MADET: A Manually Curated Knowledgebase for Microbiomic Effects on Efficacy and Toxicity of Anticancer Treatments

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Abstract

A plethora of studies have reported the associations between microbiota and multiple diseases, leading to at least four databases to demonstrate microbiota-disease associations, i.e., gutMDisorder, mBodyMap, GMrepo and Amadis. Moreover, gut microbiota also mediates drug efficacy and toxicity, whereas a comprehensive database to elucidate the microbiota-drug associations is lacking. Here we report an open-access knowledgebase, MADET (Microbiomics of Anticancer Drug Efficacy and Toxicity), which harbors 453 manually annotated microbiota-drug associations from 24 papers. MADET provides user-friendly functions allowing users to freely browse, search, and download the data conveniently from the database. Users can customize their search filters in MADET using different types of keywords, including bacterial name (e.g., *Akkermansia muciniphila*), anticancer treatment (e.g., anti-PD-1 therapy) or cancer type (e.g., lung cancer) with different types of experimental evidence of microbiota-drug association and causation. We have also enabled user submission to further enrich the data document in MADET. The MADET database is freely available at https://www.madet.info. We anticipate that MADET will serve as a useful resource for a better understanding of the microbiota-drug associations and facilitate the future development of novel biomarkers and live biotherapeutic products for anticancer therapies.

Keywords: database, microbiota, anticancer treatment, efficacy, toxicity.

1. Introduction

Gut microbiota plays an important role in carcinogenesis and cancer treatment outcomes [1, 2]. Bacteria including *Helicobacter pylori* [3], *Fusobacterium nucleatum* [4], *Peptostreptococcus anaerobius* [5], enterotoxigenic *Bacteroides fragilis* [6], polyketide synthase-positive (*pks*$^+$) *Escherichia coli* [7], and *Campylobacter jejuni* [8], have been reported to contribute to carcinogenesis and tumor development via releasing toxins and activating procarcinogenic signaling pathways [1, 2, 4]. On the other hand, microbes including *Lactobacillus reuteri* [9], *Lactobacillus gallinarum* [10], and *Streptococcus thermophilus* [11] are reported to suppress tumorigenesis and cancer progression via multiple pathways, such as inhibiting the metabolism of tumor proliferation [11]. To date, several databases have been constructed to document these positive or negative associations between gut microbiota and tumor development, such as mBodyMap [12], gutMDisorder [13], GMrepo [14], and Amadis [15]. However, the important effects of microbiota on the efficacy and toxicity of anticancer drugs are not systematically documented.

Gut microbiota modulates the efficacy and toxicity of anticancer drugs through multiple mechanisms including immunomodulation, metabolism, and enzymatic degradation [16]. Notably, the efficacy of immunotherapies (e.g., anti-PD-1 therapy) in cancer patients is positively associated with the abundance of some specific bacterial species (e.g., *Akkermansia muciniphila* [17], *Bacteroides fragilis* and *Bifidobacterium longum* [18]). These commensal gut microbes may reinforce the efficacy of immune checkpoint inhibitors (ICIs) via regulation of the host immune responses (such as increased level of CD4$^+$ T cells and/or CD8$^+$ T cells in the tumor microenvironment) [17, 19]. Several live biotherapeutic products are under development for their synergistic anticancer effects with immunotherapies, and the clinical trials based on these bacterial products are ongoing, including CBM588 (a *Clostridium butyricum* strain) for treating advanced kidney cancer [20]. Moreover, toxicities of anticancer treatments are impacted by gut microbiota. For example, chemotherapeutic agent

irinotecan may be metabolized by gut bacterial β-glucuronidase (which can be found in four major bacterial phyla: Bacteroidetes, Firmicutes, Verrucomicrobia, and Proteobacteria) into its toxic form SN-38, and therefore may inflict toxicity in the gastrointestinal tract, such as epithelial damage and diarrhea [21]. Another example is that immune-related adverse effect (irAE) of ICI therapy, most commonly colitis, has been reported to be associated with the abundance of the Bacteroidetes phylum in the human gut [22]. In a nutshell, microbiota could be employed as a potential biomarker for predicting treatment outcomes and an interventional target for improving the effectiveness of cancer therapies. We therefore argue that with the accumulating evidence of the important roles of microbiota in anticancer treatments, including chemotherapeutic agents, radiotherapy and immunotherapies, it is urgent to develop an open-access and user-friendly knowledgebase to allow for documenting, retrieving and sharing experimental data of these microbiotas and their effects on the efficacy and toxicity of anticancer drugs.

To this end, in this study we implement a knowledgebase, termed MADET (Microbiomics of Anticancer Drug Efficacy and Toxicity; freely available at https://www.madet.info), to provide the most up-to-date manual curation of reports on the interplays between microbiota and anticancer drugs for the researchers in microbiology, pharmacology and other related areas (**Figure 1**). To the best of our knowledge, MADET is the first database providing experimental evidence of associations between microbiota and anticancer drugs with user-friendly functionalities, including data download and flexible keyword search with bacterial name, treatment, or cancer type. We anticipate MADET will serve as a steppingstone for the development of novel microbiomic biomarkers for predicting the outcome of anticancer drugs and live biotherapeutic products for improving the outcome of anticancer drugs.

