

MIBiG 4.0: advancing biosynthetic gene cluster curation through global collaboration

Mitja M. Zdouc^{1,†}, Kai Blin^{2,*†}, Nico L.L. Louwen¹, Jorge Navarro¹, Catarina Loureiro¹, Chantal D. Bader³, Constance B. Bailey⁴, Lena Barra⁵, Thomas J. Booth², Kenan A.J. Bozhüyük^{3,6}, José D.D. Cediél-Becerra⁷, Zachary Charlop-Powers⁸, Marc G. Chevrette^{7,9}, Yit Heng Chooi¹⁰, Paul M. D'Agostino^{3,11}, Tristan de Rond¹², Elena Del Pup¹, Katherine R. Duncan¹³, Wenjia Gu¹⁴, Novriyandi Hanif¹⁵, Eric J.N. Helfrich^{16,17,18}, Matthew Jenner^{19,20}, Yohei Katsuyama^{21,22}, Aleksandra Korenskaia²³, Daniel Krug^{3,24,25}, Vincent Libis^{26,27}, George A. Lund²⁸, Shrikant Mantri^{29,30}, Kalindi D. Morgan³¹, Charlotte Owen³², Chin-Soon Phan³³, Benjamin Philmus³⁴, Zachary L. Reitz³⁵, Serina L. Robinson³⁶, Kumar Saurabh Singh^{1,37,38}, Robin Teufel³⁹, Yaojun Tong⁴⁰, Fidele Tugizimana^{41,42}, Dana Ulanova^{43,44}, Jaclyn M. Winter⁴⁵, César Aguilar^{46,47}, Daniel Y. Akiyama⁴⁸, Suhad A.A. Al-Salihi⁴⁹, Mohammad Alanjary¹, Fabrizio Alberti⁵⁰, Gajender Aleti⁵¹, Shumukh A. Alharthi⁵², Mariela Y. Arias Rojo⁵³, Amr A. Arishi^{10,54}, Hannah E. Augustijn^{1,55}, Nicole E. Avalon⁵⁶, J. Abraham Avelar-Rivas⁵⁷, Kyle K. Axt³⁴, Hellen B. Barbieri⁴⁸, Julio Cesar J. Barbosa⁴⁸, Lucas Gabriel Barboza Segato⁵⁸, Susanna E. Barrett^{59,60}, Martin Baunach⁶¹, Christine Beemelmans^{3,24}, Dardan Beqaj⁶², Tim Berger⁶³, Jordan Bernaldo-Agüero^{64,65}, Sandra M. Bettenbühl^{16,17}, Vincent A. Bielinski⁶⁶, Friederike Biermann^{1,16,17}, Ricardo M. Borges⁶⁷, Rainer Borriss^{68,69}, Milena Breitenbach^{16,17}, Kevin M. Bretscher^{55,70,71}, Michael W. Brigham⁷², Larissa Buedenbender⁷³, Brodie W. Bulcock¹⁰, Carolina Cano-Prieto², João Capela⁷⁴, Victor J. Carrion^{55,70,75}, Riley S. Carter^{59,60}, Raquel Castelo-Branco⁷⁶, Gabriel Castro-Falcón⁵⁶, Fernanda O. Chagas⁶⁷, Esteban Charria-Girón^{25,77}, Ayesha Ahmed Chaudhri^{16,17}, Vasvi Chaudhry⁷⁸, Hyukjae Choi^{79,80}, Yukyung Choi⁸¹, Roya Choupannejad⁸², Jakub Chromy⁸³, Melinda S. Chue Donahey⁷, Jérôme Collemare⁸², Jack A. Connolly⁸³, Kaitlin E. Creamer^{84,85}, Max Crüsemann⁶¹, Andres Arredondo Cruz⁵³, Andres Cumsille⁷, Jean-Felix Dallery⁸⁶, Luis Caleb Damas-Ramos², Tito Damiani⁸⁷, Martinus de Kruijff³, Belén Delgado Martín⁷⁵, Gerardo Della Sala⁸⁸, Jelle Dillen⁸⁹, Drew T. Doering⁹⁰, Shravan R. Dommaraju^{59,60}, Suhan Durusu^{16,17}, Susan Egbert⁵⁸, Mark Ellerhorst⁹¹, Baptiste Faussurier^{26,27}, Artem Fetter¹³, Marc Feuermann⁹², David P. Fewer⁹³, Jonathan Foldi⁸³, Andri Frediansyah^{94,95}, Erin A. Garza⁹⁶, Athina Gavriliidou²³, Andrea Gentile^{97,98}, Jennifer Gerke⁹⁹, Hans Gerstmann^{100,101,102}, Juan Pablo Gomez-Escribano¹⁰³, Luz A. González-Salazar⁴⁶, Natalie E. Grayson⁵⁶, Claudio Greco⁵², Juan E. Gris Gomez⁴⁶, Sebastian Guerra^{7,9}, Shaday Guerrero Flores¹⁰⁴, Alexey Gurevich^{3,24}, Karina Gutiérrez-García¹⁰⁵, Lauren Hart^{106,107}, Kristina Haslinger¹⁰⁸, Beibei He¹⁰⁹, Teo Hebra⁸⁷, Jethro L. Hemmann¹¹⁰, Hindra Hindra^{111,112}, Lars Höing³⁹, Darren C. Holland¹⁰, Jonathan E. Holme¹¹³, Therese Horch², Pavlo Hrab^{1,114}, Jie Hu¹¹⁵, Thanh-Hau Huynh¹¹⁶, Ji-Yeon Hwang¹¹⁷, Riccardo Iacovelli¹¹⁸, Dumitrita Iftime⁶², Marianna Iorio⁹⁷, Sidharth Jayachandran², Eunah Jeong⁸¹, Jiayi Jing¹, Jung J. Jung¹¹⁶, Yuya Kakumu^{16,17}, Edward Kalkreuter¹¹⁹, Kyo Bin Kang⁸¹, Sangwook Kang¹¹⁶, Wonyong Kim¹²⁰, Geum Jin Kim^{80,121}, Hyunwoo Kim¹²², Hyun Uk Kim¹²³, Martin Klapper¹²⁴, Robert A. Koetsier¹, Cassandra Kollten¹¹, Ákos T. Kovács^{55,125}, Yelyzaveta Kriukova^{3,11},

