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BuDb: A Curated Drug Discovery Database for Buruli Ulcer

Samuel K. Kwofie[*,‡,††], Daniel Tweneboah Anyimadu[*], Solomon Aryee[*], Blessing Asare[*], Natalie Kokroko[*], Jeffrey A. Owusu[*], Baron Afutu[†], Odame Agyapong[*], Lydia Mosi[‡], Edwin Kyei-Baffour[‡], Kweku S. Enninful[§], Clement Agoni[¶,**] and Michael D. Wilson[§,||]

[*]*Department of Biomedical Engineering, School of Engineering Sciences, College of Basic & Applied Sciences, University of Ghana, PMB LG 77, Legon, Accra, Ghana*

[†]*Department of Computer Engineering, University of Ghana, Legon, Accra, Ghana*

[‡]*West African Centre for Cell Biology of Infectious Pathogens, Department of Biochemistry, Cell and Molecular Biology, College of Basic and Applied Sciences, University of Ghana, Accra, Ghana*

[§]*Department of Parasitology, Noguchi Memorial Institute for Medical Research (NMIMR), College of Health Sciences (CHS), University of Ghana, P.O. Box LG 581, Legon, Accra, Ghana*

[¶]*Conway Institute of Biomolecular and Biomedical Research, School of Medicine, University College of Dublin, Belfield, Dublin 4, Ireland*

[||]*Department of Medicine, Loyola University Medical Center, Maywood, IL, 60153, USA*

[**]*Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu Natal, Westville Campus, Durban, South Africa*

[††]Corresponding author. Email: *Skkwofie@ug.edu.gh*

ABSTRACT: Buruli ulcer (BU), a severe skin disease is caused by *Mycobacterium ulcerans*. There are concerns of therapeutic inefficacy of existing drugs coupled with chemoresistance. Databases have been shown to augment data mining and integrative systems pharmacology approaches towards the search for novel therapeutic moieties. So far, there is no known integrated database solely dedicated to BU drug discovery. In this work, Buruli ulcer database (BuDb) is a "one-stop-shop" knowledgebase for supporting BU drug discovery. It contains both manually verified literature and database-curated data on BU. The BuDb provides comprehensive information on the various drug targets, tested compounds, existing drugs, ethnopharmacological plants and information on the genome of *M. ulcerans*. It also contains cross-referenced links to databases including PubMed, PubChem, DrugBank, NCBI, Gene Ontology (GO), UniProt, Prota4u, String database, KEGG Pathway and KEGG genome database. The BuDb has been implemented with accessibility features such as keyword and specific searches as well as browsing. BuDb is the first useful online repository of its kind integrated with enriched datasets that can aid in the discovery of new biotherapeutic entities for BU. BuDb can be freely accessed at http://197.255.126.13:3000/.

KEYWORDS: *Mycobacterium ulcerans*; mycolactone; Buruli ulcer; database; drug discovery.

1. INTRODUCTION

Buruli ulcer (BU) is a chronic, ulcerative and devastating skin disease caused by *Mycobacterium ulcerans*, a nontuberculous mycobacterial species.[1–4] The mycobacterial infection was initially identified in Australian

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patients by Peter MacCallum in 1948.[5,6] The word, Buruli, was inspired by Buruli County in Uganda, where an overwhelming number of incidents were recorded and announced in 1960.[7,8] BU is one of the most underestimated neglected tropical diseases in humans, a list which includes tuberculosis and leprosy.[9] Presently, BU is reported in over 33 countries worldwide, particularly among individuals living in tropical and subtropical areas.[8,10] Every year, new cases of BU are recorded globally, with West and Central African countries being the most prominent.[8,10] Most of those infected are children below the age of 15 years living in isolated rural regions with no or limited access to healthcare.[10]