2. Methods

2.1. Data collection

To collect the state-of-the-art scientific reports on pharmacomicrobiomics of anticancer drugs, we searched the literature using the keywords "microbiome" and "cancer treatment (e.g., 5-FU, anti-PD-1 or radiotherapy, etc)" on PubMed and extracted 24 published papers involving how the composition of microbiota is associated with the efficacy and toxicity of anticancer drugs. Fourteen of the 24 papers focused on the associations between microbiota and ICIs, and six papers examined the effects on chemotherapeutic agents and their combinations (**Figure 2A**). We further included four publications on cancer radiotherapy studies, given the fact that radiotherapy has been widely applied to cancer treatment. In total, 453 associations between microbiota and drug outcome have been manually identified and recorded in MADET.

We also analyzed our collected studies based on the cancer type and the country where the research was conducted (**Figure 2BC**). Melanoma and gastrointestinal cancers attracted major attention from anti-cancer pharmacomicrobiomics researchers, which comprise 7 and 6 papers, respectively. We further set up several criteria in terms of experimental types for categorizing the collected 453 microbiota-drug associations: "Limited" (only with animal data); "Moderate" (clinical observation of association); "Relatively strong" (clinical observation of association and experimental validation of causation using animal model); and "Strong" (clinical observation of association and validated of causation by clinical trial). Among those, the majority (413 associations) have a "Moderate" strength of evidence (**Figure 2D**). Only one association was labeled as "Strong": a *Clostridium butyricum* strain CBM 588 increases the effect of immunotherapy (nivolumab and ipilimumab) in treating patients with kidney cancer, which was validated by a Phase 1 clinical trial [20].

2.2. MADET construction

MADET was developed and implemented utilizing widely applied open-source packages including Vue (front-end), Spring Boot and MyBaits (back-end), and MySQL (relational database design), to provide reliable delivery of a complex scalable web application (**Figure 1**). The modern and separate front-end/back-end architecture of MADET allows collaboration between developers with different specializations and simplifies the upgrading process for future improvement. The main proxy uses a high-performance Nginx server (https://www.nginx.com) to communicate between the front-end and the back-end programs. The front-end of MADET was constructed with a commercial-used open-source Vue.js framework (https://vuejs.org) and Element UI Toolkit (https://element.eleme.io) for the design of a professional user interface experience design. The back-end of MADET has been designed to be a microservice architecture software, which is facilitated by Java Spring Boot (https://spring.io/projects/spring-boot). The microservice architecture implemented three independent functions modules (services), i.e., the search, browse, and upload services. This highly modular architecture allows MADET to provide software as a service (SaaS) and the possibility of turning MADET into a mobile app and adding new services in the future. The actual data stored in MySQL (sql) can be easily converted to other data formats such as xlsx (Microsoft Excel) and csv (comma separated values). The MADET website resides on Tencent Cloud to leverage the burden of various website configurations and security measures while preserving full control of the web application and data integrity to MADET developers.

3. MADET utilities

MADET provides four major functionalities, including database browsing, searching, downloading and user submission with a user-friendly interface (**Figure 3**). The *Homepage* contains two sections. The top section provides a brief introduction to the MADET database and the generic statistical information, such as treatment and

cancer type, of the current MADET version using interactive pie charts. Users can click on each pie chart to be redirected to corresponding result pages. For example, if "China" from the pie chart is clicked, MADET will show filtered search results that contain studies conducted in China. The Browse page enables users to view all data available on MADET and allows users to set customized filters to shortlist the results. Each MADET entry contains twelve columns, including Bacterium, Treatment, Potential effects on efficacy, Potential effects on toxicity, Cancer type and Reference, Treatment, Potential effects on efficacy, Potential effects on toxicity, and Cancer type. All selected data will be displayed as a table. Several column headers are provided with an arrow, clicking on which will show a drop-down menu of subcategories will appear for users to narrow down the results. The filter will auto-apply when a new attribute is selected, and the table will auto-refresh to display the filtered results. Multiple subcategories from different attributes can be selected at the time for customized filters. If the number of entries exceeds the limit on one page, users can click the pages button at the bottom of the table to scroll through the data. Searches on microbiota-drug interactions of interest is straightforward. Three types of searching are available on the "Search" page, including "Bacterium", "Treatment", and "Cancer type". After obtaining the desired keywords provided by the user, the search engines will only search the database entries with the provided keywords. We have also provided default keyword for each search type. Users can simply click the "Search" button to see the results extracted using the default keywords. The search results are displayed as a table similar to the table on the Browse page. A drop-down menu is provided from "Treatment" and "Cancer type", respectively, to narrow down the search results of interest. MADET allows users to download its data for high-throughput or computational analysis. Users can download the sql (MySQL) or xlsx format of the data collected by MADET through the download page. To further enrich the data documented in MADET, we have enabled users to submit their own research data via our submission function on the "Upload" page. We request the users to describe the information that should be covered in our database in

detail, including treatment, bacterium and cancer type. The submitted data will be manually reviewed by the MADET team prior to data publishing in the database. The users will be contacted if more clarification is needed via their name and email address provided during data submission. We will confirm with the users once their data has been accepted for publishing in the MADET database.

4. Case study

Some interesting findings involving microbiota-drug associations can be discovered using our MADET database. First, certain bacterial species may exert opposite effects on modulating the efficacy of different drugs. For instance, by searching MADET with the keyword "*Fusobacterium nucleatum*", we are able to see that the bacterial species *F. nucleatum* is negatively associated with the decreased anticancer effects of 5-FU chemotherapy for colorectal cancer [23] as well as positively related to the promoted efficacy of PD-L1 blockade on the other hand [19]. This suggests that a comprehensive evaluation may be needed prior to the administration of next-generation probiotics targeting microbiota-drug association.

