BIOGRAPHICAL SKETCH

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NAME: Kenaking, Terrence P

eRA COMMONS USER NAME (credential, e.g., agency login): kenakintp

POSITION TITLE: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
University of Alberta, Edmonton, Alberta, Canada	B.Sc.	05/1971	Chemistry
University of Alberta, Edmonton, Alberta, Canada	Ph. D.	05/1975	Pharmacology
University College, London, United Kingdom	Postdoctoral	09/1975 – 06/78	Pharmacology

A. Personal Statement: Throughout my career I have been engaged in using pharmacologic tools and concepts to characterize the activity of molecules in biological systems in terms of quantified molecular properties such that their activity can be predicted in all other systems including therapeutic ones.

- This work has taken the form of leading drug discovery programs in industry (α-adrenoceptor agonists in CV shock, cardiotonics in heart failure, lusitropics in heart failure, β-adrenoceptor agonists in obesity and asthma, GLP-1 in diabetes, CCR5 entry inhibitors in HIV, MC4R molecules in obesity) and also through writing generally instructive monologues on the topic applying Pharmacology in drug discovery (10 books to date).

- In the course of this work I proposed the production of signaling bias from 7 transmembrane receptors on theoretical grounds and followed with data to explore this phenomenon. This work has continued into methods and concepts to quantify signaling bias in terms of a molecular scale for use in medicinal chemistry programs to optimize these effects.

- In addition, through the HIV CCR5 work (which led to the discovery of the allosteric HIV entry inhibitor aplaviroc), I have explored methods to quantify complex allosteric protein effects to provide scales of molecular activity that are system independent and thus can be used to quantify structure-activity relationships.

B. Positions and Honors

- 1978-1986 Senior Research Scientist - Dept of Pharmacology, Burroughs Wellcome Co. , RTP, NC
- 1986-1991 Senior Research Investigator-Dept of Pharmacology, Glaxo Research Institute, RTP NC
- 1991-1995 Principle Research Scientist- Dept. of Cellular Biochemistry, Glaxo Research Inst, RTP NC
- 1995-2000 Principal Research Scientist- Dept of Receptor Biochemistry, GlaxoWellcome Research and Development .R.T.P., NC 2000-2001 Principal Research Scientist- Systems Research: Discovery Biology, GlaxoSmithKline Research and Development, R.T.P., NC
- 2001-2009 Principal Research Investigator, Molecular Discovery, Systems Research, GlaxoSmithKline Research and Development, R.T.P., NC
- 2009-2011 Director, Biological Reagents and Assay Development, Platform Science Technologies, GlaxoSmithKline Research and Development, R.T.P., NC
- 2011-present Research Professor, Dept. of Pharmacology, UNC School of Medicine, Chapel Hill, NC

Honors

- 2020 ASPET Goodman and Gilman Award for Receptor Pharmacology
- 2014 Gaddum Memorial Award
- 2017: Honorary Fellow of the British Pharmacological Society
- 2011 Ariens Award, Dutch Pharmacological Society
- 2008 Poulsson Medal for Pharmacology awarded by the Norwegian Society of Pharmacology
- 2006: 3rd International Lecture on Analytical Pharmacology Award, International Union of Pharmacology (IUPHAR), 15th World Congress of International Pharmacology, Beijing, China
- 1999: U.S. Research Excellence Award, GlaxoWellcome
- 1976: The Pharmacological Society of Canada Award
- 1974:University of Alberta Dissertation Fellowship
- 1971: Society of Chemistry and Industry Merit Award
- 1971: Professor Osman James Walker Memorial Scholarship in Chemistry

Service: Advisory Boards

- NIMH National Cooperative Drug Discovery Group Scientific Advisory Board (UNC/Duke/Pfizer)
- EU Consortium Signals4Health; 2010

Patents held: U.S. Patent #5153209 issued 10/6/92: Pyridone nitrile useful in treating cardiovascular disease treating cardiovascular disease

Editorial Boards:

- Editor-in-Chief Journal of Receptors and Signal Transduction
- Editorial Board: Trends in Pharmacological Sciences / Clinical and Experimental Pharmacology and Physiology.
- Panel of independent assessors for the National Health and Medical Research Council of Australia,
- Founding member IUPHAR Committee on Receptor Nomenclature

C. Contributions to Science

1. My earliest work was aimed at the development of quantitative pharmacological tools to convert observational data (parameters derived from a defined experimental system) into predictive data (through scales of affinity and efficacy, enable prediction of drug effects in all systems including therapeutic ones). This work began in the laboratory of Nobel laureate Sir James Black in the United Kingdom and continued through my tenure at Burroughs-Wellcome and GlaxoSmithKline. Ideas were disseminated through original papers and reviews and also through the publication of 10 books on pharmacology. This work was extended to produce models of agonism aimed at predicting agonist effect in all systems. In addition the classification of 'Affinity-dominant' vs 'Efficacy-dominant' agonists allowed predictions of agonism in tissues of varying receptor density.

Books Written:

- Kenakin, T. P. The Pharmacologic Analysis of Drug Receptor Interaction, pp. 1-335, Raven Press, New York, 1987
- Kenakin, T. P. The Pharmacologic Analysis of Drug Receptor Interaction, Second edition (pp 1-496) of above - June 1993
- Kenakin, T.P. Molecular Pharmacology: A Short Course, (pp 1-235), Blackwell Science, 1997
- Kenakin, T. P. The Pharmacologic Analysis of Drug Receptor Interaction, Third edition (pp 1-491), Lippincott-Raven, New York , July 1997
- Lutz, M. and Kenakin, T.P. Quantitative Molecular Pharmacology and Informatics in Drug Discovery, pp 1-400, John Wiley and Sons,1999
- Kenakin, T.P. A Pharmacology Primer: Theory, Application and Methods, Academic Press/ Elsevier, Amsterdam, pp 1124 (2004)
- Kenakin, T.P. A Pharmacology Primer: Theory, Application and Methods, (2nd Ed.) Academic Press/ Elsevier, Amsterdam, October 2006
- Kenakin, T.P. A Pharmacology Primer: Theory, Application and Methods, (3rd Ed.) Academic Press/ Elsevier, Amsterdam, November 2009
- Kenakin, T. P. Pharmacology in Drug Discovery: Understanding Drug Response. Elsevier, Amsterdam, 2011

Kenakin, T.P. A Pharmacology Primer: Techniques for more effective and strategic drug discovery, (4th Ed.) Academic Press/ Elsevier, Amsterdam, April, 2014

- Kenakin, T.P. 'A Pharmacology Primer: Techniques for More Effective and Strategic Drug Discovery., Elsevier/Academic Press, 4th edition, 2014, pp1-430.
- Kenakin, T.P. 'A Pharmacology Primer: Techniques for More Effective and Strategic Drug Discovery., Elsevier/Academic Press, 5th edition, , pp1-479. 2018

Relevant Papers:

- Kenakin, T.P. Inverse, protean, and ligand-selective agonism: Matters of receptor conformation. (2001) FASEB J. 15:598-611.
- Kenakin, T.P. New concepts in pharmacological efficacy at 7TM receptors: IUPHAR Review 2, (2013) Br. J. of Pharmacol., 168: 554–575.
- Kenakin, T. P. (2003) Predicting Therapeutic Value in the Lead Optimization Phase of Drug Discovery Nature Reviews Drug Discovery 2: 429-437.