Mycolactone is the major virulence factor identified to date.[11] The etiology of the disease is due to the infection of an individual by *Mycobacterium ulcerans*, a bacteria that has acquired a plasmid that encodes for mycolactone and is able to cause cell death.[12–14] Some experiments further show that *M. ulcerans* strains that lack mycolactone cannot establish disease in mice models.[15] Understanding how the bacteria establish infection and how it is transmitted is still not clear enough at present. Mycolactone is a macrolide toxin with an immunomodulatory role and is implicated in skin dermis or subcutaneous tissue necrosis.[16,17] It binds to the adipocytes in the subcutaneous fat and has a cytotoxic impact on them.[18,19] The resultant necrosis provides a suitable substrate for the proliferation and growth of the *mycobacterium*.[20] Clinical manifestation of the disease appears in the form of oedema, plaque, papule, or nodule, which, if left untreated, tears the skin apart and develops into an ulcer.[10,21] BU has the potential to damage nerves, appendages and blood arteries, as well as infiltrate the bone leading to osteomyelitis.[22]

According to the World Health Organization (WHO), patients with BU lesions receive either rifampicin and clarithromycin or rifampicin and streptomycin as a primary treatment for eight weeks.[8] However, in the worst-case scenario, BU lesions are usually treated with comprehensive surgical removal of the infected skin and underlying tissue, followed by skin grafting.[23] There are few treatment options, and the advent of treatment-resistant isolates is a major concern that calls for developing new remedies. Conventional drug discovery methods are time-consuming and labor-intensive. Conversely, cheminformatics has progressed, with many recent drug discovery efforts being incorporated in the computational techniques.[24,25] Notable among such efforts is a previous report which computationally predicted natural product-derived binders of isocitrate lyase. These phytochemicals have the potential to be developed further into potent anti-BU drugs with improved therapeutic efficacy.[25,26] In addition to computational efforts, phytochemical studies of the leaves of *Holarrhena floribunda* and *Sorindeia juglandifolia* revealed some compounds with *in vitro* activities against *M. ulcerans*.[27,28]

Currently, less attention has been focused on systemic genomic or transcriptomic (multi-omics) research for BU in different ethnic populations. Most studies are on the genome of the bacteria, but this is usually trying to understand the geographical distribution of the bacteria, transmission and evolution of the bacteria as the transmission is still not fully understood.[29–37] Research focusing on the genomics of affected populations tried to find possible single nucleotide polymorphisms that may be associated with increased susceptibility to the disease.[24,38]

Data on various biotherapeutic targets involved in the pathophysiology of BU.[24,39] and compounds tested *in vitro, in silico*, or *in vivo* against the respective targets are required,[39] since this information could accelerate the BU drug discovery process. In addition, genomic data on *M. ulcerans* and information on ethnopharmacological plants could also speed up the discovery of novel therapeutics for BU.[40] However, gathering this information is constrained by time-wasting text mining and biocuration of published corpus and vast BU nonspecific databases. This consequently impedes the drug development efforts for BU. Therefore, the crux of this study is to assemble a BU-specific database.

Databases are developed from the complex processes of data mining and curation in drug discovery.[41,42] A number of biomedical databases have been developed[43,44] and depending on the type and purpose of the data, can be grouped into general or unspecified and disease-specific databases.[41,45] General or unspecified drug discovery databases contain a wide range of data on various organisms or diseases. Drug Bank (http://www.drugbank.ca),[46] Zinc (https://zinc.docking.org/),[47] ChEMBL (https://www.ebi.ac.uk/chembl/),[48] ChemSpider (http://www.chemspider.com/) and PubChem (https://pubchem.ncbi.nlm.nih.gov)[49] are some of the databases.[50] However, a disease-specific drug discovery database contains detailed data on either a specific disease or an organism. Notable examples include HCVpro database (https://www.cbrc.kaust.edu.sa/hcvpro/),[51] TB database (http://tbdb.bu.edu/)[52] and DenvInD (https://webs.iiitd.edu.in/raghava/denvind/search.php).[53] These databases provide information on relevant biotherapeutic entities such as proteins, lead compounds, drugs and metabolic pathways, among others and hence facilitate the processes involved in drug discovery.[41]

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Table 1. Databases containing information on *mycobacteria*.

