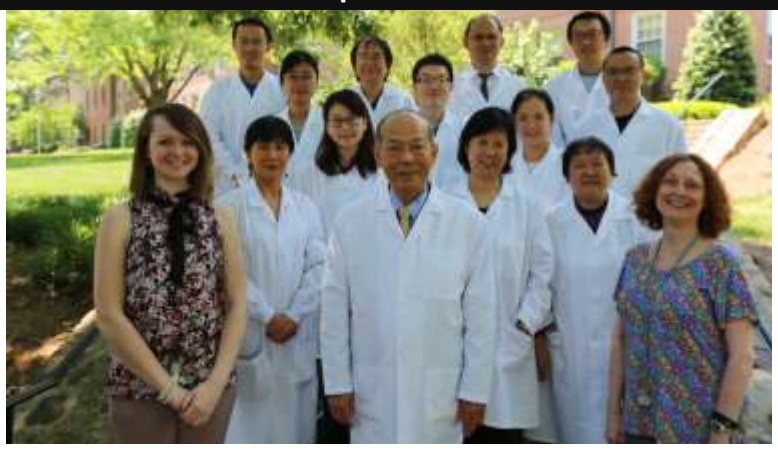
Examples of Recent Publications & Patents

1. M.J. Wang, Y.Q. Liu, L.C. Chang, C.Y. Wang, Y.L. Zhao, M. Goto, X.B. Zhou, K. Qian, X. Nang, L. Yang, X.M. Yang, H.Y. Hung, S.L. Morris-Natschke, S.L. Pan, C.M. Teng, S.C. Kuo, T.S. Wu, Y.C. Wu, and K.H. Lee, "Design, Synthesis, Mechanisms of Action, and Toxicity of Novel 20(S)-Sulfonylamidine Derivatives of Camptothecin as Potent Antitumor Agents," J. Med. Chem., 57, 6008-6018 (2014).
2. W. Lai, L. Huang, L. Zhu, G. Ferrari, C. Chan, W. Li, K.H. Lee, and C.H. Chen, "Gnidimacrin, a Potent Anti-HIV Diterpene, Can Eliminate Latent HIV-1 Ex Vivo by Activation of PKC Beta," J. Med. Chem., 58, 8638-8646 (2015).
3. K.H. Lee, S.L. Morris-Natschke, Y. Zhao, and K. Musgrove, "Chinese Herbal Medicine-derived Products for Prevention or Treatment of Diseases Affecting Quality of Life," in *Medicinal Plants — Recent Advances in Research and Developments,* H.S. Tsay, L.F. Shyur, D.C. Agrawal, Y.C. Wu, and Wang, S.Y., Eds., pp. 1-35, Springer Press, Singapore (2016).
4. Y. Zhao, Q. Gu, S.L. Morris-Natschke, C.H. Chen, and K.H. Lee, "Incorporation of Privileged Structures into Bevirimat Can Improve Activity against Wild-type and Bevirimat-resistant HIV-1," J. Med. Chem., 59, 9262-9268 (2016).
5. Q. Liu, Y.Y. Cheng, W. Li, L. Huang, Y. Asada, M.T. Hsieh, S.L. Morris-Natschke, C.H. Chen, K. Koike, and K.H. Lee, "Synthesis and Structure-Activity Relationship Correlations of Gnidimacrin Derivatives as Potent HIV-1 Inhibitors and HIV Latency Reversing Agents," J. Med. Chem., 62, 6958-6971 (2019).
6. K.H. Lee, S. Morris-Natschke, YY Cheng, M.T. Hsieh, C.H. Chen, L. Huang, W. Li, Y. Asada, K. Koike, Q. Liu, U.S. Patent #62/863,585 Gnidimacrin Derivatives as Potent HIV-1 Inhibitors and Latency Reversing Agents (2019).
7. K.H. Lee, "Strategies and Perspectives on New Drug Discovery from Chinese Herbal Medicine." Invited Lecture at the 56th Symposium on Phytochemistry at University of Tokyo, Japan on 11/19/2019, Abstract pp. 1-6.
8. H.F. Wu, S.L. Morris-Natschke, X.D. Xi, M.H. Yang, Y.Y. Cheng, S.S. Yu and K.H. Lee, "Recent Advances in Natural Anti-HIV Triterpenoids and Analogues," *Med. Res. Rev*., 40, 2339-2385 (2020)

Recap: NPRL By the Numbers

- Collaborating with more than **65** laboratories and **125** individual scientists worldwide
- More than **50** Years of continuous funding by the NIH
- More than **264** Postdoctoral scholars, graduate students and visiting professors/ scholars have studied at NPRL under the guidance of Dr. Kuo-Hsiung Lee
- More than **956** research articles published in refereed journals, with **98** published in the *Journal of Medicinal Chemistry*
- More than **121** patents issued both domestically and internationally
- More than **457** invited speeches, lectures and presentations
- Dr. Kuo-Hsiung Lee serves a member of the editorial advisory board for **29** journals, including *Journal of Medicinal Chemistry*, *Current Medicinal Chemistry*, and *Journal of Natural Products*

Recent NPRL Research Group



Current NPRL Group Members

Dr. Kuo-Hsiung Lee, Kenan Distinguished Professor & NPRL Director

Dr. Susan Morris-Natschke, Research Professor

Dr. Masuo Goto, Research Assistant Professor

Dr. Kyoko Nakagawa-Goto, Adjunct Associate Professor

Dr. Lan Xie, Adjunct Professor

Dr. Yung-Yi Cheng, Research Program Director

Menghan Zhang, Graduate Student

Angela Su, Research Assistant

Teresa Zheng, Research Assistant

Yichen Zhong, Research Assistant

Sarah O'Connor, Executive Assistant

Experimenting with Calligraphy...

蒼龍日暮還行雨　老樹春深更着花

"Like an old dragon continues to produce rain after sunset, the old tree still blooms brilliant flowers in the late spring"

To achieve glory by writing

To achieve virtue

To achieve distinction

To achieve longevity for the human being, society, and the nation

仁者壽
立言立德立功
壽人壽世壽國