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Design of anti-viral cocktails with combination index-polygonogram method using CompuSyn simulation

Quantitative determination of synergism or antagonism with the combination index theorem of Chou-Talalay and automated CompuSyn simulation has been used for anti-viral and anti-cancer drug combination studies in over 10,000 scientific papers. Over 98% of them have been 2-drug combinations *in vitro*. In this paper, the co-originator of the combination index (CI) method and the co-author of the CompuSyn software, will illustrate step-by-step how to design anti-HIV cocktails with 2 to 5 drug combinations *in vitro* using polygonogram for maximal synergy. For example, A, B, C, D and E anti-HIV agents, we can quantitatively determine the ranks of synergy of each pairs (e.g., A+B, B+C, C+D, A+C, A+D and B+D, A+E, B+E,... for lines); of each triplets (e.g., A+B+C, B+C+D, A+B+D and A+C+D, A+C+E,... for triangles); of each quartets (e.g., A+B+C+D, B+C+D+E,... for the square/rectangulars) and for all 5 drugs for the pentagon. Not all 26 possible combinatory combinations for 5 drugs need to be carried out, depending on the need. The polygonogram concept was introduced in 1994-98 by Chou TC and Chou J.H. It was designated that synergy is presented in solid red color and antagonism is presented in broken green color, for each line, triangle, rectangular and pentagon, the strength of synergism or antagonism is graded by the thickness of the solid red lines/shapes or the broken green lines/shapes. Actual experiments revealed the following findings: Polygonogram allows simple visual inspection to instantly conclude which combos yield greater synergism over others within many complicated massive amount of data and conclusions; combination with more drugs not necessarily yield more synergy; synergism or antagonism need to be determined experimentally and not to be predicted by drug mechanisms; it is possible to approximately or semi-quantitatively project the rank of synergism or antagonism of different triangles or squares/regctangulars, even prior to carrying out the actual experiments, using the components combos. It is concluded that the CI-Polygonogram provide simple, efficient and quantitative solutions to complicated drug combinations (including cocktails) with computerized automated simulations or constructions with sound theoretical basis and thus warrant important applications in pharmaceutical R&D. The currently in use anti-HIV or anti-cancer cocktails/combos, approved by Patent Office/FDA, are not necessarily represent the best/optimal combinations with maximal synergy, however, many of them have acclaimed multi-billion dollar revenues; synergy claims have become not only the scientific and regulatory issues but also the legal/litigation issues, that need a consensus to avoid the damaging consequences.

Biography

Ting-Chao Chou has received his PhD in Pharmacology from Yale University and Postdoctoral Fellowship from Johns Hopkins University School of Medicine. He has joined Memorial Sloan-Kettering Cancer Center (MSKCC) and became a Member and Professor of Pharmacology at Cornell University Graduate School of Medical Sciences in 1988. He is an Honorary Professor of Chinese Academy of Medical Sciences and Visiting Professor at five universities. He has published 444 papers with 23,817 citations (Google Scholar) with h-index of 67. He has introduced The Median-Effect Theory of the Mass-Action Law (1976) and co-developed The Combination Index Theorem, CalcuSyn and CompuSyn software. His theoretical paper introducing the CI method and software has been cited 4,648 times in over 711 bio-medical journals. He is an Inventor/Co-Inventor of 39 US Patents and Founder & President of PD Science LLC, USA.

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