Databases	Specific information	Reference
Mycobrowser https://mycobrowser.epfl.ch/	A repository for proteomic and genomic data.	56
GenoMycDB http://www.dbbm.fiocruz.br/labwim/bioinfoteam/templates/archives/GenoMycDB/GenoMycDB.html	Functional genomic analysis including mycobacterial protein classification and species evolution.	57
tbvar http://genome.igib.res.in/tbvar/	Genome variation resource for Tb	58
BioCyc https://mycobacterium.biocyc.org/	Contains information on organism phenotypic properties such as human-microbiome body site, aerobicity, and temperature range.	59
TB Database http://tbdb.bu.edu/	An integrated platform for Tuberculosis research.	52
TDR target https://tdrtargets.org/	A web-based database containing diverse datasets to facilitate drug discovery for neglected disease pathogens.	60

Towards consolidating drug discovery data for mycobacterial species, online repositories containing information on mycobacteria have been mentioned (Table 1). Their dependability has contributed to the discovery of potential drugs.[54,55]

Despite the usefulness of the information provided by these currently existing databases, the datasets on *M. ulcerans* are unformatted and widely scattered across different resources. In light of this, a more pragmatic trend is to develop databases dedicated to a specific disease.[52] There is a need to design an integrated knowledge base primarily focused on essential queries pertaining to BU with comprehensive data relevant to BU drug discovery.

Here, we present Buruli ulcer database (BuDb), which serves as "a one-stop" knowledge base and a dedicated resource for BU drug discovery. The enriched BuDb catalogues are manually curated and the comprehensive data on various drug targets, tested compounds via *in silico*, *in vivo*, or *in vitro* techniques, existing drugs, ethnopharmacological plants and the genome of *M. ulcerans* are recorded. BuDb has also been cross-referenced to databases including PubMed,[49] PubChem,[49] DrugBank,[46] NCBI,[61] Gene Ontology (GO),[62] UniProt,[63] Prota4u, STRING database,[64] KEGG Pathway and KEGG genome database.[65] The diversity of integrated datasets in BuDb can supplement the efforts geared towards discovering novel biotherapeutic entities for BU.

2. CONSTRUCTION OF DATABASE AND CONTENT

2.1. Data sources, processing and compilation

Databases and journal articles served as the main resources for the manually curated datasets contained in BuDb (Fig. 1). Given the variety of sources from which our data were derived, all BU-related information from databases and the literature were collected and compiled. A search query was conducted with the keywords "Buruli ulcer" OR "*Mycobacterium ulcerans*" via PubMed[66] to curate data from published literature containing information on BU. The PubMed search retrieved 1492 publications as of 29th May 2022. A total of 67 out of the number of publications retrieved contained drug-related information on BU and were cross-referenced in the database. In addition, cross-referenced data captured as link or URL address were also extracted from functional annotation databases, including the DrugBank database,[46] PubChem,[49] UniProt (https://www.uniprot.org/),[63] KEGG Genome (https://www.genome.jp/kegg/genome/),[67] BioCyc, Tropical Disease Research (TDR) Target[68] and NCBI repositories (https://www.ncbi.nlm.nih.gov/).[61] Afterward, all the data collected and compiled were refined and structured into five data fields: Drug target, tested compounds, existing drugs, ethnopharmacological

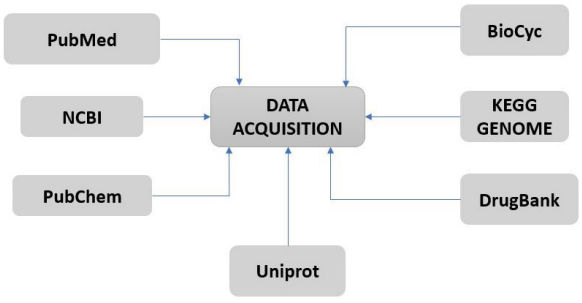

Fig. 1. A schematic illustration of some of the data sources compiled for the development of BuDb database.