Second, even for the same anticancer drug, we found that same bacterial species showed opposite potential effects against different cancer type or across different countries. For example, searching "*Roseburia intestinalis*" in MADET showed this species is positively associated with the efficacy of immune checkpoint inhibitor (ICI) therapy in patients with lung cancer in France [24], whereas *R. intestinalis* was reported to be negatively associated with the efficacy of ICI therapies in melanoma patients in the USA [18]. Similar results on *Parabacteroides distasonis*, *Lactobacillus vaginalis*, and *Eubacterium hallii* can be unveiled through searches in MADET with relevant keywords. These findings highlight that the factors including cancer types, geographic locations and analytical methods may affect the conclusion of microbiomic effect on anticancer drugs. Moreover, the functional differences may be strain dependent, i.e., heterogeneous bacterial strains within the same species may have opposite functions on

drug outcome. Thus, MADET provides a valuable platform to summarize and analyze the precise mechanism of the observed microbiota-drug associations demonstrated in the current literature.

5. Conclusion

With the rapid expansion of our knowledge of gut microbiota during the past decade, multiple bacterial species have been identified as promising candidates for biomarkers of drug susceptibility and live biotherapeutic products for improving drug outcomes. By manually curating 453 associations between microbiota and anticancer drugs with a variety of factors including bacterial species, treatment, cancer type and strength of evidence, the MADET database provides the first comprehensive knowledgebase of the associations between microbiota and anticancer therapeutic outcomes. Users utilize MADET to examine the up-to-date microbiota-drug associations of their bacterium/drug of interest, to advance the generation of novel research hypotheses. MADET will keep evolving with the new data provided by the novel studies on microbiota-drug associations. We anticipate that MADET will serve as a convenient platform for facilitating pharmacomicrobiomics research, including the development of novel biomarkers for predicting drug outcomes as well as novel live biotherapeutic products for improving the outcomes of anticancer drugs.

Data availability: The MADET database is freely available at https://www.madet.info. Any code or other data related this work will be available upon reasonable request.

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References

[1] N.L. Ting, H.C. Lau, J. Yu, Cancer pharmacomicrobiomics: targeting microbiota to optimise cancer therapy outcomes, Gut (2022) 1-14.

[2] S.L. Clay, D. Fonseca-Pereira, W.S. Garrett, Colorectal cancer: the facts in the case of the microbiota, J Clin Invest 132(4) (2022) 1-10.

[3] L. Cao, S. Zhu, H. Lu, M. Soutto, N. Bhat, Z. Chen, D. Peng, J. Lin, J. Lu, P. Li, C. Zheng, C. Huang, W. El-Rifai, *Helicobacter pylori*-induced RASAL2 through activation of nuclear factor-kappab promotes gastric tumorigenesis via beta-catenin signaling axis, Gastroenterology 162(6) (2022) 1716-1731 e17.

[4] M. Castellarin, R.L. Warren, J.D. Freeman, L. Dreolini, M. Krzywinski, J. Strauss, R. Barnes, P. Watson, E. Allen-Vercoe, R.A. Moore, R.A. Holt, *Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma, Genome Res 22(2) (2012) 299-306.

[5] X. Long, C.C. Wong, L. Tong, E.S.H. Chu, C. Ho Szeto, M.Y.Y. Go, O.O. Coker, A.W.H. Chan, F.K.L. Chan, J.J.Y. Sung, J. Yu, *Peptostreptococcus anaerobius* promotes colorectal carcinogenesis and modulates tumour immunity, Nat Microbiol 4(12) (2019) 2319-2330.

[6] L. Chung, E. Thiele Orberg, A.L. Geis, J.L. Chan, K. Fu, C.E. DeStefano Shields, C.M. Dejea, P. Fathi, J. Chen, B.B. Finard, A.J. Tam, F. McAllister, H. Fan, X. Wu, S. Ganguly, A. Lebid, P. Metz, S.W. Van Meerbeke, D.L. Huso, E.C. Wick, D.M. Pardoll, F. Wan, S. Wu, C.L. Sears, F. Housseau, *Bacteroides fragilis* toxin coordinates a pro-carcinogenic inflammatory cascade via targeting of colonic epithelial cells, Cell Host Microbe 23(2) (2018) 203-214 e5.

[7] C. Pleguezuelos-Manzano, J. Puschhof, A. Rosendahl Huber, A. van Hoeck, H.M. Wood, J. Nomburg, C. Gurjao, F. Manders, G. Dalmasso, P.B. Stege, F.L. Paganelli, M.H. Geurts, J. Beumer, T. Mizutani, Y. Miao, R. van der Linden, S. van der Elst, C. Genomics England Research, K.C. Garcia, J. Top, R.J.L. Willems, M. Giannakis, R. Bonnet, P. Quirke, M. Meyerson, E. Cuppen, R. van Boxtel, H. Clevers, Mutational signature in colorectal cancer caused by genotoxic *pks*(+) *E. coli*, Nature 580(7802) (2020) 269-273.

[8] Z. He, R.Z. Gharaibeh, R.C. Newsome, J.L. Pope, M.W. Dougherty, S. Tomkovich, B. Pons, G. Mirey, J. Vignard, D.R. Hendrixson, C. Jobin, *Campylobacter jejuni* promotes colorectal tumorigenesis through the action of cytolethal distending toxin, Gut 68(2) (2019) 289-300.