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Noel Kubach²³, Aditya M. Kunjapur¹²⁶, Aleksandra K. Kushnareva^{3,24}, Andreja Kust^{84,85}, Jessica Lamber^{3,24,127}, Martin Larralde¹²⁸, Niels J. Larsen², Adrien P. Launay¹²⁹, Ngoc-Thao-Hien Le²⁶, Sarah Lebeer^{89,130}, Byung Tae Lee¹²³, Kyungha Lee⁸¹, Katherine L. Lev^{106,107}, Shu-Ming Li⁶³, Yong-Xin Li¹⁰⁹, Cuauhtémoc Licona-Cassani^{46,131}, Annette Lien¹, Jing Liu¹⁰⁹, Julius Adam V. Lopez^{132,133}, Nataliia V. Machushynets⁵⁵, Marla I. Macias¹³⁴, Taifo Mahmud³⁴, Matiss Maleckis¹³⁵, Añadir Maharai Martinez-Martinez⁴⁶, Yvonne Mast^{103,136}, Marina F. Maximo⁴⁸, Christina M. McBride^{106,107}, Rose M. McLellan^{137,138}, Khyati Mehta Bhatt⁸², Chrats Melkonian^{1,139}, Aske Merrild¹⁴⁰, Mikko Metsä-Ketelä¹⁴¹, Douglas A. Mitchell⁵⁹, Alison V. Müller^{3,24,127}, Giang-Son Nguyen¹¹³, Hera T. Nguyen¹⁰, Timo H. J. Niedermeyer¹⁴², Julia H. O'Hare⁶⁷, Adam Ossowicki^{70,75}, Bohdan O. Ostash^{143,144}, Hiroshi Otani^{90,145}, Leo Padva⁶¹, Sunaina Paliyal²⁹, Xinya Pan^{55,70,71}, Mohit Panghal^{29,30}, Dana S. Parade³, Jiyeon Park¹¹⁶, Jonathan Parra^{146,147,148}, Marcos Pedraza Rubio^{70,75}, Huong T. Pham⁸¹, Sacha J. Pidot¹⁴⁹, Jörn Piel¹⁵⁰, Bita Pourmohsenin²³, Malik Rakhmanov³⁹, Sangeetha Ramesh¹⁵¹, Michelle H. Rasmussen¹⁵², Adriana Rego⁷⁶, Raphael Reher⁶³, Andrew J. Rice⁵⁹, Augustin Rigolet⁵⁵, Adriana Romero-Otero^{2,135}, Luis Rodrigo Rosas-Becerra^{55,57}, Pablo Y. Rosiles¹²⁹, Adriano Rutz¹⁵³, Byeol Ryu⁵⁶, Libby-Ann Sahadeo⁵⁸, Murrel Saldanha⁷, Luca Salvi⁶², Eduardo Sánchez-Carvajal¹⁵⁴, Christian Santos-Medellin¹¹⁵, Nicolau Sbaraini¹⁰, Sydney M. Schoellhorn¹⁵⁵, Clemens Schumm^{3,127,156}, Ludek Sehnal^{62,157}, Nelly Selem¹⁰⁴, Anjali D. Shah^{158,159}, Tania K. Shishido^{82,160}, Simon Sieber¹⁶¹, Velina Silviani^{79,80}, Garima Singh^{162,163}, Hemant Singh²⁹, Nika Sokolova¹⁰⁸, Eva C. Sonnenschein⁵², Margherita Sosio⁹⁷, Sven T. Sowa³⁹, Karin Steffen¹⁶⁴, Evi Stegmann^{62,165}, Alena B. Streiff¹⁵⁰, Alena Strüder⁶², Frank Surup^{25,77}, Tiziana Svenningsen¹⁴⁰, Douglas Sweeney⁵⁶, Judit Szenei², Azat Tagirdzhanov^{3,24}, Bin Tan^{16,17}, Matthew J. Tarnowski⁵², Barbara R. Terlouw¹, Thomas Rey^{166,167}, Nicola U. Thome^{55,168}, Laura Rosina Torres Ortega¹, Thomas Tørring¹⁴⁰, Marla Trindade¹⁶⁹, Andrew W. Truman¹⁷⁰, Marie Tvilum¹⁴⁰, Daniel W. Udway⁹⁰, Christoph Ulbricht⁶¹, Lisa Vader², Gilles P. van Wezel^{55,71}, Max Walmsley⁸³, Randika Warnasinghe⁵⁸, Heiner G. Weddeling³⁹, Angus N.M. Weir^{100,171}, Katherine Williams^{158,172}, Sam E. Williams², Thomas E. Witte¹⁷³, Steffaney M. Wood Rocca^{56,96}, Keith Yamada¹⁴¹, Dong Yang¹⁷⁴, Dongsoo Yang¹⁷⁵, Jingwei Yu¹⁷⁶, Zhenyi Zhou¹⁷⁷, Nadine Ziemert²³, Lukas Zimmer⁶¹, Alina Zimmermann¹⁰³, Christian Zimmermann¹⁷⁸, Justin J.J. van der Hooft^{1,41}, Roger G. Linington¹⁷⁹, Tilmann Weber^{2,*} and Marnix H. Medema^{1,*}

¹Bioinformatics Group, Wageningen University & Research, Droevendaalsesteeg 1, 6708 PB Wageningen, The Netherlands

²The Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, Building 220, Søtofts Plads, 2800 Kongens Lyngby, Denmark

³Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Helmholtz Centre for Infection Research (HZI), Campus E8.1, 66123 Saarbrücken, Germany

⁴School of Chemistry, Chemistry Building, University of Sydney, Eastern Ave, Camperdown NSW 2050, Sydney, New South Wales, Australia

⁵Department of Chemistry, University of Konstanz, Universitätsstraße 10, 78464 Konstanz, Germany

⁶Myria Biosciences AG, Tech Park Basel, Hochbergstrasse 60C, 4057 Basel, Switzerland

⁷Department of Microbiology and Cell Science, University of Florida, 1355 Museum Drive, Gainesville, Florida, 32611, USA

⁸Ginkgo Bioworks, 27 Drydock Avenue, 8th Floor, Boston, MA 02210, USA

⁹University of Florida Genetics Institute, University of Florida, 2033 Mowry Rd, Gainesville, FL 32611, USA

¹⁰School of Molecular Sciences, University of Western Australia, 35 Stirling Highway, Perth 6009, Australia

¹¹Chair of Technical Biochemistry, Technical University of Dresden, Bergstraße 66, 01069 Dresden, Germany

¹²School of Chemical Sciences, University of Auckland, 23 Symonds St, Auckland 1010, New Zealand

¹³Newcastle University, Biosciences Institute, Catherine Cookson Building, Newcastle upon Tyne, NE2 4HH, UK

¹⁴Sutro Biopharma, 111 Oyster Point Blvd, South San Francisco, CA, 94080, USA

¹⁵Department of Chemistry, Faculty of Mathematics and Natural Sciences, IPB University, Gedung Kimia Wing 1 Lantai 3, Jalan Tanjung Kampus IPB Dramaga, Bogor, Jawa Barat 16680, Indonesia

¹⁶Institute for Molecular Bio Science, Goethe University Frankfurt, Max-von-Laue Strasse 9, 60438 Frankfurt am Main, Germany

¹⁷LOEWE Center for Translational Biodiversity Genomics (TBG), Senckenberganlage 25, 60325 Frankfurt am Main, Germany

¹⁸Senckenberg Society for Nature Research, Senckenberganlage 25, 60325 Frankfurt am Main, Germany

¹⁹Department of Chemistry, University of Warwick, Gibbet Hill Rd, Coventry, CV4 7AL, UK

²⁰Warwick Integrative Synthetic Biology Centre (WISB), University of Warwick, Gibbet Hill Rd, Coventry, CV4 7AL, UK