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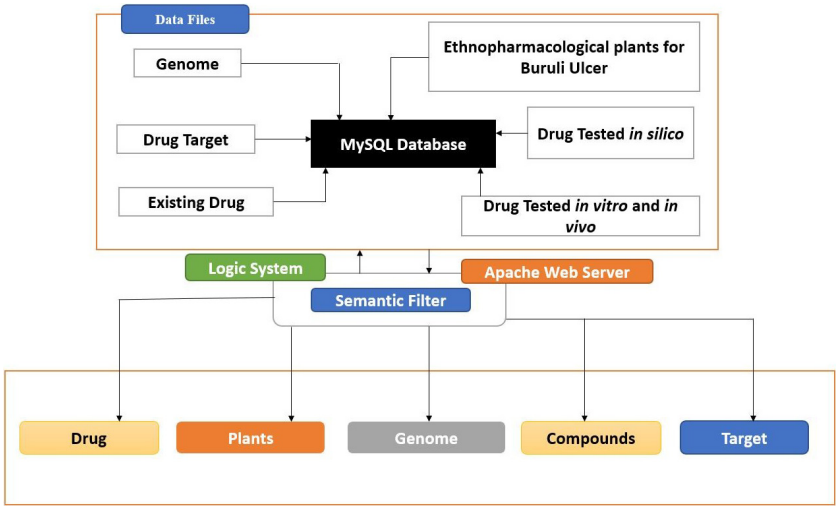

Fig. 2. (Color online) A schematic diagram of the database architecture of BuDb showing the relationship between the incorporated data files, logic systems and user query interface.

plants and genomic information on *M. ulcerans*, which were utilized in the construction of the BuDb database.

2.2. Database architecture and web interface

BuDb is a web-based database built on Apache HTTP server and uses MySQL server to store data. The responsive front-end query is implemented in JavaScript, PHP, HTML5 and CSS3, and the architecture is highlighted in Fig. 2.

3. RESULTS AND DISCUSSION

3.1. Data curation and statistics

BuDb contains a manually curated dataset of known *Mycobacterium ulcerans* and BU drug targets, tested compounds (*in vivo*, *in silico*, or *in vitro*), existing drugs, ethnopharmacological plants and information on the genome of *M. ulcerans* (Fig. 3). A brief description of the various datasets in BuDb has been provided.

3.1.1. *Drug target*

A protein drug target is associated with specific disease mechanisms and binds to a drug to generate the intended therapeutic effect.[69] BuDb contains 244 non-host essential proteins that are vital for the survival of *M. ulcerans* (Fig. 3). Some of the data entries in the drug target field include the gene name, gene symbol and the unique identity of the gene. Other entries in the drug target field include the organism name, associated metabolic pathways, drug target function, protein and

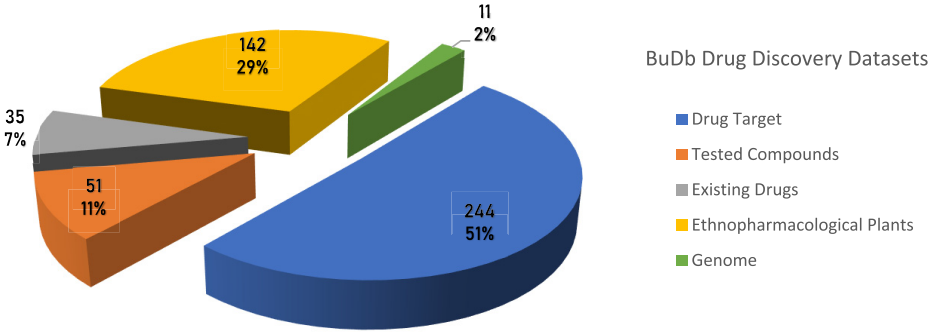

Fig. 3. (Color online) A pie chart displaying the percentage breakdown of the manually curated datasets in BuDb database. Drug target has the most entry data in the BuDb, with a statistical percentage of (51%). Ethnopharmacological plants, tested compounds, existing drugs and genome account for 29%, 11%, 7% and 2% of the total, respectively.