[9] H.N. Bell, R.J. Rebernick, J. Goyert, R. Singhal, M. Kuljanin, S.A. Kerk, W. Huang, N.K. Das, A. Andren, S. Solanki, S.L. Miller, P.K. Todd, E.R. Fearon, C.A. Lyssiotis, S.P. Gygi, J.D. Mancias, Y.M. Shah, Reuterin in the healthy gut microbiome suppresses colorectal cancer growth through altering redox balance, Cancer Cell 40(2) (2022) 185-200 e6.

[10] N. Sugimura, Q. Li, E.S.H. Chu, H.C.H. Lau, W. Fong, W. Liu, C. Liang, G. Nakatsu, A.C.Y. Su, O.O. Coker, W.K.K. Wu, F.K.L. Chan, J. Yu, *Lactobacillus gallinarum* modulates the gut microbiota and produces anti-cancer metabolites to protect against colorectal tumourigenesis, Gut (2021).

[11] Q. Li, W. Hu, W.X. Liu, L.Y. Zhao, D. Huang, X.D. Liu, H. Chan, Y. Zhang, J.D. Zeng, O.O. Coker, W. Kang, S.S.M. Ng, L. Zhang, S.H. Wong, T. Gin, M.T.V. Chan, J.L. Wu, J. Yu, W.K.K. Wu, *Streptococcus thermophilus* inhibits colorectal tumorigenesis through secreting beta-galactosidase, Gastroenterology 160(4) (2021) 1179-1193 e14.

[12] H. Jin, G. Hu, C. Sun, Y. Duan, Z. Zhang, Z. Liu, X.M. Zhao, W.H. Chen, mBodyMap: a curated database for microbes across human body and their associations with health and diseases, Nucleic Acids Res 50(D1) (2022) D808-D816.

[13] L. Cheng, C. Qi, H. Zhuang, T. Fu, X. Zhang, gutMDisorder: a comprehensive database for dysbiosis of the gut microbiota in disorders and interventions, Nucleic Acids Res 48(D1) (2020) D554-D560.

[14] S. Wu, C. Sun, Y. Li, T. Wang, L. Jia, S. Lai, Y. Yang, P. Luo, D. Dai, Y.Q. Yang, Q. Luo, N.L. Gao, K. Ning, L.J. He, X.M. Zhao, W.H. Chen, GMrepo: a database of curated and consistently annotated human gut metagenomes, Nucleic Acids Res 48(D1) (2020) D545-D553.

[15] L. Li, Q. Jing, S. Yan, X. Liu, Y. Sun, D. Zhu, D. Wang, C. Hao, D. Xue, Amadis: A comprehensive database for association between microbiota and disease, Front Physiol 12 (2021) 697059.

[16] S. Roy, G. Trinchieri, Microbiota: a key orchestrator of cancer therapy, Nat Rev Cancer 17(5) (2017) 271-285.

[17] B. Routy, E. Le Chatelier, L. Derosa, C.P.M. Duong, M.T. Alou, R. Daillere, A. Fluckiger, M. Messaoudene, C. Rauber, M.P. Roberti, M. Fidelle, C. Flament, V. Poirier-Colame, P. Opolon, C. Klein, K. Iribarren, L. Mondragon, N. Jacquelot, B. Qu, G. Ferrere, C. Clemenson, L. Mezquita, J.R. Masip, C. Naltet, S. Brosseau, C. Kaderbhai, C. Richard, H. Rizvi, F. Levenez, N. Galleron, B. Quinquis, N. Pons, B. Ryffel, V. Minard-Colin, P. Gonin, J.C. Soria, E. Deutsch, Y. Loriot, F. Ghiringhelli, G. Zalcman, F. Goldwasser, B. Escudier, M.D. Hellmann, A. Eggermont, D. Raoult, L. Albiges, G. Kroemer, L. Zitvogel, Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors, Science 359(6371) (2018) 91-97.

[18] V. Matson, J. Fessler, R. Bao, T. Chongsuwat, Y. Zha, M.L. Alegre, J.J. Luke, T.F. Gajewski, The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients, Science 359(6371) (2018) 104-108.

[19] Y. Gao, D. Bi, R. Xie, M. Li, J. Guo, H. Liu, X. Guo, J. Fang, T. Ding, H. Zhu, Y. Cao, M. Xing, J. Zheng, Q. Xu, Q. Xu, Q. Wei, H. Qin, *Fusobacterium nucleatum* enhances the efficacy of PD-L1 blockade in colorectal cancer, Signal Transduct Target Ther 6(1) (2021) 398.

[20] N. Dizman, L. Meza, P. Bergerot, M. Alcantara, T. Dorff, Y. Lyou, P. Frankel, Y. Cui, V. Mira, M. Llamas, J. Hsu, Z. Zengin, N. Salgia, S. Salgia, J. Malhotra, N. Chawla,

A. Chehrazi-Raffle, R. Muddasani, J. Gillece, L. Reining, J. Trent, M. Takahashi, K. Oka, S. Higashi, M. Kortylewski, S.K. Highlander, S.K. Pal, Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial, Nat Med 28(4) (2022) 704-712.

[21] R.M. Pollet, E.H. D"Agostino, W.G. Walton, Y. Xu, M.S. Little, K.A. Biernat, S.J. Pellock, L.M. Patterson, B.C. Creekmore, H.N. Isenberg, R.R. Bahethi, A.P. Bhatt, J. Liu, R.Z. Gharaibeh, M.R. Redinbo, An Atlas of beta-glucuronidases in the human intestinal microbiome, Structure 25(7) (2017) 967-977 e5.