- ²¹ Department of Biotechnology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1, Yayoi, Bunkyo-ku, Tokyo, 113-8657, Japan
- ²² Collaborative Research Institute for Innovative Microbiology, The University of Tokyo, 1-1-1, Yayoi, Bunkyo-ku, Tokyo, 113-8657, Japan
- ²³ Translational Genome Mining for Natural Products, Interfaculty Institute of Microbiology and Infection Medicine Tübingen (IMIT), Interfaculty Institute for Biomedical Informatics (IBMI), University of Tübingen, Sand 14, 72076 Tübingen, Germany
- ²⁴ Saarland University, Campus E8.1, 66123 Saarbrücken, Germany
- ²⁵ Department of Microbial Drugs, Helmholtz Centre for Infection Research (HZI), Inhoffenstr. 7, 38124 Braunschweig, Germany
- ²⁶ Université Paris Cité - Inserm Unit 1284, 75015 Paris, France
- ²⁷ Translational Genome Mining for Natural Products, Generare Bioscience, 75011 Paris, Île-de-France, France
- ²⁸ Sustainable Soils and Crops, Rothamsted Research, West Common, Harpenden, Hertfordshire, AL5 2JQ, UK
- ²⁹ Computational Biology Lab, National Agri-Food and Biomanufacturing Institute (NABI), Sector 81, S.A.S. Nagar, Mohali, Punjab 140306, India
- ³⁰ Regional Centre for Biotechnology, NCR Biotech Science Cluster, 3rd Milestone, Faridabad-Gurugram Expressway, Faridabad - 121001 Haryana (NCR Delhi), India
- ³¹ Department of Chemistry and Biochemistry, University of Northern British Columbia, 3333 University Way, Prince George, BC, V2N 4Z9, Canada
- ³² Biochemistry and Metabolism, John Innes Centre, Norwich Research Park, Colney Lane, Norwich, NR4 7UH, UK
- ³³ Latvian Institute of Organic Synthesis, Aizkraukles street 21, LV-1006 Riga, Latvia
- ³⁴ Department of Pharmaceutical Sciences, Oregon State University, 1601 SW Jefferson Way, Corvallis, OR 97331-3507, USA
- ³⁵ Department of Ecology, Evolution and Marine Biology, University of California, 1169 Biological Sciences II, Santa Barbara, CA 93106, USA
- ³⁶ Department of Environmental Microbiology, Swiss Federal Institute of Aquatic Science and Technology, Ueberlandstrasse 133, 8600 Dübendorf, Switzerland
- ³⁷ Plant-Microbe Interactions, Institute of Environmental Biology, Utrecht University, 3584 CH Utrecht, The Netherlands
- ³⁸ Faculty of Environment, Science and Economy, University of Exeter, TR10 9FE, Penryn, Cornwall, UK
- ³⁹ Department of Pharmaceutical Sciences, University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland
- ⁴⁰ State Key Laboratory of Microbial Metabolism, School of Life Sciences and Biotechnology, Shanghai Jiao Tong University, Minhang District, Shanghai 200240, China
- ⁴¹ Department of Biochemistry, University of Johannesburg, C2 Lab Building 224, Kingsway Campus, Cnr University & Kingsway Road, Auckland Park, Johannesburg 2006, South Africa
- ⁴² International Research and Development (R&D) Division, Omnia Nutriology, Omnia Holdings Ltd, Building H, Monte Circle, 178 Montecasino Blvd, Fourways, Sandton, 2055, South Africa
- ⁴³ Department of Marine Resource Science, Faculty of Agriculture and Marine Science, Kochi University, 200 Otsu, Monobe, Nankoku-shi, Kochi, 783-8502, Japan
- ⁴⁴ Marine Core Research Institute, Kochi University, 200 Otsu, Monobe, Nankoku-shi, Kochi, 783-8502, Japan
- ⁴⁵ Department of Pharmacology and Toxicology, University of Utah, 30 S 2000 E, Salt Lake City, Utah, 84112, USA
- ⁴⁶ Industrial Genomics Laboratory, Centro de Biotecnología FEMSA, Escuela de Ingeniería y Ciencias, Tecnológico de Monterrey, Av. Eugenio Garza Sada 2501sur, Nuevo Leon, 64700, México
- ⁴⁷ Department of Chemistry, Purdue University, 610 Purdue Mall, West Lafayette, IN, 47907, USA
- ⁴⁸ Department of Organic Chemistry, Institute of Chemistry, University of Campinas (UNICAMP), Rua Monteiro Lobato 270, Campinas, São Paulo, 13.083-862, Brazil
- ⁴⁹ Department of Applied Sciences, University of Technology, Al-Sina'a St., 10066, Baghdad, Iraq
- ⁵⁰ School of Life Sciences, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, UK
- ⁵¹ Department of Food and Animal Sciences, College of Agriculture, Tennessee State University, Nashville, TN 37209, USA
- ⁵² Department of Biosciences, Swansea University, Singleton Park, Swansea, SA2 8PP, UK
- ⁵³ Escuela Nacional de Estudios Superiores Unidad Leon, Universidad Nacional Autónoma de México, Blv. UNAM #2011, Predio El Saucillo y, Comunidad de los Tepetates, El Potrero, 37684 León de los Aldama, Gto., Mexico
- ⁵⁴ Department of Botany and Microbiology, College of Science, King Saud University, P.O. Box 2455, Riyadh, 11451, Saudi Arabia
- ⁵⁵ Institute of Biology, Leiden University, Sylviusweg 72, 2333BE Leiden, The Netherlands
- ⁵⁶ Center for Marine Biotechnology and Biomedicine, Scripps Institution of Oceanography, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0212, USA
- ⁵⁷ Unidad de Genómica Avanzada, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Km 9.6 Libramiento Norte Carretera Irapuato-León, 36824, Irapuato, Mexico
- ⁵⁸ Department of Chemistry, University of Manitoba, 66 Chancellors Circle, Winnipeg, MB R3T 2N2, Canada
- ⁵⁹ Department of Chemistry, University of Illinois Urbana-Champaign, 600 S. Matthews Ave, Urbana, IL 61801, USA
- ⁶⁰ Carl R. Woese Institute for Genomic Biology, University of Illinois Urbana-Champaign, 1206 W. Gregory Drive, Urbana, IL 61801, USA
- ⁶¹ Institute of Pharmaceutical Biology, University of Bonn, Nussallee 6, 53115 Bonn, Germany
- ⁶² Interfaculty Institute of Microbiology and Infection Medicine Tübingen, Microbial Bioactive Compounds, University of Tübingen, Auf der Morgenstelle 28, 72076, Tübingen, Germany
- ⁶³ Institute of Pharmaceutical Biology and Biotechnology, University of Marburg, Robert-Koch-Str. 4, 35037 Marburg, Germany
- ⁶⁴ Departamento de Microbiología Molecular, Instituto de Biotecnología, Universidad Nacional Autónoma de México, Av. Universidad 2001, Chamilpa, 62210 Cuernavaca, Morelos, México
- ⁶⁵ Facultad de Ciencias Biológicas, Universidad Nacional Mayor de San Marcos, Av. Germán Amézaga S/N, Ciudad Universitaria, UNMSM, Lima 15081, Perú
- ⁶⁶ Departamento de Bioquímica, Instituto de Química, Universidade Federal do Rio de Janeiro, Avenida Athos da Silveira Ramos, no 149, Rio de Janeiro, 21941-909, Brazil
- ⁶⁷ Instituto de Pesquisas de Produtos Naturais Walter Mors, Universidade Federal do Rio de Janeiro, CCS - Av. Carlos Chagas Filho, 373 - Bloco H - Cidade Universitária, Rio de Janeiro - RJ, 21941-599, Brazil
- ⁶⁸ Department of Biology, Humboldt University Berlin, Invaliden-Str. 42, 10115 Berlin, Germany
- ⁶⁹ Institute of Marine Biotechnology (IMaB), University of Greifswald, Walter-Rathenau-Str. 49A, 17489 Greifswald, Germany

