Supplementary Information to

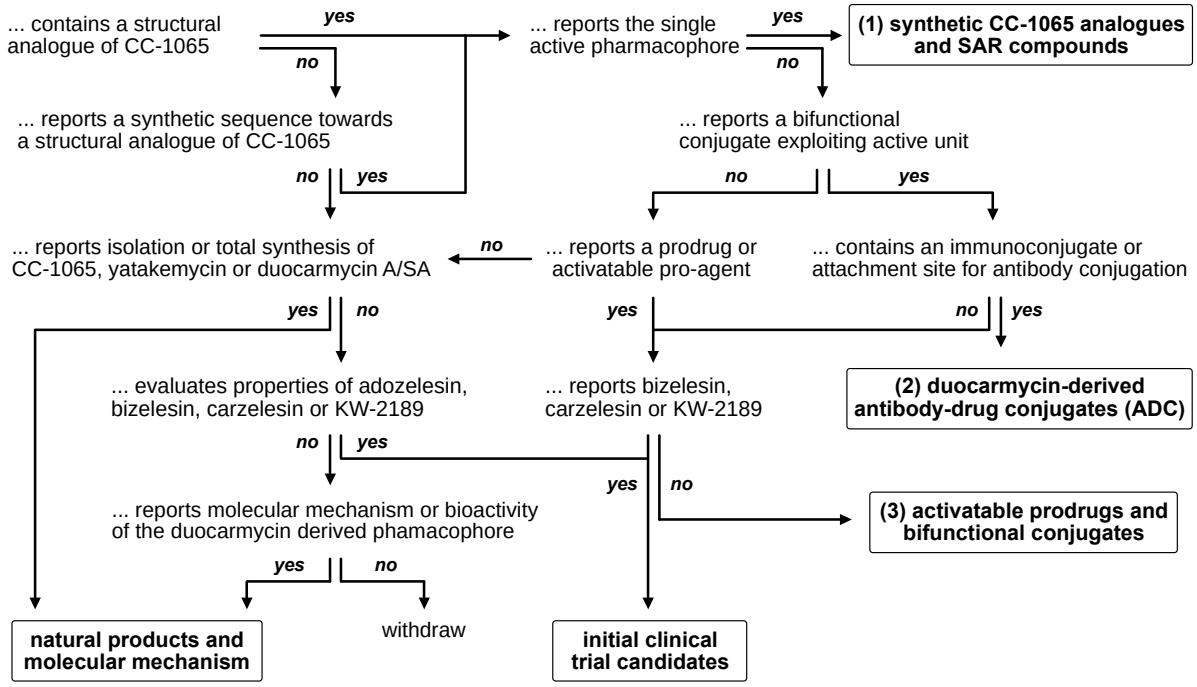
40 years of duocarmycins: a graphical structure/function review of their chemical evolution, from SAR to prodrugs and ADCs

Jan G. Felber* and Oliver Thorn-Seshold*

Department of Pharmacy, Ludwig Maximilians University of Munich
Butenandtstr. 5-13, D-81377 Munich, Germany.
E-mail: jan.felber@cup.lmu.de, oliver.thorn-seshold@cup.lmu.de

*The accompanying hyperlinked **A0 Poster** of the 200 Duocarmycins is actively curated; the current version is downloadable from the authors' website. Please inform us of any errors with the Poster. We are happy to acknowledge substantial suggestions by a cloth print of the updated poster, valued at 2.56 San Serriffe dollars.*

1. Systematic literature review (SLR) – extended



Supplementary Figure S1 Strategy and methods applied to collect and sort primary research items referring to duocarmycins according to systematic literature review (SLR).

The goal of this literature search was to collate the vast majority of references, that (a) report the isolation, molecular mechanism and use of natural products that structurally relate to CC-1065, that (b) report the results of early clinical trial compounds or their synthesis, evaluation or clinical results, that (1) report syntheses and/or evaluation of bioactivity of synthetic CC 1065 analogues or their respective seco-analogues, that (2) report synthesis, evaluation of bioactivity and/or therapeutic use in vivo of activatable proagents or bifunctional conjugates employing a synthetic CC 1065 analogue or its seco-version or that (3) report conjugation/assembly and/or therapeutic efficacy of (multi)functional antibody-drug conjugates incorporating a synthetic CC 1065 analogue or its seco version. This literature collection should be exploited as a database that allows a systematic analysis of both primary reports and metadata to decipher the chemical evolution of structure that the duocarmycin/CC-1065 derived alkylating unit has undergone over the last 40 years.