UniProt[63] accession numbers. Available cross-referenced links include PubMed and other functional annotated databases such as STRING database (https://string-db.org/),[64] GO annotation (http://geneontology.org/),[62] TDR Target[68] and KEGG pathway. These proteins captured in BuDb can help accelerate the identification of therapeutic targets in BU drug discovery.[24]

3.1.2. *Tested compounds*

BuDb contains 51 compounds that have been tested using *in silico*,[25] *in vitro*[70] and *in vivo*[71] methods (Fig. 3). Among the data, entries found under the tested compounds include the name of compounds, inhibitory concentration (IC_{50}) values, experimental techniques, 2D structures, molecular formulas and molecular weights. BuDb links these compounds to PubMed, PubChem and DrugBank. The minimum inhibitory concentration (MIC) and IC_{50} values of the respective compounds captured in BuDb indicate the extent to which the compounds inhibit a particular biological activity.[72] The curated bioactive compounds can help reduce the time involved in designing lead compounds for BU drug discovery.[72]

3.1.3. *Existing drugs*

An overall number of 35 available drugs/potential antibiotic therapies against *M. ulcerans* are provided in the BuDb (Fig. 3). This data field contains information on the names of experimental drugs, class of drugs, target protein in *M. ulcerans*, similar targets in other species, drug interaction phase, mechanism of action and mode of administration. Cross-referenced links included PubMed, DrugBank and other external databases such as KEGG DRUG repository (https://www.genome.jp/kegg/drug/),[65] ChEMBL (https://www.ebi.ac.uk/chembl/)[73] and BindingDB (https://www.bindingdb.org/bind/index.jsp).[74] The existing drug fields provide information on current treatment drugs, the phase of drug interactions, whether approved, investigational, or experimental and their respective biotherapeutic targets. It also provides information on how the drugs inhibit the activities of these targets in the virulence of BU. This can help invigorate the search for novel therapeutics for BU treatment.

3.1.4. *Ethnopharmacological plants*

Ethnopharmacological plants are biologically active plants traditionally employed to treat diseases.[75] Acknowledging that BU is mostly prevalent in rural areas with poor or no medical facilities, most rural folks resort to the traditional use of plants for treating BU lesions.[28] Most of these plants contain secondary metabolites and phytochemicals, which therapeutically target *M. ulcerans*.[28] Hence, ethnopharmacological plants can help facilitate the search for lead compounds that are therapeutically efficacious against BU.[76] BuDb contains 139 ethnopharmacological plants with three tonic mixtures prepared from some specially selected plant species used in BU treatment (Fig. 3). Some of the data entries under this field include the name of species, family and country of collection, parts of plants used, common or local names, extraction method and solvent(s) used. Moreover, the respective secondary metabolites, antimicrobial assay methods and MIC values have been provided. Included are links to PubMed and other plants databases such as PROTA4U (https://www.prota4u.org/database/) and GBIF (https://www.gbif.org/).