- ⁷⁰Department of Crop Protection, Instituto de Hortofruticultura Subtropical y Mediterránea “La Mayora” (IHSM-UMA-CSIC), Campus Universitario de Teatinos, 29010, Málaga, Spain
- ⁷¹Department of Microbial Ecology, Netherlands Institute of Ecology (NIOO-KNAW), Droevendaalsesteeg 10 6708 PB Wageningen, The Netherlands
- ⁷²School of Cellular and Molecular Biology, Faculty of Biological Sciences, University of Leeds, 6 Clarendon Way, Woodhouse, Leeds, LS2 3AA, UK
- ⁷³CICA – Centro Interdisciplinar de Química e Biología, Universidade da Coruña, As Carballeiras, s/n, Campus de Elviña, 15071 A Coruña, Spain
- ⁷⁴Centre of Biological Engineering, University of Minho, 4710-057, Braga, Portugal
- ⁷⁵Department of Microbiology, Faculty of Science, Campus Universitario de Teatinos s/n, University of Málaga, 29010 Málaga, Spain
- ⁷⁶Interdisciplinary Centre of Marine and Environmental Research (CIIMAR/CIMAR), University of Porto, 4450-208 Matosinhos, Portugal
- ⁷⁷Institute of Microbiology, Technische Universität Braunschweig, Spielmannstraße 7, 38106 Braunschweig, Germany
- ⁷⁸Microbial Interactions in Plant Ecosystems, IMIT/ZMBP, Eberhard Karls University of Tübingen, 72076 Tübingen, Germany
- ⁷⁹College of Pharmacy, Yeungnam University, 280 Daehak-ro Gyeongsan-Si, Gyeongsangbuk-do 38541, Republic of Korea
- ⁸⁰Research Institute of Cell Culture, Yeungnam University, 280 Daehak-ro Gyeongsan-Si, Gyeongsangbuk-do 38541, Republic of Korea
- ⁸¹College of Pharmacy and Drug Information Research Institute, Sookmyung Women’s University, 100 Cheongpa-ro 47 gil, Seoul 04310, Republic of Korea
- ⁸²Fungal Natural Products, Westerdijk Fungal Biodiversity Institute, Uppsalalaan 8, 3584CT Utrecht, The Netherlands
- ⁸³Manchester Institute of Biotechnology, Department of Chemistry, School of Natural Sciences, Faculty of Science and Engineering, University of Manchester, 131 Princess Street, Manchester M1 7DN, UK
- ⁸⁴Innovative Genomics Institute, University of California Berkeley, 2151 Berkeley Way, Berkeley, CA 94720, USA
- ⁸⁵Department of Earth and Planetary Science, University of California, 307 McCone Hall Berkeley, CA 94720-4767, USA
- ⁸⁶Université Paris-Saclay, INRAE, UR BIOGER, 22 place de l’Agronomie, 91120 Palaiseau, France
- ⁸⁷IOCB Prague, Czech Academy of Science, Flemingovo náměstí 542/2, 160 00 Praha 6, Czech Republic
- ⁸⁸Department of Ecosustainable Marine Biotechnology, Stazione Zoologica Anton Dohrn, Giardini del Molosiglio, Via A.F. Acton 55, 80133 Naples, Italy
- ⁸⁹Department of Bioscience Engineering, Research Group Laboratory of Applied Microbiology and Biotechnology, University of Antwerp, Groenenborgerlaan 171, 2020 Antwerp, Belgium
- ⁹⁰US Department of Energy Joint Genome Institute, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley, CA 94720, USA
- ⁹¹Biochemistry of Microorganisms, Faculty of Life Sciences: Food, Nutrition, and Health, University of Bayreuth, Fritz-Hornschuch-Straße 13, 95326 Kulmbach, Germany
- ⁹²SIB Swiss Institute of Bioinformatics, Centre Medical Universitaire, 1 rue Michel Servet, 1211 Geneva 4, Switzerland
- ⁹³Department of Microbiology, University of Helsinki, Viikinkaari 9, 00017, Helsinki, Finland
- ⁹⁴Research Center for Food Technology and Processing, Research Organization of Agriculture and Food, National Research and Innovation Agency (BRIN), Jl. Jogja - Wonosari Km 31.5, DI. Yogyakarta 55861, Indonesia
- ⁹⁵Microbial Metabolites for Food Research Group, National Research and Innovation Agency (BRIN), Jl. Jogja - Wonosari Km 31.5, Gunungkidul, DI. Yogyakarta 55861, Indonesia
- ⁹⁶Microbial and Environmental Genomics Group, J. Craig Venter Institute, 4120 Capricorn Lane, La Jolla, CA 92037, USA
- ⁹⁷NAICONS Srl, viale Ortles 22/4, 20139 Milan, Italy
- ⁹⁸Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Biosciences complex – Pavilion 02, Sciences and Technology Campus 11/A, 43124 Parma, Italy
- ⁹⁹Institute for Organic Chemistry, Leibniz Universität Hannover, Schneiderberg 38, 30167 Hannover, Germany
- ¹⁰⁰VIB-KU Leuven Center for Microbiology, Flanders Institute for Biotechnology, Kasteelpark Arenberg 31, 3001 Leuven, Belgium
- ¹⁰¹Department of Biology, Laboratory for Biomolecular Discovery & Engineering, KU Leuven, Kasteelpark Arenberg 31, 3001 Leuven, Belgium
- ¹⁰²Department of Biosystems, Biosensors Group, KU Leuven, Willem de Croylaan 42, box 2428, 3001 Leuven, Belgium
- ¹⁰³Leibniz Institute DSMZ - German Collection of Microorganisms and Cell Cultures GmbH, Inhoffenstraße 7B, 38124 Braunschweig, Germany
- ¹⁰⁴Centro de Ciencias Matemáticas National Autonomous University of Mexico (UNAM) Antigua Carretera a Pátzcuaro # 8701, Sin Nombre, Residencial San José de la Huerta, 58089 Morelia, Mich.
- ¹⁰⁵Biosphere Sciences and Engineering Division, Carnegie Institution for Science, 3520 San Martin Dr, Baltimore, MD, 21218, USA
- ¹⁰⁶Program in Chemical Biology, University of Michigan, 210 Washtenaw Avenue, Ann Arbor, MI, USA
- ¹⁰⁷Life Sciences Institute, University of Michigan, 210 Washtenaw Avenue, Ann Arbor, Michigan, USA
- ¹⁰⁸Department of Chemical and Pharmaceutical Biology, University of Groningen, Antonius Deusinglaan 1, 9713AV Groningen, The Netherlands
- ¹⁰⁹Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, China
- ¹¹⁰Department of Biomolecular Chemistry, Leibniz Institute for Natural Product Research and Infection Biology (HKI), Adolf-Reichwein-Straße 23, 07745 Jena, Germany
- ¹¹¹Institute of Infectious Disease Research, McMaster University, 1280 Main Street West, Hamilton, Ontario, L8S4L8, Canada
- ¹¹²Department of Biology, McMaster University, 1280 Main Street West, Hamilton, Ontario, L8S4K1, Canada
- ¹¹³Department of Biotechnology and Nanomedicine, SINTEF Industry, P.O.Box 4760 Torgard, N-7465 Trondheim, Norway
- ¹¹⁴Microbiology Group, Wageningen University & Research, Droevendaalsesteeg 1, 6708 PB Wageningen, The Netherlands
- ¹¹⁵Corteva Agriscience, 9330 Zionsville Road, Indianapolis, Indiana 46268, USA
- ¹¹⁶Natural Products Research Institute, College of Pharmacy, Seoul National University, 101 Daehak-ro, Jongro-gu, Seoul 110-744, Korea
- ¹¹⁷Molecular Targets Program, Center for Cancer Research, National Cancer Institute, Frederick, Maryland 21702-1201, USA
- ¹¹⁸Production Host Engineering Team, VTT Technical Research Centre of Finland Ltd, Maarintie 3, 02150 Espoo, Finland
- ¹¹⁹Department of Chemistry and Biochemistry, Laboratories of Molecular Recognition, Florida State University, 95 Chieftan Way, Tallahassee, FL 32306, USA
- ¹²⁰Department of Applied Biology, College of Agriculture and Life Sciences, Chonnam National University, 77 Yongbong-ro, Buk-gu, Gwangju, 61186, South Korea