The search for this systematic literature review (SLR) has gone through many cycles using PubMed, ResearchGate, Google Scholar and Google for journal publications and review articles and FreePatentsOnline and Google Patents for related patents. During a first phase the phrases [“CC 1065” or “duocarmycin”] in combination with [“analogue” or “prodrug” or “derivative” or “review”] have been used and related references have been categorised according to (a1) isolation, early reports or total syntheses of CC-1065 related natural product and (a2) mechanism of action; (b) early small molecule based clinical trial compounds and related articles; (1a) synthetic derivatives that allow to conclude on structure-activity-relationship (SAR) and (1b) reports of synthons that allow are relevant for synthetic duocarmycin-analogues; (2a) functional proagents based on the seco-duocarmycin/cyclobenz[e]indole (CBI) functional unit or (2b) bifunctional conjugates that bear at least one duocarmycin analogue or its seco-version or (3) antibody-drug conjugates that employ a duocarmycin-type alkylating unit as pharmacophore for therapeutic use. More specifically, reports have been collected that refer to the natural products “duocarmycin A”, “duocarmycin SA”, “yatakemycin”, the specific clinical trial compounds “adozelesin”, “bizelesin”, “carzelesin” or “pibrozelesin/KW 2189”, the ADC-related research items [“duocarmyin” or “CBI” or “CPI”] in combination with [“ADC” or “antibody-drug conjugate”] and the clinical trial candidates “SYD985”, “MDX-1302” or “MGC018”.

Secondly, the major driving scientific groups behind each area of research have been identified (L. H. Hurley, D. L. Boger, M. Lee, H. Sugiyama, L. F. Tietze, H. Saito and W. A. Denny/M. Tercel, Byondis BV). For each group all references that report aspects related to the duocarmycin-derived phamacophore have been collected and categorized accordingly. The major scientific research groups or pharmaceutical companies, that drive CBI-based ADCs recently, have been identified (Byondis B.V./Syntarga B.V., Medarex Inc., Genentech Inc., Immunogen Inc. and others) and journal publications have been searched at Google Scholar, whereas patents have been search at FreePatentsOnline and Google Patents. Lastly, recent review articles (Wang 2021, Pors 2020, Lee 2015, Tietze 2011, Pors 2011 and Tietze 2009) have been screened and references have been cross-compared to collate a conclusive library.

2. List of main contributors and their co-authors (≥3 authorships)

(1) Dale Boger: Prof. of Chemistry, The Scripps Research Institute (TSRI), La Jolla:
https://www.scripps.edu/boger/ - 125 Publications:

Paul S. Kitos (14), Douglas S. Johnson (12), Ishizaki Takayoshi (11), Inkyu Hwang (10), Hamideh Zarrinmayeh (10), Robert M. Garbaccio (9), Weiya Yun (9), Christopher W. Boyce (8), Karen MacMillan (8), Stephan A. Munk (8), Qing Jin (7), David B. Kastrinsky (7), James P. Lajiness (7), Jeffrey A. McKie (7), Hui Cai (6), Nianhe Han (6), Michael P. Hedrick (6), Oranart Suntornwat (6), Scott E. Wolkenberg (6), Robert S. Coleman (5), Jay P. Parrish (5), Mark Searcey (5), Mark S. Tichenor (5), George A. Vielhauer (5), Pier G. Baraldi (4), Takahide Nishi (4), Philippe Mesini (4), Thomas J. Rayl (4), William M. Robertson (4), Christine M. Tarby (4), John D. Trzupek (4), Amanda L. Wolfe (4), Bernd Bollinger (3), Kristopher E. Boyle (3), Katherine K. Duncan (3), Joel Goldberg (3), Donald L. Hertzog (3), Nikhil K. Parelkar (3), Winston C. Tse (3), Philip Turnbull (3), Scott J. Weir (3), Ronald Wysocki (3).

(2) Hiroshi Sugiyama: Prof. Chemical Biology, Kyoto University:
http://kuchem.kyoto-u.ac.jp/chembio/ - 58 Publications:

Toshikazu Bando (45), Ken-Ichi Shinohara (18), Masafumi Minoshima (14), Isao Saito (12), Shunta Sasaki (12), Gengo Kashiwaza (10), Kaori Hashiya (9), Akihiko Narita (9), Rhys Dylan Taylor (6), Tsuyoshi Fujiwara (5), Zhi-Fu Tao (5), Jun Fujimoto (4), Hiroki Nagase (4), Tatsuhiko Shimizu (4), Anandhakumar Chandran (3), Yusuke Kawamoto (3), Rina Maeda (3), Gadesh N. Pandian (3), Toshiki Takagaki (3).

