Toward Consensus on Definitions of PD and Synergy for Claims in Drug Regulatory Decisions

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A Public Hearing Presentation at FDA-DQMM Workshop, Silver Spring MD
October 2-3, 2017

Trends of Drug Combination Methods for Synergy Determination, 1900-2017*

Method, and Reference Source	Thomson Reuters Web of Science Citation Database: Trend of Citation 2013	2014	2015	2016	2017*	Total Citations Since Publication	Average Citations per year
A. Chou, TC & Talalay, P Adv. Eng. Regul. 1984; 22:27-55 [ME & CI Theory]	283	331	308	308	210	4,252	129.8
B. Chou, TC Pharmacol. Rev. 2006;58: 621-681 [CI Review]	159	208	266	307	205	1,625	151.2
C. Chou TC Cancer Res. 2010; 70: 440-446 [CI Perspectives]	124	176	234	286	206	1,160	171.9
D. Berenbaum, MC Pharmacol. Rev. 1989; 41: 93-141	46	43	38	50	25	1,021	36.8
E. Bliss, CI Ann. Appl. Biol. 1939; 26: 585-615	70	77	73	109	60	927	11.9
F. Greco, WR et al Pharamacol. Rev. 1995; 47: 331-385	57	56	69	80	44	794	36.5
G. Steel GG & Peckham MJ Int. J. Radiant. Oncol. BioPhys. 1979; 5: 85-91	14	16	18	18	12	722	19.1
H. Elion GB, Singer S & Hitchings GH J. Biol. Chem. 1954; 208: 477-488	4	4	7	3	4	461	7.3
I. Tallarida, RJ J. Pharmacol. Exp. Ther. 2001; 298: 865-872	35	35	44	34	17	430	27.3
J. Prichard, MN & Shipman C Jr Antiviral Res. 1990; 14: 181-205	16	24	26	35	20	414	15.5
K. Webb J.L. Acad. Press. 1963; 1: 66-79, 488-512	15	8	11	7	7	350#	6.5
L. Loewe, S Pharmacol. Rev. 1957; 9: 237-242	4	5	2	0	2	124	2.1

*Based on Thomson Reuters Web of Science all database, as of September 23, 2017. (Citation numbers are higher in Google Scholar Citations).

#Based on Google Scholar Citations, as of September 23, 2017.

CompuSyn

For Single Drug and Drug Combinations

[An One Second Automated PD Data Analysis Based on The Mass-Action Law]

A Computer Program for Quantitation of Synergism and Antagonism in Drug Combinations, and the Determination of IC_{50}, ED_{50} and LD_{50} Values.

By Ting-Chao Chou (MSKCC)

and Nick Martin (MIT)

Published and Distributed by ***ComboSyn, Inc.***

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http://www.combosyn.com

– PD Science, LLC

Comparison of Two-Drug Combinations for Anti-Cancer Agents Using Econo-Green Small Size Experimentation

[Chou TC, InAm J Cancer Res 1(7): 925-954, 2011]

[Chou TC, Integrative Biol. 3: 548-559, 2011]

	In Vitro	In Animal	In Clinic (I)
Time & Effort	2 weeks	2 months	>1 year
Non-wage Cost	$200 [cells and chemicals]	$3,000 [nude mice]	Expensive Trials [Vary]
Sample Size	> 2 x 10^6 [cells]	> 65 [nude mice] [Chou-Talalay method]	> 36 [vary]
"Practical" Minimum of Data Points (Econo-Green)	16	10	10
Quantitative "Synergy" Determination	Very Easy [But frequently not done properly in the past]	Not Difficult [Rarely properly done in the past]	Difficult Use Surrogate Markers and Fractional Doses

Tales of Two Anti-HIV Clinical Trials

	AZT + 3TC	AZT + INF_{α}
Authors	J.J. Eron et al. (9 authors + Northern Am. HIV Working Party	D. Mildvan et al. (21 authors)
Publication	N. Engl. J. Med. 333: 1662-1669, 1995	Antiviral Therapy 1(2): 77-88, 1996
Journal Impact Factor	**28.5**	**3.1**
Number of Patients	**366**	**36**
Surrogate Marker	CD_4^+ , HIV-RNA	P24 Antigen, CD_4^+
Treatment Design	Fractionated Repeated Doses AZT *Single Dose*, 3TC 2 Doses	Fractionated Repeated Doses Both Drugs have 3 Doses
What They Have Proved	"Combination Effect is Greater than Each Drug Alone" Not Possible to Claim Synergism A+B > A, A+B > B ($p<0.001$). Axiom Does Not Need A Proof !	"Quantitative Determination of Synergism Using Combination Index Method" (CI < 1 determined synergism) Used Chou-Talalay Method. Adv. Enz. Regul. 22: 27-55, 1984

Conclusion: Synergy is Not determined by *p* values but rather by the CI values
Synergy is Not a Statistical Issue but rather a Mass-Action Law Issue

[Chou T.C. Integrative Biol. 3: 548-559, 2011; Am J Cancer Res 1: 925-954,2011]

New Emphasis on Pharmcodynamics (PD) Over Pharmacokinetics (PK)

[Presented at *Drug Development Summit, Zurich, Switzerland*. by Chou TC 6.08.2011; *Am J Cancer Res* 1(7): 925-954, 2011]

Items	PD	PK
Mode of action	***What drug does to the body***	***What body does to the drug***
Characteristics	Mainly **vary dose** Single Unified Theory	Mainly **vary time** Multi-factorial Mix
Principle	The median-effect principle of **the mass-action law**	Empirical phenomenal /observations
Rigorousness	**Explicitly derived equations**	**Empirically perceived formula**
Applications	Physico/chemical quantitative parameters	Probabilistic empiric parameters
Parameters & Constants [*Defined* PD And *Empirical* PK]	D_m, m, r, CI, DRI, IC_{50}, K_m, K_i, K_a and K_d Competitiveness, Exclusivity, Synergism, Antagonism [Mass-action parameters for potency, shape, dynamic order, and interaction indices]	$t_{½}$, C_{max}, Cl, AUC, Vdis Absorption, Distribution, Metabolism, Excretion [Measurement of Parameters without direct physico-chemical bearing]
Determining Efficacy	**Yes**	No
Determining Toxicity	**Yes**	No
Determinant for	***What it takes to be a good drug***	***Help proper use of a drug***