[22] K. Dubin, M.K. Callahan, B. Ren, R. Khanin, A. Viale, L. Ling, D. No, A. Gobourne, E. Littmann, C. Huttenhower, E.G. Pamer, J.D. Wolchok, Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis, Nat Commun 7 (2016) 10391.

[23] T. Yu, F. Guo, Y. Yu, T. Sun, D. Ma, J. Han, Y. Qian, I. Kryczek, D. Sun, N. Nagarsheth, Y. Chen, H. Chen, J. Hong, W. Zou, J.Y. Fang, *Fusobacterium nucleatum* promotes chemoresistance to colorectal cancer by modulating autophagy, Cell 170(3) (2017) 548-563 e16.

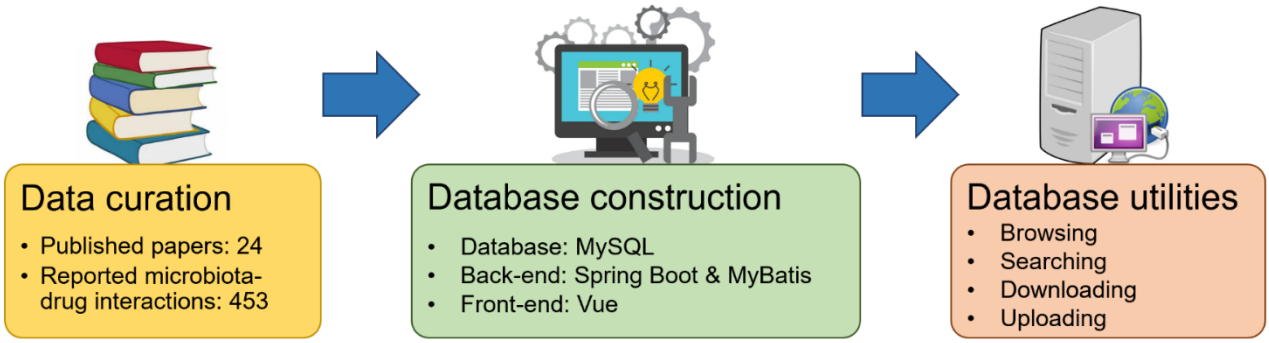
[24] L. Derosa, B. Routy, A.M. Thomas, V. Iebba, G. Zalcman, S. Friard, J. Mazieres, C. Audigier-Valette, D. Moro-Sibilot, F. Goldwasser, C.A.C. Silva, S. Terrisse, M. Bonvalet, A. Scherpereel, H. Pegliasco, C. Richard, F. Ghiringhelli, A. Elkrief, A. Desilets, F. Blanc-Durand, F. Cumbo, A. Blanco, R. Boidot, S. Chevrier, R. Daillere, G. Kroemer, L. Alla, N. Pons, E. Le Chatelier, N. Galleron, H. Roume, A. Dubuisson, N. Bouchard, M. Messaoudene, D. Drubay, E. Deutsch, F. Barlesi, D. Planchard, N. Segata, S. Martinez, L. Zitvogel, J.C. Soria, B. Besse, Intestinal *Akkermansia muciniphila* predicts clinical response to PD-1 blockade in patients with advanced non-small-cell lung cancer, Nat Med 28(2) (2022) 315-324.

Figure captions

Figure 1. The framework of MADET, including data curation, database construction and utilities.

Figure 2. Statistics of curated studies for microbiota-drug associations. The collected studies have been categorized by (A) treatment approaches, (B) cancer types (one study recruited both kidney cancer patients and lung cancer patients), (C) countries where the study was conducted, and (D) the strength of evidence.

Figure 3. Major functions provided in MADET, including browsing, searching, downloading, and uploading.



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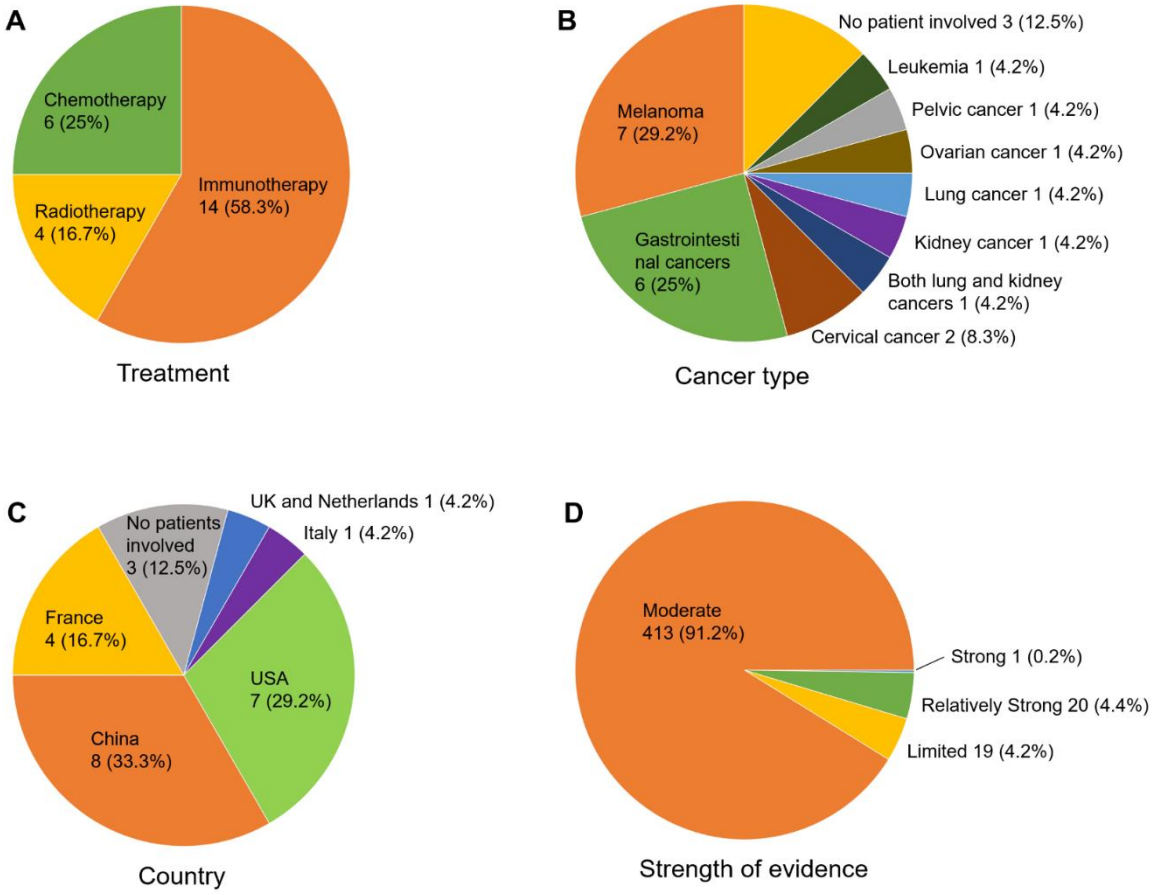