(3) Willam A. Denny: Prof. Medicinal Chemistry, Auckland University and Dr. Moana Tercel, Senior Research Fellow, Auckland University:
https://unidirectory.auckland.ac.nz/profile/b-denny; /unidirectory.auckland.ac.nz/profile/m-tercel.
49 publications with authorship of either William A. Denny or Moana Tercel:

Moana Tercel (38), William A. Denny (35), William R. Wilson (24), Graham Atwell (15), Frederik B. Pruijn (15), Ralph J. Stevenson (10), Sarath H. D. Liyanage (8), Thomas H. Pillow (8), Shangjin Yang (7), Jane Botting (6), Ho H. Lee (6), Adam V. Patterson (6), Jared Milbank (6), Amir Ashoorzadeh (4), Sarah P. McManaway (4), Sunali Mehta (4), Robert F. Anderson (3), Michael P. Hay (3), Eileen Smith (3).

(4) Lutz Tietze: Prof. Organic and biomolecular Chemistry, University of Goettingen:
Laboratory Website: http://www.tietze.chemie.uni-goettingen.de/ewelcome.php - 35 Publications:

Ingrid Schuberth (17), Birgit Krewer (13), Felix Major (8), Kianga Schmuck (7), J. Marian von Hof (6), Heiko J. Schuster (6), Frauke Alves (4), Tim Feuerstein (4), Frank Haunert (4), Tobias Herzig (4), Michael Müller (4), Olaf Panknin (3), Stephan A. Sieber (3).

(5) Laurence H. Hurley: Prof. Medicinal Chemistry, Arizona - 28 publications:

Daekyu Sun (11), Chong-Soon Lee (5), Paul A. Aristoff (4), Hsiung Chin Lin (4), Vincent L. Reynolds (4), David H. Swenson (4), Donald R. Needham-VanDev (3), Patrick J. McGovren (3), Gary L. Petzold (3), William C. Krueger (1), Li H. Li (1).

Related researchers and/or groups with independent publications and at least 3 authorships:

William C. Krueger (17), David H. Swenson (13), Mark D. Prairie (12), Gary L. Petzold (12), Patrick J. McGovren (11), Bijoy K. Bhuyan (10), Robert C. Kelly (10), Li H. Li (10), Paul A. Aristoff (7), Martha A. Warpehoski (7), Thomas F. DeKoning (5), Tanya L. Wallace (4), Ilse Gebhard (3).

(6) Moses Lee, Furman University, Greenville/Georgia State University:
https://www.researchgate.net/scientific-contributions/Moses-Lee-38856864 - 25 Publications:

John A. Hartley (14), Konstantinos Kiakos (14), Stephen J. Hudson (7), Carlie A. Price (6), Kaitlin Summerville (6), Heather L. Handl (5), Bethany Purnell (5), Heather Townes (5), Tetsuji Asao (4), Phillip Bowen (4), Brian Lingerfelt (4), Pravil Patil (4), Atsushi Sato (4), Adrienne E. Scott (4), James Toth (4), Tiffany T. Howard (3), LuAnne McNulty (3).

(7) Hiromitsu Saito, Kyowa Hakko Kogyo Co Ltd., Tokyo and Pharm. Res. Laboratories, Shimotogari:
https://www.researchgate.net/scientific-contributions/Hiromitsu-Saito-20136372 - 23 publications:

Satoru Nagamura (19), Katsushige Gomi (14), Ejii Kobayashi (13), Akira Asai (10), Nobuyoshi Amishiro (7), Akihiko Okamoto (7), Masami Okabe (6), Yutaka Kanda (3).

(8) Synthon Biopharmaceuticals/Byondis B.V., Nijmegen: www.byondis.com - 22 publications:

Patrick H. Beusker (13), Franciscus M. H. de Groot (10), Rudy G. E. Coumans (8), Willem Dokter (8), Henri J. Sprijker (8), Albertus F. Joosten (7), Ronald C. Elgersma (6), Miranda van der Lee (6), Wiro M. P. B. Menge (6), David Egging (5), Marco Timmers (5), Peter Goedings (4), Patrick Groothuis (4), Tijl Huijbregts (4), Alessandro D. Santin (4), Ruud Ubink (4), Gijs Verheijden (4), Tanja van Achterberg (3), Masoud Azodi (3), Elena Bonazzoli (3), Stefania Bellone (3), Jonathan Black (3), Natalia Buza (3), Diels van den Dobbelsteen (3), Pei Hui (3), Eline M. Loosveld (3), Gulden Menderes (3), Babak Litkouhi (3), Elena Ratner (3), Dan-Arin Silasi (3), Peter E. Schwartz (3), Monique van der Vleuten (3), Serena Wong (3).

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(a) molecular mechanism (146 items – 145 journal publications, 1 patent)

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