- ¹²¹Department of Pharmacology, College of Medicine, Dongguk University, Dongdae-ro 123, Gyeongju-si, Gyeongsangbuk-do 38066, Republic of Korea
- ¹²²College of Pharmacy and Integrated Research Institute for Drug Development, Dongguk University-Seoul, Dongguk-ro 32, Goyang 10326, Republic of Korea
- ¹²³Department of Chemical and Biomolecular Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Republic of Korea
- ¹²⁴Department of Paleobiotechnology, Leibniz Institute for Natural Product Research and Infection Biology Hans Knöll Institute, Beutenbergstr. 11a, 07745 Jena, Germany
- ¹²⁵DTU Bioengineering, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark
- ¹²⁶Department of Chemical and Biomolecular Engineering, University of Delaware, Newark, DE, USA
- ¹²⁷German Centre for Infection Research (DZIF), Inhoffenstr. 7, 38124 Hannover-Braunschweig, Germany
- ¹²⁸Center of Infectious Diseases, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, Netherlands
- ¹²⁹Bioinformatics department, Endogenomiks, El Marqués, Querétaro, Mexico
- ¹³⁰U-MaMi Centre of Excellence, Middelheimlaan 1, 2020 Antwerp, Belgium
- ¹³¹Integrative Biology Research Unit, The Institute for Obesity Research, Tecnológico de Monterrey, Av. Eugenio Garza Sada 2501 sur, Nuevo Leon, 64700. México
- ¹³²School of Innovation and Sustainability, De La Salle University, Laguna Boulevard, LTI Spine Road, Brgys. Biñan and Malamig, 4024 Biñan City, Laguna, Philippines
- ¹³³Department of Chemistry, De La Salle University, 2401 Taft Avenue, 0922 Manila, Philippines
- ¹³⁴University of Strathclyde, Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow, G4 0RE UK
- ¹³⁵Department of Biotechnology and Biomedicine, Technical University of Denmark, Søtofts Plads, Building 221, 2800 Kgs. Lyngby, Denmark
- ¹³⁶Technical University of Braunschweig, Institute of Microbiology, Rebenring 56, 38106 Braunschweig, Germany
- ¹³⁷Ferrier Research Institute, Victoria University of Wellington, Kelburn Parade, Wellington 6012, New Zealand
- ¹³⁸Maurice Wilkins Centre for Molecular Biodiscovery, Victoria University of Wellington, Kelburn Parade, Wellington 6012, New Zealand
- ¹³⁹Theoretical Biology and Bioinformatics, Department of Biology, Faculty of Science, Utrecht University, 3584 CH Utrecht, The Netherlands
- ¹⁴⁰Department of Biological and Chemical Engineering, Aarhus University, Gustav Wiedes Vej 10, 8000 Aarhus C, Denmark
- ¹⁴¹Department of Life Technologies, University of Turku, Tykistökatu 6, FIN-20520 Turku, Finland
- ¹⁴²Institute of Pharmacy, Freie Universität Berlin, Königin-Luise-Str. 2+4, 14195 Berlin, Germany
- ¹⁴³Department of Genetics and Biotechnology, Ivan Franko National University of Lviv, Hrushevskoho st 4, Lviv 79005, Ukraine
- ¹⁴⁴German-Ukrainian Core of Excellence in Natural Products Research, Zelena str. 20, Lviv 79005, Ukraine
- ¹⁴⁵Environmental Genomics and Systems Biology Division, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley, CA 94720, USA
- ¹⁴⁶Centro de Investigaciones en Productos Naturales (CIPRONA), Universidad de Costa Rica, San José, 11501-2060, Costa Rica
- ¹⁴⁷Centro Nacional de Innovaciones Biotecnológicas (CENIBiot), CeNAT-CONARE, 1174-1200, San José, Costa Rica
- ¹⁴⁸Instituto de Investigaciones Farmacéuticas (INIFAR), Facultad de Farmacia, Universidad de Costa Rica, San José, 11501-2060, Costa Rica
- ¹⁴⁹Department of Microbiology and Immunology at the Doherty Institute, University of Melbourne, Grattan Street, Parkville Victoria, Victoria 3000, Australia
- ¹⁵⁰Institute of Microbiology, Eidgenössische Technische Hochschule (ETH) Zurich, Vladimir-Prelog Weg 4, 8093 Zurich, Switzerland
- ¹⁵¹Department of Plant Pathology, University of California Davis, One Shields Avenue, Davis, CA 95616-8751, USA
- ¹⁵²Department of Chemistry, Aarhus University, Langelandsgade 140, DK-8000, Aarhus C, Denmark
- ¹⁵³Institute for Molecular Systems Biology, ETH Zürich, Otto-Stern-Weg 3, 8093 Zürich, Switzerland
- ¹⁵⁴Laboratorio de Microbiología Molecular y Biotecnología Ambiental, Centro de Biotecnología DAL, Universidad Técnica Federico Santa María, Avenida España 1680, 2390123, Valparaíso, Chile
- ¹⁵⁵Department of Chemistry and BioDiscovery Institute, University of North Texas, 1155 Union Circle, Denton, Texas 76203, USA
- ¹⁵⁶Helmholtz Centre for Infection Research (HZI), Inhoffenstr. 7, 38124 Braunschweig, Germany
- ¹⁵⁷Masaryk University, Faculty of Science, RECETOX, Kamenice 753/5, 625 00 Brno, Czech Republic
- ¹⁵⁸School of Biological Sciences, University of Bristol, Life Sciences Building, 24 Tyndall Avenue, Bristol, BS8 1TQ, UK
- ¹⁵⁹School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK
- ¹⁶⁰Institute of Biotechnology, Helsinki Institute of Life Science, University of Helsinki, Viikinkaari 5, 00790, Helsinki, Finland
- ¹⁶¹Department of Chemistry, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland
- ¹⁶²Department of Biology, University of Padova, Via U. Bassi, 58/B, 35121 Padova, Italy
- ¹⁶³Botanical Garden, University of Padova, Via Orto Botanico 15, 35123 Padova, Italy
- ¹⁶⁴Department of Biological Sciences and Evolutionary Studies Initiative, Vanderbilt University, 465 21st Ave S, Nashville, TN 37232, USA
- ¹⁶⁵German Centre for Infection Research (DZIF), Partner Site Tübingen, Hoppe-Seyler-Straße 3, 72076 Tübingen, Germany
- ¹⁶⁶DE SANGOSSE, Bonnel, 47480, Pont-Du-Casse, France
- ¹⁶⁷Laboratoire de Recherche en Sciences Végétales, Université de Toulouse, CNRS, Université Toulouse III, Toulouse INP, 24 Chemin de Borde Rouge, Auzeville, 31320, Auzeville-Tolosane, France
- ¹⁶⁸Department of Biology, Laboratory for Biomolecular Discovery & Engineering, KU Leuven, Kasteelpark Arenberg 31, 3001 Leuven, Belgium
- ¹⁶⁹Institute for Microbial Biotechnology and Metagenomics, Department of Biotechnology, University of the Western Cape, Robert Sobukwe Rd, Bellville, 7535, South Africa
- ¹⁷⁰Department of Molecular Microbiology, John Innes Centre, Norwich Research Park, Norwich, NR4 7UH, United Kingdom, Norwich, UK
- ¹⁷¹The Rosalind Franklin Institute, R113 Rutherford Appleton Laboratory, Harwell Science and Innovation Campus, Didcot, Oxfordshire, OX11 0QX, UK
- ¹⁷²School of Applied Sciences, University of the West of England, Frenchay Campus, Coldharbour Lane, Bristol, BS16 1QY, UK
- ¹⁷³Department of Chemistry and Biomolecular Sciences, University of Ottawa, 10 Marie Curie Private, Ottawa, Ontario, K1N 6N5, Canada
- ¹⁷⁴Natural Products Discovery Center, The Herbert Wertheim UF Scripps Institute for Biomedical Innovation & Technology, University of Florida, Jupiter, Florida 33458, USA
- ¹⁷⁵Synthetic Biology and Enzyme Engineering Laboratory, Department of Chemical and Biological Engineering, Korea University, Anam-ro 145, Seongbuk-gu, Seoul 02841, Republic of Korea

¹⁷⁶Institute of Plant and Food Science, Department of Biology, School of Life Sciences, Southern University of Science and Technology, 1088 Xueyuan Avenue, Shenzhen 518055, P.R. China

¹⁷⁷College of Pharmaceutical Science & Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Chaowang Road 18, Hangzhou 310014, China

¹⁷⁸Institute of Chemical, Environmental and Bioscience Engineering, TU Wien, Gumpendorfer Strasse 1a, 1060 Vienna, Austria

¹⁷⁹Department of Chemistry, Simon Fraser University, 8888 University Drive, Burnaby, British Columbia, V5A 1S6, Canada

*To whom correspondence should be addressed. Email: marnix.medema@wur.nl

Correspondence may also be addressed to Tilmann Weber. Email: tiwe@biosustain.dtu.dk