3.1.5. *Genomic information on M. ulcerans*

BuDb contains information and links to large genomic databases, including KEGG GENOME (https://www.genome.jp/kegg/genome/),[65] BioCyc (https://mycobacterium.biocyc.org/)[59] and NCBI (https://www.ncbi.nlm.nih.gov/),[61] which hold the current information on the annotation, metabolic information and other pertinent data on the genome of *M. ulcerans*. The genomic data field of BuDb contains genome assembly and annotation reports on nine strains of *M. ulcerans* (Fig. 3); among them are *M. ulcerans* str. *Harvey*, *M. ulcerans Agy99*[77] and *M. ulcerans* subsp. *shinshuense*. Some of the data entries under the genomic field include BioSample and BioProject database IDs, the assembly level and the length of the assembled genome, the number of scaffolds generated and both protein-coding and non-protein coding genes. This is to provide a snapshot of available annotated genomic data on different strains of *M. ulcerans* and further provide links to their parent databases for a detailed information on the strains. These annotated sequences could consequently facilitate the elucidation of new targets[78] in the light of emerging drug resistance.

3.1.6. *Data utility*

The curated drug targets will provide an avenue for easily accessible MU targets that can be targeted and assayed for rational drug design.[79] Tested compounds will provide leads to initial public data for some compounds that show promise and can be further

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investigated to provide new and better therapeutic options as the current treatment regimen requires a long period of antibiotic therapy.[13] Existing drugs will provide information on the current set of therapeutic interventions available that can be further improved through structural modifications or through drug combinations that can help mitigate drug resistance.[80,81] Ethnopharmacological plants curated will provide plant substrates, such as the leaves, stem and seeds, that have been shown to elicit some activity against BU to be investigated for bioactive compounds that can be purified and studied for their potential as alternative therapeutic interventions.[82,83] Curated genomic information provides important fundamental knowledge about the phenotypic potential of the bacteria and this facilitates the drug discovery in different ways. It helps in identifying pathways and genes for target-based drug design. Also, evolution and strains of interest can be determined by juxtaposing genomes with the curated complete reference genomes in the database, which can provide insights into adaptation mechanisms and conserved essential genes for accelerated drug design.[84,85]

3.2. Database interface and utility

BuDb is a web-based portal that can be accessed using a standard web browser on any internet-enabled device. The enhanced user interface is simple to use and includes several modules such as the "search", "browse" and "contact" menus (Fig. 4). The "search" menu item has two sub-query menus: "keywords" and "specific" searches. The "keyword search" item allows users to search and retrieve data entries across all fields simultaneously in the database. The "specific search" enables users to query information via any of these data fields comprising targets, plants, genomes, compounds and drugs. Also, the Browse menu of the web interface displays the various datasets available for easy data retrieval. To improve the utility of the database, user reviews or contributions can be submitted for evaluation via the "Contact" menu of BuDb.

3.3. Additional system features

To facilitate the convenient usage and comprehension of the information and data fields contained in BuDb, a user tutorial and frequently asked questions (FAQS) sections have been made available. In addition, BuDb offers a variety of cross-references to functional annotated databases and published literature that are biologically relevant for BU drug discovery. This provides an easy way to retrieve and utilize enriched drug discovery data. Cross-referenced links include databases such as the Human Metabolome Database,[86] ChemSpider,[87] ChEMBL,[88] ZINC,[89] GO annotation[62] and Therapeutic Targets Database.[90] BuDb has incorporated the downloadable datasets in tab-delimited format.

3.4. Case study: Using BuDb to retrieve information on mycolactone

Mycolactone is a polyketide-derived macrolide that *Mycobacteria* species, including *M. ulcerans*, produce and secrete.[91] Mycolactone is the toxin responsible for BU in humans, causing tissue damage and inhibiting the immune response.[19] To show the usefulness of BuDb in studying mycolactone, a simple search (Fig. 5) was conducted using "mycolactone" as the keyword.