Books Edited

- Progress in Molecular Biology and Translational Science, Vol 115: Oligomerization and Allosteric modulation in G-Protein Coupled Receptors. Elsevier, New York. Jan, 2013.
- Current Protocols in Pharmacology, Vol 1, pp 4.4.1-4.4.6, Ed. Enna, S.J., Williams, M, Ferkany, J.W., Porsolt, R., D., Kenakin, T.P., Sullivan, J.P., John Wiley and Sons, Inc., New York, 1999.
- Journal of Pharmacological and Toxicological Methods- T.P. Kenakin Guest Editor; Special Issue: Receptor-Based Drug Discovery: New Methods for Screening and Drug Characterization, Department of Receptor Biochemistry, GlaxoWellcome Research and Development, Vol 42, 1999
- Handbook of Experimental Pharmacology Series, Vol 148, General Pharmacology: The Pharmacology of Functional, Biochemical, and Recombinant Receptor Systems', ed. Kenakin, T.P. and Angus, J.A., Springer-Verlag, 2000

D. Additional Information: Research Support and/or Scholastic Performance

2. An interest in theoretical pharmacology led to the development of seven transmembrane receptor models in efforts to describe experimental dose-response curves and reduce drug activity to quantitative parameters. This led to the development of the cubic ternary complex model of 7TMR function which is a thermodynamically complete version of and an extension of the extended ternary complex model. The cubic ternary complex model subsumes all known ternary complex models of receptor function.These ides also led to pioneering work in the application of constitutive receptor activity to the screening of orphan receptors.

- Weiss JM, Morgan PH. Lutz MW. Kenakin TP. (1996) The cubic ternary complex receptoroccupancy model. I. Model description. J Theoret Biol 178:151-167
- Chen, G., Way, J., Armour, S., Watson, C., Queen. K., Jayawickreme, C., Chen, W-J., & Kenakin, T.P. (1999) Use of Constitutive G Protein-Coupled Receptor Activity for Drug Discovery. Mol. Pharmacol. 57: 125-134. Kenakin, T.P. (1996) The classification of seven transmembrane receptors in recombinant expression systems. Pharmacol Rev 48:413-463.
- Armour, S., Foord, S., Kenakin, T.P. & Chen, W-J. (1999) Pharmacological Characterization of Receptor Activity Modifying Proteins (RAMPs) and the Human Calcitonin Receptor J. Pharmacol. Toxicol. Meth. 42:217-224.

3. As leader of the HIV-1 Entry Inhibitor program at GlaxoSmithKline, our group applied theoretical models of protein allostery to the inhibition of interaction of the HIV-1 entry protein for cell infection, the CCR5 Chemokine receptor and gp120, the HIV-1 viral coat protein. Experimental data for functional allosteric effects on CCR5 and HIV-1 infection was utilized by a team of chemists to develop the drug aplaviroc as an HIV-1 entry inhibitor in humans. Phase I and II clinical trials confirmed the potent lowering of HIV viral load in AIDs patients but hepatic toxicity in Phase III precluded further clinical development. However, aplaviroc was utilized in pivotal studies to confirm the application of allosteric probe dependence for therapeutic gain for negative allosteric modulators. Working with aplaviroc, the team explored the concept of applying allosteric probe dependence to improve therapeutic profiles of drugs. Specifically, the potency of allosteric HIV-1 entry inhibitors to block HIV-1 entry vs the prevent a beneficial internalization of CCR5 receptor through chemokline aognism was quantified this led to a scale for added therapeutic effect through a dual action of blocking HIV-1 entry and preservation of chemokine function on CCR5 leading to receptor internalization and further protection again viral infection.

- Watson C, Jenkinson S, Kazmierski W & Kenakin TP. (2005) The CCR5 Receptor-based mechanism of action of 873140, a potent allosteric non-competitive HIV entry-inhibitor Mol. Pharmacol. 67: 1268-1282.

- Muniz-Medina, V.M., Jones, S., Maglich, J.M., Galardi,C., Hollingsworth, R.E., Kazmierski, W.M., Ferris, R.G., Edelstein, M.P., Chiswell,K.E., Kenakin, T.P. (2009) The Relative Activity of 'Function Sparing' HIV-1 Entry Inhibitors on Viral Entry and CCR5 Internalization: Is Allosteric Functional Selectivity a Valuable Therapeutic Property? Mol. Pharmacol. 75: 490-501
- Kenakin, T.P. (2005) New Concepts in Drug Discovery: Collateral Efficacy and Permissive Antagonism. Nature Reviews Drug Discovery 4: 919-927
- Kenakin T & Miller LJ. (2010) Seven transmembrane receptors as shapeshifting proteins: the impact of allosteric modulation and functional selectivity on new drug discovery. Pharmacol Rev. 62(2):265-304.