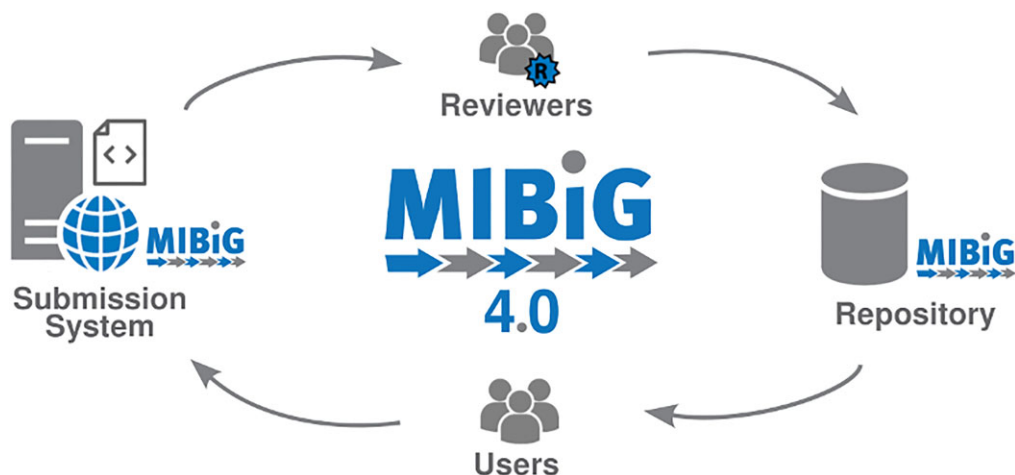
Correspondence may also be addressed to Kai Blin. Email: kblin@biosustain.dtu.dk

†The first two authors should be regarded as Joint First Authors.

Abstract

Specialized or secondary metabolites are small molecules of biological origin, often showing potent biological activities with applications in agriculture, engineering and medicine. Usually, the biosynthesis of these natural products is governed by sets of co-regulated and physically clustered genes known as biosynthetic gene clusters (BGCs). To share information about BGCs in a standardized and machine-readable way, the Minimum Information about a Biosynthetic Gene cluster (MIBiG) data standard and repository was initiated in 2015. Since its conception, MIBiG has been regularly updated to expand data coverage and remain up to date with innovations in natural product research. Here, we describe MIBiG version 4.0, an extensive update to the data repository and the underlying data standard. In a massive community annotation effort, 267 contributors performed 8304 edits, creating 557 new entries and modifying 590 existing entries, resulting in a new total of 3059 curated entries in MIBiG. Particular attention was paid to ensuring high data quality, with automated data validation using a newly developed custom submission portal prototype, paired with a novel peer-reviewing model. MIBiG 4.0 also takes steps towards a rolling release model and a broader involvement of the scientific community. MIBiG 4.0 is accessible online at <https://mibig.secondarymetabolites.org/>.

Graphical abstract



Introduction

Many organisms are prolific producers of small molecules known as specialized or secondary metabolites (SMs). These molecules often show a diversity of potent biological activities, which have been leveraged for the development of numerous drugs (1,2). SMs are generally hypothesized to increase the fitness of the producing organism or its host. In microbes, the biosynthetic genes required for the production of an SM are co-regulated and frequently physically clustered in the genome, in a so-called biosynthetic gene cluster (BGC), and often transferred horizontally (3). BGCs, which by definition consist of two or more genes, encode the proteins/enzymes used in biosynthesis, resistance and regulation of SMs and are the object of ‘genome mining’ strategies that leverage analysis of genome sequence data for the discovery of (novel) metabolites (4).

Over the last decades, various methods using manually curated detection rules based on prior knowledge (5–7), and more recently, machine learning-based tools for genome mining have been developed (8–12). These tools rely on accurately

curated and machine-readable experimental data for annotation, rule definition and training purposes. Unfortunately, machine-readable data are neither readily available from the scientific literature nor universally required by journals to be directly deposited in databases. While there are efforts to mine data from the literature using computational methods (13,14), these approaches currently often come with limitations when compared with human curators and may not be compatible with copyright laws. Therefore, manual data curation performed by researchers remains the gold standard for the generation of machine-readable data.

The largest manually curated resource on SM BGCs is the Minimum Information about a Biosynthetic Gene Cluster (MIBiG) data repository (15). Initiated in 2015 and based on the MIBiG Data Standard, it now holds over 2500 hand-curated entries of experimentally validated BGCs and their products, alongside additional information such as biological activities and gene annotations. In rare cases, a single gene may be responsible for the biosynthesis of a natural product, such as a large non-ribosomal peptide syn-

thases; these standalone genes are also entered into MIBiG due to their relevance to specialised metabolism. Conceptualized as an open data repository curated by and for the SM community, the MIBiG repository has seen three iterations of online community-driven data annotation and curation hackathons (also known as ‘annotathons’), with >250 participants from 33 countries (16,17). Despite its size, the MIBiG repository still only describes a part of the continuously growing known biosynthetic space, which motivates further efforts in curating and systemizing information on BGCs.

Here, we present version 4.0 of the MIBiG data standard and repository. Besides a thorough update of the underlying MIBiG data standard, we have substantially grown the number of available entries by initiating a large-scale community curation effort. In the first half of 2024, 267 contributors created 557 new entries and modified 590 existing entries in the scope of eight community annotathons (six general open events and two final data curation sessions with a more dedicated team). In this version of MIBiG, we focused on maintaining and further improving data quality in terms of completeness and accuracy. We encouraged contributors to fully complete entries before submission, which has significantly decreased the number of so-called minimum entries (entries with only the minimally required information) in the database. We also introduced a new peer-review model where modifications to entries are examined and approved by one or more volunteer expert reviewers, who can request corrections from data submitters. Additionally, we have established an initial prototype for efficient and standardized data submission, and during the annotathons we utilized a web interface (MIBiG Submission Portal) that allows for parallel, distributed data input featuring automated input validation. The latter refers to the tests that are performed by the submission portal itself to ensure the correct data types and formats are filled in. Together, these efforts further consolidate MIBiG as the leading database on experimentally characterized BGCs and prepare for the transition to a dynamic, rolling-release curation model.

Materials and methods

Rework of the MIBiG Data Standard

The MIBiG Data Standard (from here onwards, Data Standard) is the ‘blueprint’ of all allowed data in the MIBiG repository. It defines mandatory and optional data fields, allows the use of controlled vocabularies and automated validation and enables the organization of complex data in a consistent, human- and machine-readable way. In this update, we extensively revised the Data Standard to accommodate advances in SM research and to extend the scope and ease of (re-)use of covered (meta)data.

Literature references and evidence qualifiers

Previously, all literature references associated with a MIBiG entry were collected in a single block, making it difficult to locate the origin of specific experimental data. In this update, we reorganized the Data Standard such that each data category (e.g. biosynthetic information, compound details, etc.) has its own list of literature references. Furthermore, evidence qualifiers can be selected from a controlled vocabulary (e.g. ‘heterologous expression’) that concisely summarizes the ex-

perimental support for the claims. While newly added entries adhere to these changes, entries added in previous versions of MIBiG still follow the legacy format, and will be updated gradually over time. To summarize the data quality of an entry concisely, we also introduced a ‘Quality’ identifier, and it is possible to filter entries based on high, medium or questionable quality of data. Note that this label only reflects the presumed data quality of an MIBiG entry and does not address the quality of the underlying literature.

Biosynthesis information, multiple loci and class updates

Biosynthetic information is now organized in a ‘biosynthesis’ section, tracking biosynthetic types, modules, operons and newly introduced ‘biosynthetic path’, which allows contributors to describe cases where a single BGC can lead to multiple products or describe sub-clusters of genes that produce building blocks. The ‘multiple loci’ system has been re-introduced, allowing the specification of satellite genes or gene clusters that are involved in the biosynthesis but are not clustered with the ‘main’ BGC. Nevertheless, we still require that multiple biosynthetic genes are clustered in the same genomic region, to exclude non-clustered pathways. Furthermore, it is now possible to mark genes that are located within the boundaries of a BGC but do not partake in the biosynthesis, such as pseudo-genes or transposable elements. Additionally, we have separated biosynthetic classification from compound classification (e.g. we removed ‘alkaloid’ as a biosynthetic class) and introduced a custom biosynthesis-inspired chemical ontology for SMs (Supplementary Data 1, section 3.4) based on the work by Dewick (1). Furthermore, we have newly defined the non-ribosomal peptide synthetase Type VI (modular, non-condensation-domain peptide-bond-forming), extending the current classification (18).