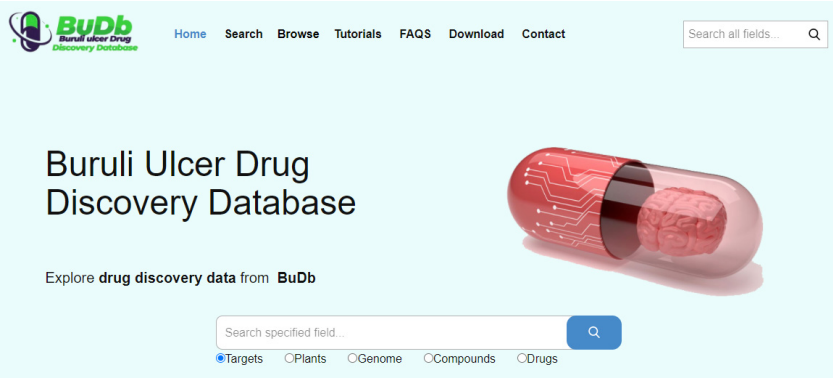

Fig. 4. (Color online) The home page of BuDb showing the user query interface.

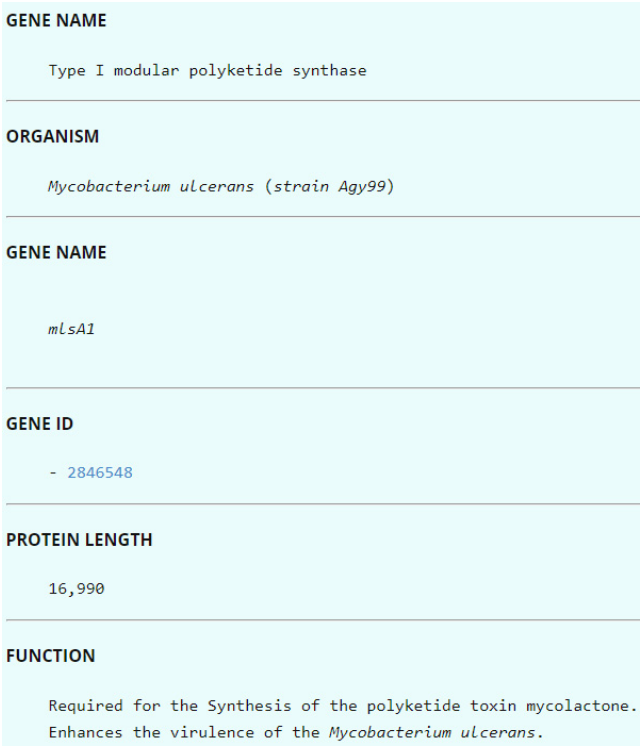

Fig. 5. (Color Online) A user interface displaying the results of a query for mycolactone.

The search retrieved multiple results for mycolactone related to the Type 1 modular polyketide synthase in the "Drug Target" data fields. The query retrieved the Type 1 modular polyketide synthase as the enzyme required for the synthesis of the polyketide toxin mycolactone. Furthermore, mycolactone enhances the virulence of the *M. ulcerans* by blocking blood platelets and mast cells from undergoing exocytosis and hence impairing the wound healing processes.

Further, the search results showed that mycolactone has immunosuppressive properties that enable it to inhibit phagocytic activities of neutrophils and white blood cells that are transported to infected cells. Cross-reference links to KEGG pathway and GO annotation databases also provided the structure, metabolic pathways and functions of Type 1 modular polyketide synthase enzyme gene. The information provided on mycolactone in BuDb is advantageous in searching for lead compounds that can inhibit the activity of Type 1 modular polyketide synthase activity.

3.5. Limitations and future prospects

The current version of BuDb was developed using only BU-related datasets. Future updates would integrate machine learning algorithms to facilitate the identification of potentially bioactive compounds against targets of *M. ulcerans*. Currently, there are no BU-specific ontologies available, the GO and other ontologies were incorporated into BuDb.

4. CONCLUSION

This is the first reported development of a BUDb. BuDb is a manually curated knowledgebase containing information on drug targets, tested compounds, existing drugs, ethnopharmacological plants and the genome of *M. ulcerans*. In addition, it contains cross-reference links to essential functional annotation databases. The enriched integrated datasets could invigorate the search for new biotherapeutic agents.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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