4. Through the industrial HIV-1 program and also through other allosteric discovery programs, we carried out pivotal experiments to create what is now the standard model for 7TMR functional allosteric effects. This model combines the Stockton-Ehlert allosteric binding model with the Black/Leff operational model for function and was published in 2005 (see below). Through the application of this model, a number of allosteric effects can be quantified into predictive parameters (namely □, the allosteric modification of affinity, □ the allosteric modification of efficacy and □B, the direct efficacy of the allosteric modulator).
- Kenakin T. (2005) New concepts in drug discovery: collateral efficacy and permissive antagonism.Nat Rev Drug Discov. 4(11):919-27
- Kenakin T. (2007) Collateral efficacy in drug discovery: taking advantage of the good (allosteric) nature of 7TM receptors. Trends Pharmacol Sci. 28(8):407-15.
- Kenakin, T. P. (2009) 7TM receptor allostery: Putting numbers to shapeshifting proteins. Trends in Pharmacological Sciences, 30(9), 460-469.
- Kenakin, TP (2013) Analytical Pharmacology and allosterism: The importance of quantifying drug parameters in drug discovery Drug Disc. Today 10: 229-235.
- Kenakin, TP (2017) The Quantitative Characterization of Functional Allosteric Effects.
- Curr Protoc Pharmacol. 2017 Mar 17;76:9.22
- Huang XP, Karpiak J, Kroeze WK, Zhu H, Chen X, Moy SS, Saddoris KA, Nikolova VD, Farrell MS, Wang S, Mangano TJ, Deshpande DA, Jiang A, Penn RB, Jin J, Koller BH, Kenakin T, Shoichet BK, Roth BL.Allosteric ligands for the pharmacologically dark receptors GPR68 and GPR65.Nature. 2015 Nov 26;527(7579):477-83

5. Consideration of noted disparities of experimental data and predictions of monotonic stimulus-response transduction mechanisms and the application of molecular dynamics to receptor theory led us to propose the first mechanism to explain biased receptor signaling (this mechanism is still considered to explain the effect and recent 19F-NMR data directly support the mechanism). The stabilization of unique receptor conformations by ligands that go then go on to differentially active cellular functional pathways leads to biased signaling and a tremendous expansion of the possible scope for 7TMR therapeutic selectivity. We also published a viable model to quantify biased effects to enable medicinal chemists to manipulate these properties for improved drug therapies. The concept of biased signaling and the quantitative scale developed from these experiments (the □□Log(□/KA) scale) is being applied to the quantification of the effects of receptor mutation and also agonist selectivity.
- Kenakin, T. P. & Morgan, P. H. (1989) The theoretical effects of single and multiple transducer receptor coupling proteins on estimates of the relative potency of agonists. Mol. Pharmacol. 35:214-22.
- Kenakin, T.P. (1995) Agonist-receptor efficacy II: Agonist trafficking of receptor signals. Trends Pharmacol. Sci. 16: 232-238.
- Kenakin, T.P. , Christopoulos, A. (2013) Signalling bias in new drug discovery: detection, quantification and therapeutic impact. Nature Rev. Drug Disc. 12: 205-215. 2013.
- Kenakin T, Watson C, Muniz-Medina V, Christopoulos A, Novick S. (2012) A simple method for quantifying functional selectivity and agonist bias. ACS Chem Neurosci. 3(3):193-203.
- Kenakin, TP (2017) A System-independent Scale (ΔLog(max/EC50)) of Agonism and Allosteric Modulation for Assessment of Selectivity, Bias and Receptor Mutation. Mol Pharmacol. 2017 Jul 5. pii: mol.117.108787.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28%28%28%28%28%28%28NCBI%29%20AND%20Kenakin[Author]%29%20OR%20Kenakin%20T[Author]%29%20OR%20Kenakin%2C%20Terry[Author]%29%20OR%20Kenakin%20TP[Author]%29%20OR%20Kenakin%2C%20Terry%20P[Author]%29%20OR%20Kenakin%2C%20Terrence[Author]%29%20OR%20Kenakin%2C%20Terrance[Author]%29%20OR%20%28Kenakin%20T%