Biological activity and resource integration

MIBiG also accepts additional BGC-related data. In this update, we have reworked fields registering the biological activity of BGC-associated SMs: activities are now considered properties of a specific assay, and a controlled vocabulary (Supplementary Data 1, section 3.3) is available for defining bioactivity in a reproducible way. Additionally, we have included an optional ‘Concentration’ field, allowing submission of both qualitative and quantitative bioactivity data. At the same time, additional metadata parameters increase the scope of the already extensive Data Standard, and as such MIBiG references external resources where possible. Newly introduced links include references to the Minimum Information about a Tailoring Enzyme (MITE) data repository for annotation of tailoring enzyme-encoding genes (19), and CyanoMetDB for compound information on cyanobacterial SMs (20).

Community mobilization and data curation

Inspired by the contributions made to MIBiG 3.0, we again sought participation from the scientific community. Following calls on social media, 398 researchers signed up to participate in a series of eight 3-h online annotation sessions, accommodating different time zones (Figure 1). This enormous interest posed organizational challenges in terms of coordination and communication, prompting us to develop a new model for community participation. Individual contributors

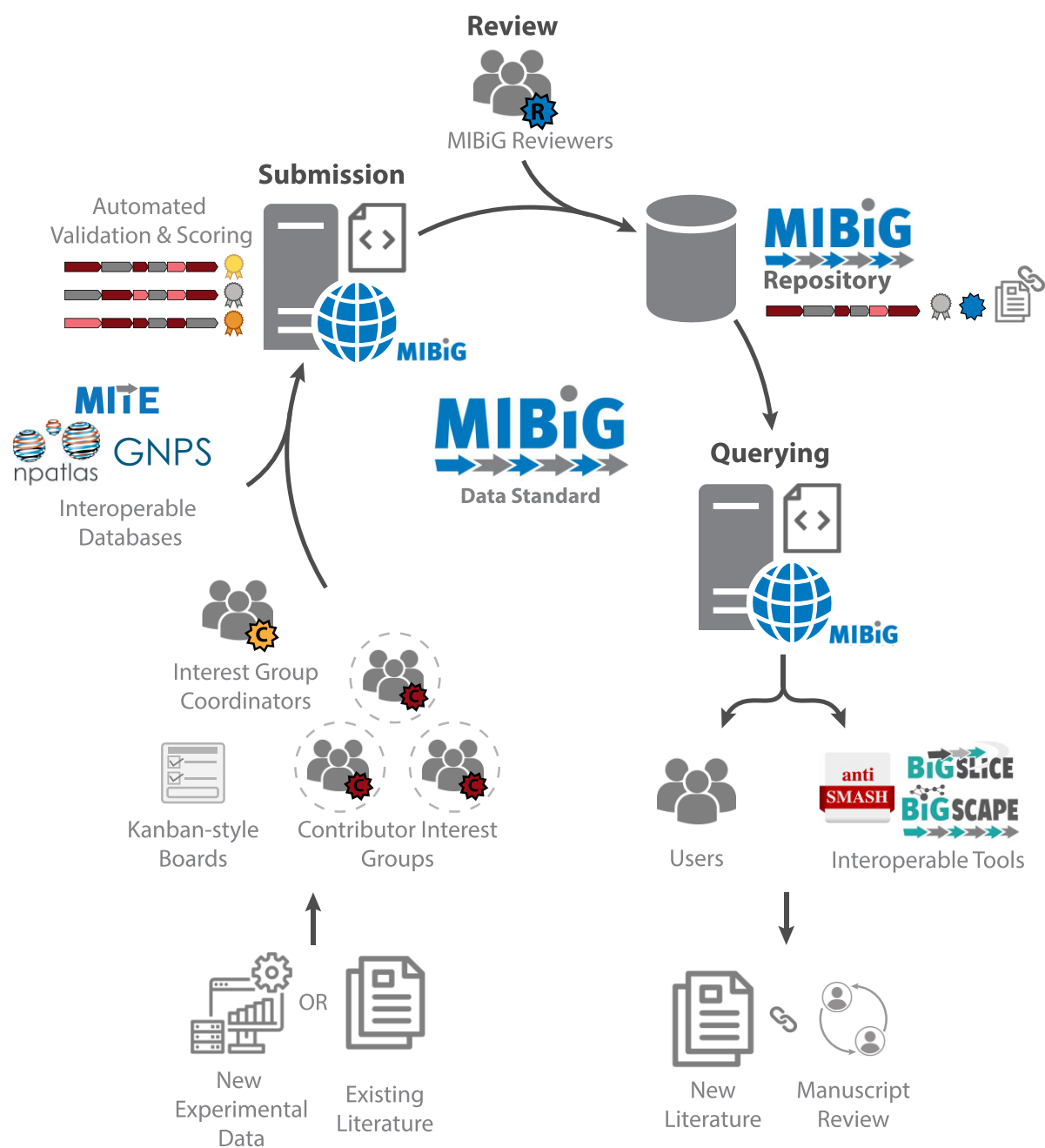


Figure 1. General workflow of the MIBiG annotation process. Data are submitted by annotation contributors (organized by expertise into Interest Groups) or independent submitters to the database from new experimental data or existing/recent literature. The entries are then assessed by reviewers and revised when needed. Finally, they end up in the online MIBiG repository and become accessible by querying them online on the MIBiG web page or via interoperable tools.

were part of one or more Interest Groups that communicated using the MIBiG Slack (<https://mibigannotations.slack.com/>) channel and were headed by Interest Group Coordinators: topic matter experts responsible for answering biosynthesis- and chemistry-related questions. Kanban-style boards (free version of Trello, <https://trello.com/>) were employed to coordinate work on entries. Data submission was performed using a MIBiG Submission Portal prototype, a bespoke web interface that uses validated fields for data processing (code available at <https://github.com/nlouwen/submission-prototype>). Several curators with relevant expertise volunteered to take Reviewer roles, focusing on assessing the quality

of newly generated or modified entries using the newly introduced peer review system. Aimed towards further improving the quality and confidence of entries, Reviewers could leverage the Kanban-style boards (Figure 2) to request revisions of entries if errors were found. To facilitate data curation, we prepared extensive online documentation (Supplementary Data 1) and instructional videos, and trained Interest Group Coordinators and Reviewers for their roles in online meetings. Participants who made a significant contribution (defined as participating in at least two 3-h sessions or an equivalent time investment) were invited to be co-authors in the present publication.

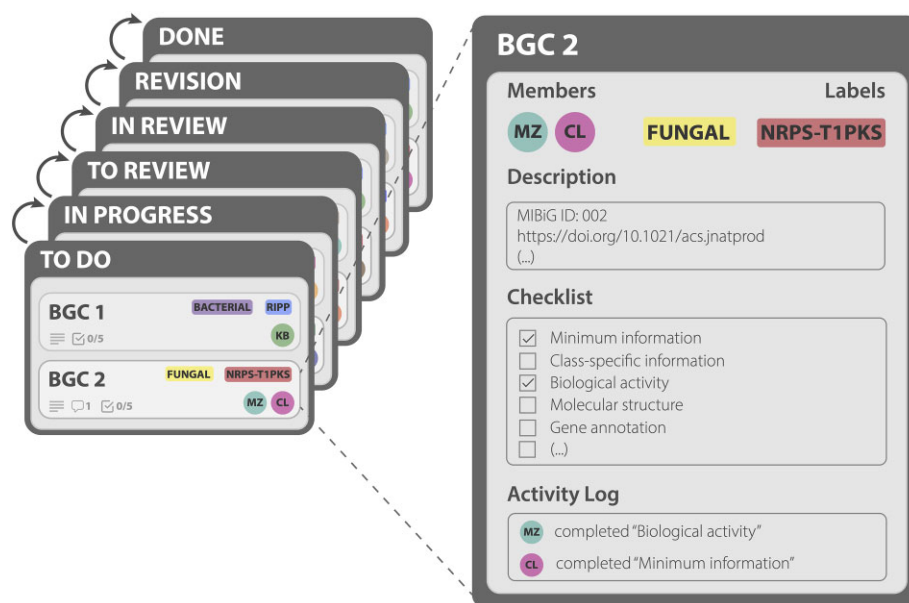


Figure 2. Architecture of the Kanban board used for the MIBiG annotations. Every BGC would have its own ‘card’, where annotators with specific expertise could fill in and then check a specific part of its annotation. Once the checklist was complete, the card would move to review and, potentially, revision to repair any issues identified by the reviewers.