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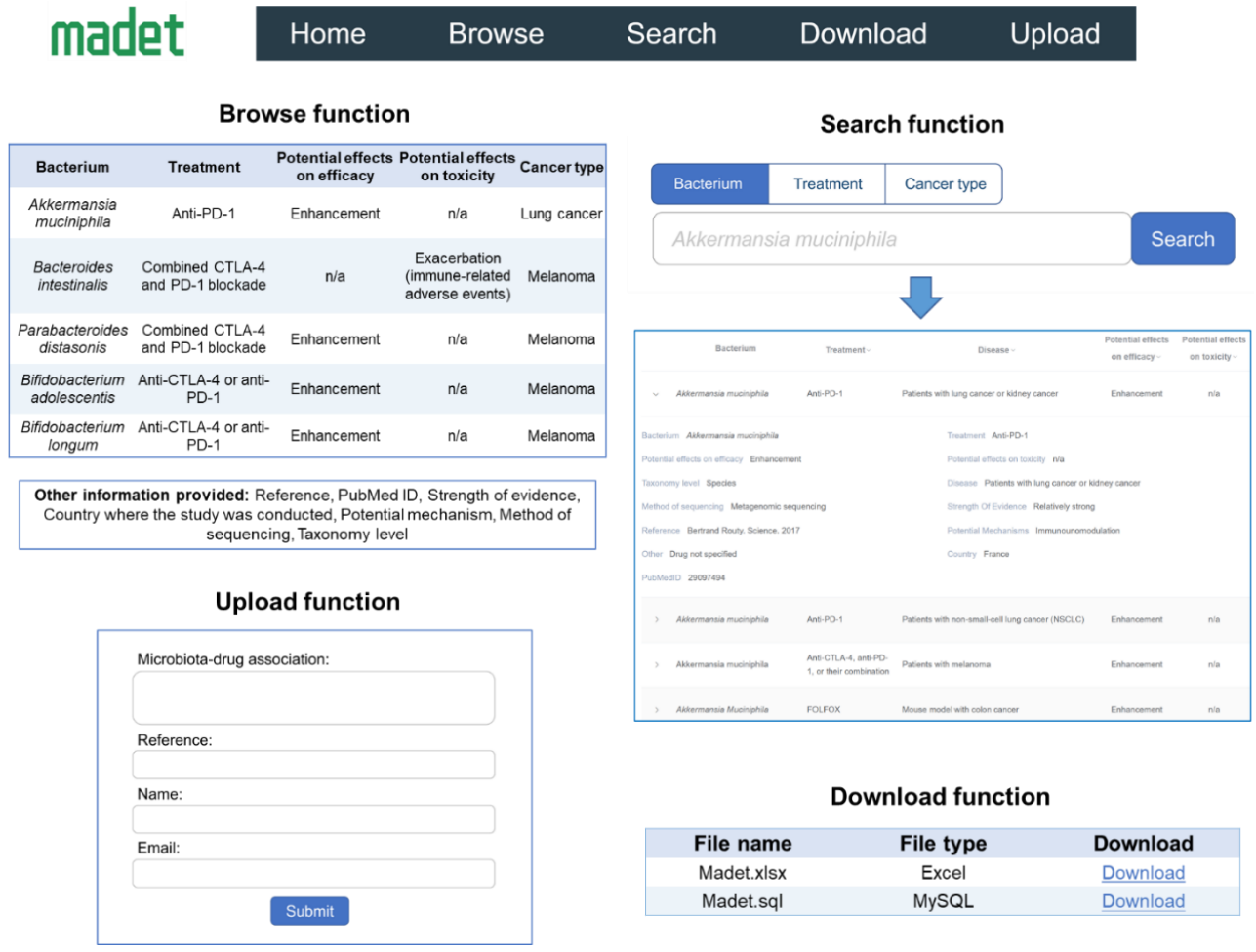