20Editor%20IN%20Chief%20Journal%20OF%20Receptors[Author]%20AND%20Signal%20Transduction[Author]%29

Ongoing Research Support

- 1R01DA040693 (NIH/NIDA) PI: Zhang 04/15/16 – 01/31/21

Allosteric Modulation of the CB1 Receptor
The goals of this project are to investigate structurally diverse CB1 allosteric modulators for potential biased signaling. To better understand the signaling mechanism of CB1 allosteric modulators and develop pathway selective molecular probes, this project proposes to design and synthesize CB1 allosteric modulators, and use an array of in vitro assays to characterize probe dependent effects on signaling, and employ these probes to investigate different signaling pathways in in vivo models to link quantifiable patterns of efficacy with in vivo phenotypic responses.Role: Co-Investigator

*R21 MH120422 (Xi-Ping Huang and Terry Kenakin) NIMH, Designing and Developing PAM-antagonists for GPR68: 2019-2021

- 5106480: NIH-R56 (XP Huang, T Kenakin) : Designing and Developing Functionally Selective Allosteric Modulators for GPR68
5104135: UNC-Roth PDSP screening
ACTIVE

- HHSN-271-2013-00171C (Roth) 09/08/2008-08/29/2018 NIH/NIMH

NIMH Psychoactive drug screening program
The main objective of the National Institute of Mental Health's- Psychoactive Drug Screening Program (NIMH PDSP) is to comprehensively characterize the in vitro pharmacology of novel research, therapeutic and diagnostic reagents for NIMH-sponsored investigators.

- U24 DK116195 (Roth, Jin, Shoichet) 09/15/2017 - 08/31/2023 NIH

Illuminating the druggable GPCR-ome
Aim 1: Illuminate the pharmacology and discover chemical probes for oGPCRs, and use these to interrogate their function, signaling, pharmacology and physiology; Aim 2: Create engineered CRISPR-tagged mice that, combined with DREADD technology, will reveal the function, signaling, physiology, cell-type and regional expression of oGPCRs; Aim 3: Provide integrated infrastructure—computational, pharmacological, chemical, genetic and administrative—to coordinate collaborations, assemble and integrate large datasets, and to disseminate this information openly to the community.

- Kenakin 12/01/2018 – 11/30/2021 RTI/IGNITE

Therapeutics Development for Cocaine Addition
This grant is concerned with the discovery of new ligands as probes of the still large number of seven transmembrane orphan receptors present in the human genome. Through a combination of virtual docking of large libraries, highthroughput screening and medicinal chemistry, ligands will be identified for use as probes to determine the physiological roles of these receptors. This effort is part of a large worldwide consortium of scientific groups sharing data, resources and expertise.

Completed Research Support
5050135: (Roth) U24 (pending)

- R56MH111769 (Kenakin/Huang) 01/01/2017-12/31/2018 NIH/NIMH

Designing and Developing Functionally Selective Allosteric Modulators for GPR68
GPR68 is a ubiquitous seven transmembrane receptor thought to be a proton sensor. Agonism is produced by H+ ion therefore modulation of this signal is achieved by allosteric potentiation or inhibition of the H+ effect. We discovered the first selective allosteric modulator for GPR68 (ogerin) and wish to

find other positive and negative allosteric modulators of the H+ effect to use as in vivo probes of this receptor to elucidate the physiological role of this receptor. Our initial studies have indicated that it is involved in learning but H+ ion effects are also important in cancer and inflammation.