Results and discussion

Advancing the MIBiG data repository

In this iteration of the MIBiG annotations, we put a greater emphasis on self-organization and facilitating motivated contributors to act independently and confidently when curating data. During the call for participation, researchers not only signed up to participate, but also contributed to assembling a list of recent publications associated with the biosynthesis of SMs. This initial effort yielded 552 publications supporting new entries and 266 publications for improvements of existing entries, which were used as a starting point for the curation process. Over the course of the annotations, 267 contributors made a total of 8304 edits (e.g. adding an entirely new entry, adding biological activity to an existing entry, etc.), resulting in 557 new and 590 modified existing entries. With the present update, MIBiG now contains a total of 3059 entries, a 22% increase in comparison to MIBiG 3.0. Of these, 1655 entries are now associated with 3604 biological activities, and 2634 entries have 5002 associated chemical structures. However, 672 entries still lack chemical structures; hence, future efforts will include attention to improving this aspect, especially with regard to structural information for ribosomally synthesized and post-translationally modified peptides. Additionally, 7677 references and 8582 evidence qualifiers were provided, 171 biosynthetic paths were described for 110 entries and cross-references to 173 MITE and 93 CyanoMetDB entries were established. A summary of the changes in comparison to MIBiG version 3.1 can be seen in Figure 3.

Of the total 1147 contributed entries (557 new, 590 modified), 464 (40%) have been reviewed at the time of manuscript preparation. While all entries are available, those that are reviewed are highlighted in the MIBiG repository website to reflect the additional confidence. For applications using the MIBiG data where a high confidence level is required (e.g. machine learning applications), we recommend the use of reviewed entries only (the website facilitates filtering/sorting on this). We expect the ‘reviewed’ part of

the MIBiG repository to grow continuously once we have transitioned to the MIBiG rolling release model, and over time, we aim to formally review all entries in the MIBiG repository.

Initiating the MIBiG rolling release model

The aforementioned efforts demonstrate the value of leveraging large community initiatives such as the MIBiG annotations. We estimate that contributors volunteered ~4000 h in curating and reviewing entries, an effort in time and expertise that could not be raised by any single research group. Besides expanding the MIBiG repository, the annotations were appreciated for their community-building aspect, fostering communication and exchange of ideas in the SM research community. In addition, the interaction with other resources prompted improvements to these databases as well, e.g. when curators could not find matching entries for a structure in the NP Atlas, thus encouraging wider cooperation beyond MIBiG itself. The broad interest of the community motivated the planning of a ‘rolling release’ model of MIBiG. In addition to the biennial efforts that will lead to ‘major’ releases of MIBiG (e.g. the current v4.0, or the next major release v5.0), curators will be able to contribute new or modify existing entries on an *ad hoc* basis, leading to quarterly ‘minor’ releases (i.e. 4.1 and 4.2). Contributors will be able to correct bugs and add references at any time, instead of waiting for the ‘major’ release cycle to perform all edits at once. This new system is currently under development, and we invite the scientific community to participate in the discussion on how to structure contributions and governance (i.e. by communicating with the corresponding authors of this publication or using the MIBiG Slack Workspace <https://mibigannotations.slack.com>). Furthermore, to facilitate future MIBiG updates and curation we encourage authors to release BGC sequence data during the publication submission and peer review process, or immediately thereafter, and to provide the respective accession details in the manuscript text.

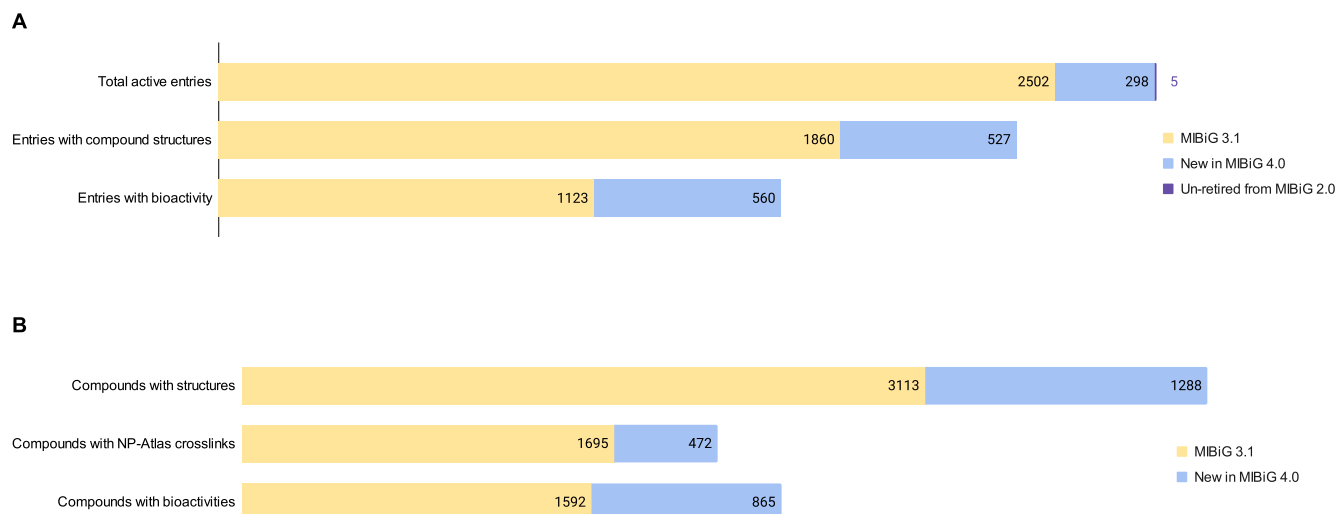


Figure 3. Quantitative overview of updates to the MIBiG database in comparison with the previous version 3.1. Numbers in panel (a) refer to MIBiG entries, while numbers in panel (b) refer to individual compounds (a single MIBiG entry may contain more than one compound).

In summary, we have conducted a large-scale community effort to make experimental data on SM BGCs freely accessible and machine-readable. As a resource created for and by the scientific community, the MIBiG repository is freely accessed on an entry-by-entry basis or can be downloaded and parsed in bulk. MIBiG 4.0 also serves as the stepping stone for creating the infrastructure to establish a Wikipedia-like model of continuous community curation. Such a decentralized organization will guarantee continuous development of MIBiG and help in including the next generations of scientists in the annotation and development process.

Data availability

The MIBiG repository is available at <https://mibig.secondarymetabolites.org/>. Files in JSON format following the MIBiG data standard (<https://github.com/mibig-secmet/mibig-json>) can be found on the MIBiG webpage (<https://mibig.secondarymetabolites.org/download>) and on the MIBiG Zenodo Community page (<https://doi.org/10.5281/zenodo.13367755>). Further materials are available on GitHub (<https://github.com/mibig-secmet>). All data are freely available with no restrictions for academic and commercial reuse under the OSI-approved CC BY 4.0 Open Source license (<https://creativecommons.org/licenses/by/4.0/>).

Supplementary data

Supplementary Data are available at NAR Online.

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Conflict of interest statement

J.H. and C.S.M. are employees of Corteva Agriscience. B.R.T. is a consultant for BioConsortia Inc. J.J.J.vdH. is member of the Scientific Advisory Board of NAICONS Srl, Milano, Italy and consults for Corteva Agriscience, Indianapolis, IN, USA. M.H.M. is a member of the Scientific Advisory Board of Hexagon Bio.

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