1

Data curation

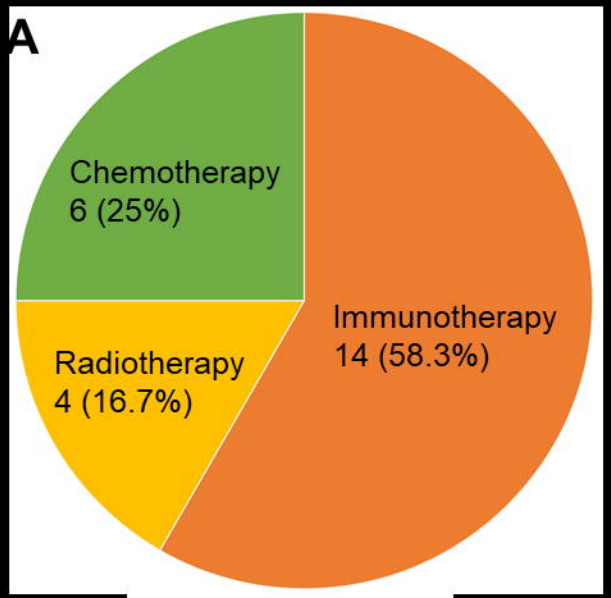
- Published papers: 24
- Reported microbiota-drug interactions: 453

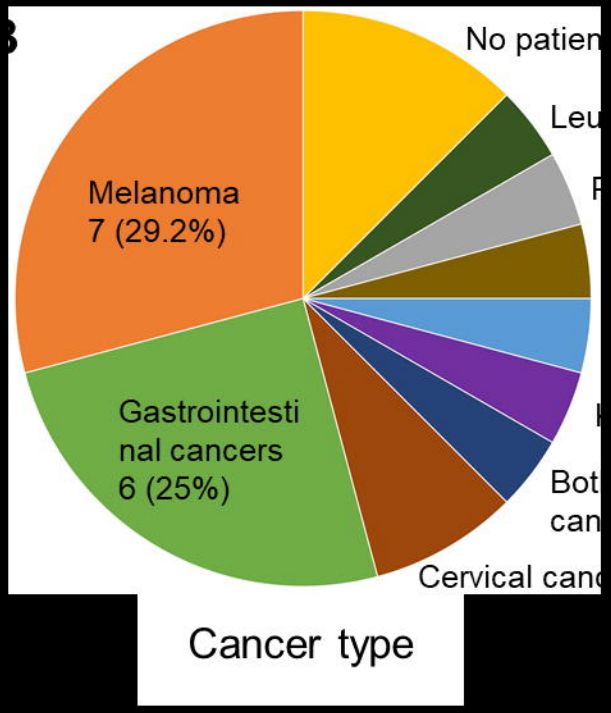
Database construction

- Database: MySQL
- Back-end: Spring Boot & MyBatis
- Front-end: Vue

Database utilities

- Browsing
- Searching
- Downloading
- Uploading


A
Chemotherapy
6 (25%)
Immunotherapy
14 (58.3%)
Radiotherapy
4 (16.7%)
Treatment


No patien
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7 (29.2%)
Gastrointesti
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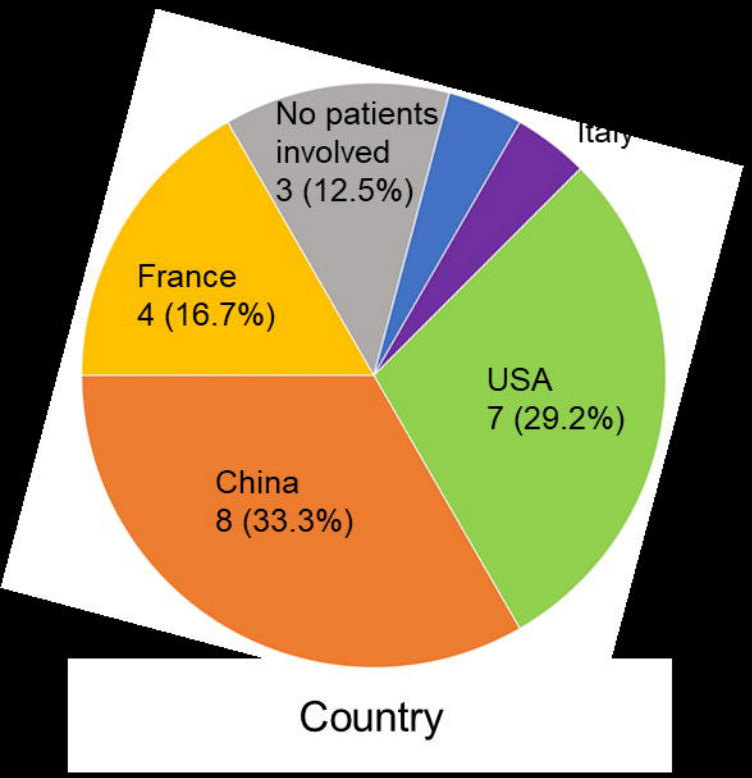
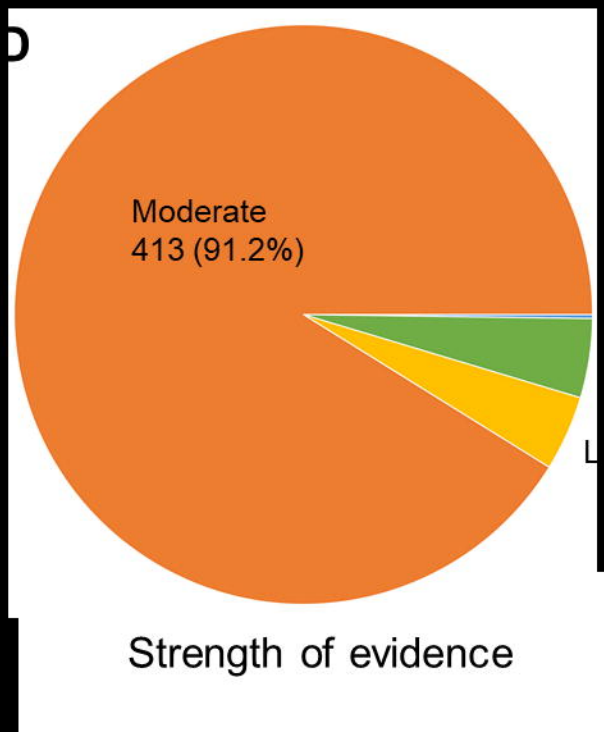
6 (25%)
Bot
can
Cervical canc
Cancer type


No patients
involved
3 (12.5%)
France
4 (16.7%)
USA
7 (29.2%)
China
8 (33.3%)
Country


D
Moderate
413 (91.2%)
Strength of evidence

madet

Home Browse Search Download Upload

Bacterium	Treatment	Potential effects on efficacy	Potential effects on toxicity	Cancer type
Bacteroides intestinalis	Combined CTLA-4 and PD-1 blockade	n/a	Exacerbation (immune-related adverse events)	Melanoma
Bifidobacterium adolescentis	Anti-CTLA-4 or anti-PD-1	Enhancement	n/a	Melanoma

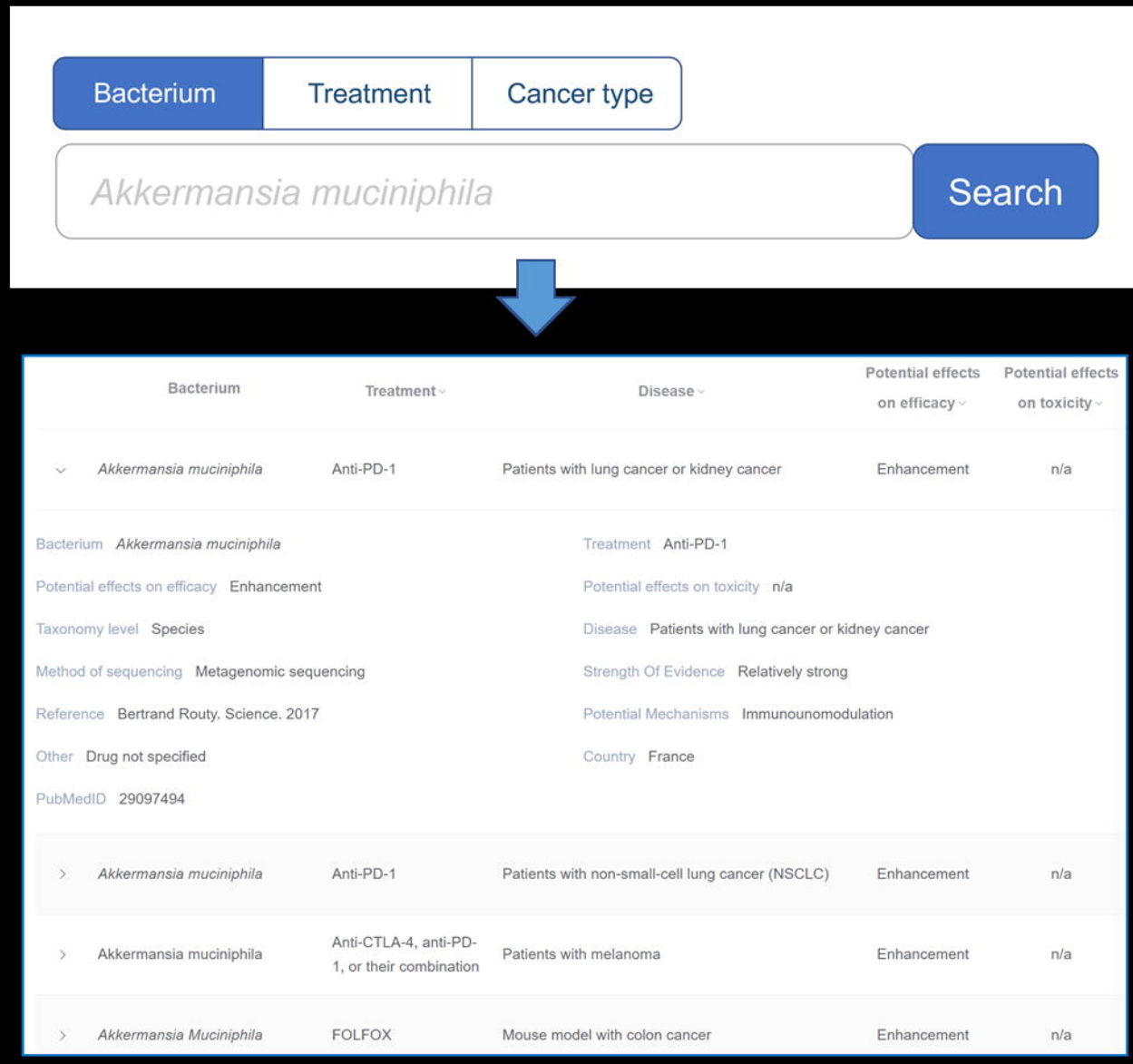
Microbiota-drug association:

Reference:

Name:

Email:

Submit



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